CLASSICAL HOMOCYSTINURIA

A treatable disorder

HCU Network Australia
HCUNetworkAustralia.org.au

Patient Information

ABOUT THIS BOOKLET

Good communication is at the heart of better patient care and outcomes, but achieving a common understanding between patients and clinicians can be difficult.[1] The goal of this booklet is to help the reader (the patient, their family or caregiver) understand more about classical homocystinuria (HCU), how it is diagnosed and the therapies it requires.

Information in this booklet is based on the recently published Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency[2] – written for doctors and other medical specialists as a practical guide to the recognition, diagnosis and management of HCU.

This booklet has been produced by HCU Network Australia, a health promotion charity, that undertakes a variety of activities to benefit individuals, and their families, living with HCU in Australia and beyond. Their aim is to improve health outcomes through education, research and support.

DISCLAIMER

This guide is for information only and should not be relied upon in place of medical advice. Any medical information is not intended as a substitute for informed medical advice. Consult a doctor or other health care professional for diagnosis and treatment of HCU. While all reasonable care in compiling the information has been made we make no warranty as to its accuracy.

SUPPORTERS

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FOREWORD

People with rare diseases, such as HCU, are scattered across the world. Their rarity leads to a lack of awareness not only among the general public, but also among the healthcare and research communities. This scarcity of awareness and expertise means delayed diagnosis and difficulties accessing treatment and care.

As a parent of two sons affected by HCU, I am acutely aware of the long diagnostic journey many families face and the uncertainties around its diagnosis and management. As founder of the HCU Network Australia I am passionate about uniting the HCU community and raising awareness of this rare disease in Australia and around the world – and as such, I am pleased that a milestone on the HCU journey has recently been reached with the publication of a set European Guidelines for the diagnosis and management of classical homocystinuria.

HCU Network Australia has worked to incorporate these guidelines with other relevant information into one document for people with HCU to read and share with others.

Tara Morrison
Founding Director, HCU Network Australia

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Who should read this booklet?

This booklet focuses on classical homocystinuria (HCU), also known as cystathionine beta-synthase (CBS) deficiency, the most common of the homocystinuria group of inherited metabolic disorders.

Individuals with HCU, their families, caregivers and friends may find it helpful to read this booklet. We hope that after reading it you will understand more about HCU – what it is, how it is diagnosed, what tests are needed and what other health conditions are linked to HCU. Understanding more about HCU may help you cope more easily with the condition, as well as helping you discuss tests and treatments with your medical care team.

Does all the information apply to me?

This booklet only deals with classical homocystinuria, its diagnosis, treatment and potential complications. There are other forms of homocystinuria, not discussed here, that have their own specific genetic causes, clinical symptoms and treatment needs.

Your doctor and medical care team can help by pointing out which parts of this booklet may be helpful to you, explaining anything you may not understand and answering any questions you may have.

The information in this booklet is based on guidelines written for doctors and other medical specialists and the recommendations may not be right for you. Your doctors may suggest other tests or treatments based on your particular health condition(s) or other factors – but remember you can always ask them questions.

Don't understand all the terms being used?

You may come across new medical words or terms being used by your doctors and other medical specialists – do not be afraid to ask them to explain anything you do not understand. There is a short glossary at the end of this booklet that may also help.

The information contained in this booklet is general in nature and should not be relied upon in place of medical advice. Any medical information contained in this booklet is not intended as a substitute for informed medical advice. Consult a doctor or other health care professional for diagnosis and treatment of HCU.

HCU BASICS

Homocystinuria is a rare condition associated with raised levels of an amino acid called homocysteine.

HCU gets its name from the high levels of the amino acid homocysteine detected in the urine (homocystin-uria). Homocysteine is made from another amino acid, called methionine, which we get from the food we eat.

When food is digested the larger nutrients (carbohydrates, fats and proteins) are broken down into smaller molecules so they can be absorbed by our bodies and travel to where they are needed. The proteins in foods such as nuts, meat, fish, and dairy products are broken down into smaller amino acids, one of which is methionine. Some of the methionine is reused by the body to make new proteins, but some is broken down to form homocysteine (figure 1).

Normally, homocysteine is then converted into the amino acids cystathionine and cysteine (figure 2), but sometimes the process is faulty and leads to high homocysteine levels and, over time, these can cause problems.

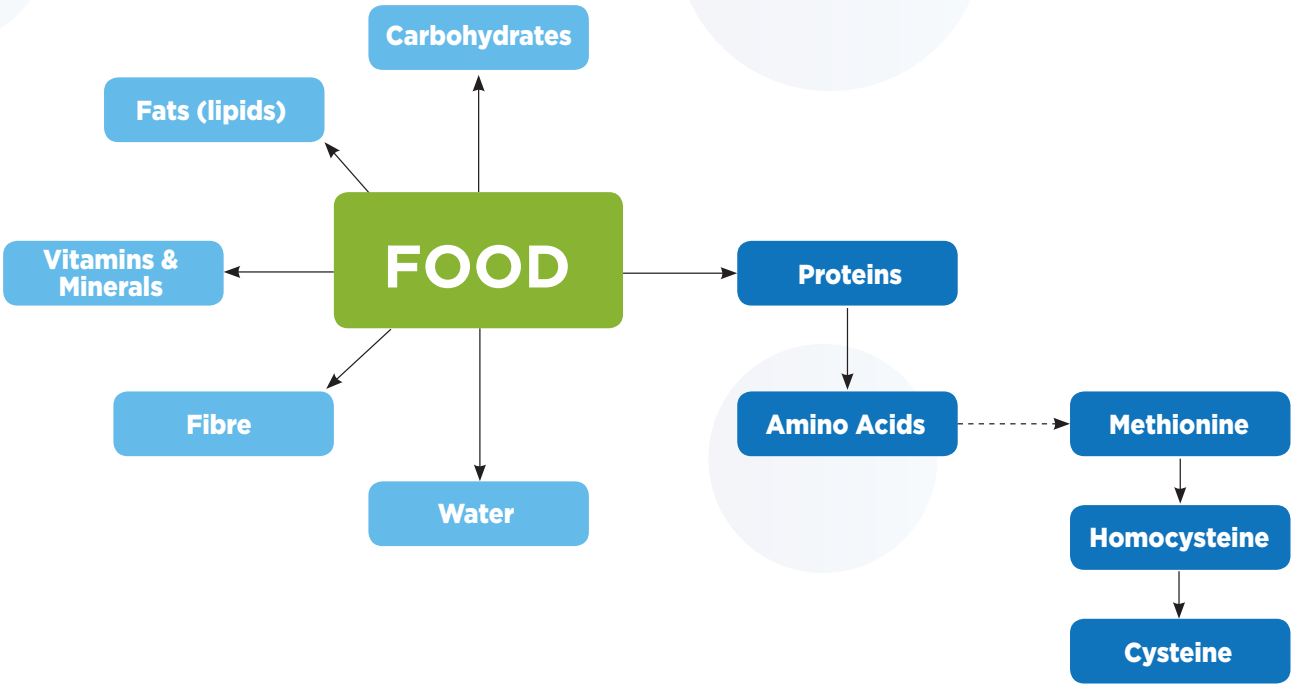


Figure 1: Food is made up of seven basic components: carbohydrates, fats, proteins, fibre, water, vitamins and minerals. Your digestive system breaks the larger nutrients (carbohydrates, fats and proteins) into simpler molecules so they can be absorbed by the gut. Proteins are broken down into smaller amino acids, one of which is methionine. Some of the methionine is then converted by the body to homocysteine which is then converted to cysteine.3,4

HOMOCYSTINURIA IS A METABOLIC DISORDER

The term 'metabolism' refers to all the various chemical processes that are continuously going on inside our bodies, enabling us to function normally. A metabolic pathway is a series of chemical reactions that transforms one or more chemicals into something that is needed by our body. Metabolic disorders occur when there are problems with one (or more) of these chemical reactions.

Enzymes, such as CBS, are special proteins that help control the chemical reactions that occur in the various metabolic pathways in our bodies. The CBS enzyme converts homocysteine to cystathionine. In people with HCU, the CBS enzyme is faulty leading to high levels of homocysteine and methionine, and low levels of cystathionine and cysteine. Vitamins B6 (pyridoxine), B12 (cobalamin) and folate are also needed to help make the breakdown processes of methionine and homocysteine work efficiently (figure 2).

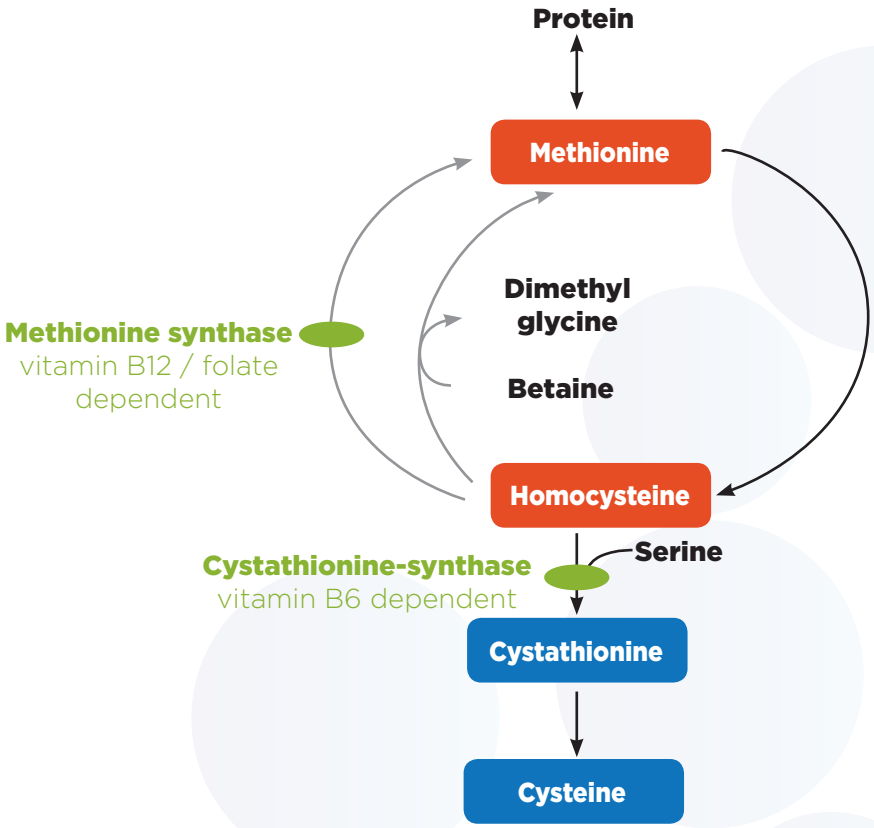


Figure 2: A simplified version of the metabolism of methionine and homocysteine – if the balance of the methionine metabolic pathway is upset by a faulty cystathionine beta-synthase (CBS) enzyme, then levels of homocysteine and methionine in the body will increase, and levels of cystathionine and cysteine will decrease. Vitamin B6 is needed for the CBS enzyme to work efficiently, while betaine, vitamin B12 and folate are needed for the alternative pathways which convert homocysteine back to methionine. Adapted from Testai et al 2010.

What problems can occur in people with HCU?

The genetic fault causing HCU is present at birth, but problems do not develop immediately.

The severity of HCU varies and depends on whether the faulty CBS enzyme is completely inactive or can still break down some homocysteine.

Without treatment, people with a severe form of HCU often have developmental delay in early childhood, followed by progressive problems affecting their eyes and skeleton. In contrast, people with a mild form of HCU may not be aware anything is wrong until after they have a blood clot as an adult.

Early diagnosis and treatment can make a real difference to the life of someone with HCU by preventing the problems listed below. In people diagnosed later, treatment can prevent further complications. The parts of the body most commonly affected by untreated HCU are the eyes, skeleton, brain and the blood vessels:

PROBLEMS ASSOCIATED WITH UNTREATED HCU

EYES
- Severe and progressive short-sightedness (myopia) at a young age
- Lens dislocation (ectopia lentis)

SKELETON
- Tall stature with long arms and legs
- Protruding or sunken chest (pectus carinatum or excavatum)
- Highly arched foot (pes cavus)
- Knock knees (genu valgum)
- Curved spine (scoliosis)
- Increased risk of broken bones due to weak bones (premature osteoporosis)

BRAIN
- Developmental delay and intellectual disabilities
- Seizures
- Clumsiness
- Psychiatric disorders (e.g. anxiety, depression, obsessive-compulsive disorder)
- Behavioural problems

BLOOD VESSELS
- Blood clots (thrombosis)
  - Deep venous thrombosis (DVT, blood clot in a leg vein)
  - Pulmonary embolism (blood clot from a DVT carried to the lungs)
  - Strokes (blood clot in the brain)

HCU is a treatable disorder

There are several different treatments available for individuals with HCU. People with a mild form of HCU often respond to large doses of vitamin B6 (pyridoxine). This is probably because their CBS enzyme is still working but is unstable, so there is less enzyme present than there should be – the vitamin B6 is thought to help stabilise the enzyme.

People who do not respond to vitamin B6 treatment need to be on a special diet that is low in methionine. A low-methionine diet has less methionine available to be broken down, so less homocysteine is made and less accumulates in the body.

Methionine is an essential amino acid – a building block of proteins we need for healthy growth and development that we can only get from food. When you have HCU your diet is important and there needs to be a balance between providing the right amount of methionine needed by your body, while maintaining homocysteine at acceptable levels.

High protein foods like meat, poultry, fish, dairy and eggs contain the highest amounts of methionine, followed by legumes and nuts, cereal based foods and vegetables. Some people may need to closely watch their protein intake, while others may tolerate a vegetarian diet or even small amounts of animal-based protein. Specialised formulas or supplement drinks rich in other amino acids can help improve your nutritional balance and homocysteine levels. Folic acid is usually added to the diet, and vitamin B12 and betaine may be needed in some patients to help promote the conversion of homocysteine back to methionine (figure 2).

Learning to manage a low-methionine (protein) diet during day-to-day life is not easy. You can get help from specialised metabolic clinics or dieticians experienced in managing these types of diets and from talking to other people with HCU and their families

HCU IS AN INHERITED METABOLIC DISORDER

Inherited disorders are medical conditions caused when there are problems with a gene. Genes are passed onto us from our parents and they determine the way we are, for example, the colour of our eyes and hair. Each gene instructs our bodies to produce a particular protein. These proteins are then used by the cells in our bodies to do particular jobs such as digesting food or building muscles and bones.

Genes are complex molecules and occasionally get changed slightly (mutated) or even go missing. Everyone has two copies of each gene – one inherited from each parent. For many genes, we only need to inherit one working copy; people remain healthy if they have one faulty copy of the gene, but they get problems if both copies are faulty. This is what happens in HCU where an affected child has two faulty copies of the CBS gene. Each parent has one faulty copy (that has been passed onto the child), but also a normal working copy of the gene, so the parents do not have HCU and are called carriers.

If the parents have another baby, they may each pass on their faulty gene again, in which case the new baby will also have HCU; if one parent passes on their normal copy of the gene, the baby will be a carrier and, if both parents pass on their normal copy, the baby will neither have HCU nor be a carrier. Overall, when both the parents are carriers the chances of having a child with HCU is 1 in 4 for each pregnancy (figure 3).

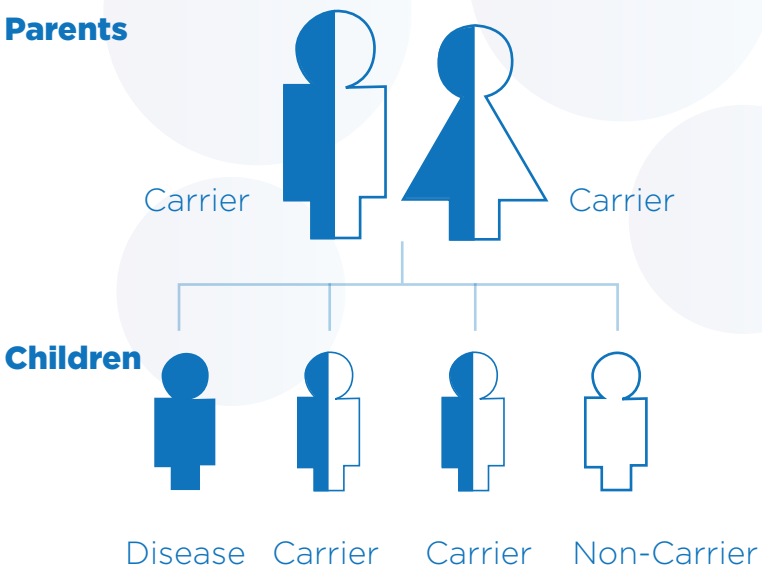


Figure 3: Homocystinuria is an autosomal recessively inherited disorder. This means that an individual must inherit a defective copy of the CBS gene from each carrier parent.

IS HCU A RARE DISEASE?

There is no single accepted definition for a rare disease. Rare Voices Australia define a rare disease as any disorder or condition affecting fewer than 5 in every 10,000 people (less than about 0.05% of the population).[5] Similarly, in Europe a rare disease is when fewer than 1 in 2,000 people are affected, while in the United States fewer than 200,000 people need to be affected (which equates to about 1 in 1,500 or less of the current population).[6]

Taken as a whole, rare diseases are common – about 8% of Australians live with a rare disease.[7]

Although HCU is a rare disease it is more common in some countries than others. The reported estimates of classical HCU range from about 1 in 1,800 people in Qatar to 1 in 900,000 people in Japan.[2] In Australia it is estimated to affect about 1 in 100,000 people.[8] The true number of people with HCU, especially with milder cases, is unknown but it is thought to affect at least 1 in 200,000 people worldwide.[9]

THE DIAGNOSIS

The Diagnostic journey

The HCU diagnostic journey can be a long and frustrating one for both the individual and their families.

HCU is a rare disease so the variable, non-specific symptoms in a child are not always recognised. For example, some people have a severe form of the disease that affects lots of different parts of their body from an early age, whilst others only show signs of the disease when they are adults. Children are more likely to first see a doctor because of an eye or developmental delay problem, whereas an adult is more likely to be diagnosed after a blood clot.

In Australia, babies are tested at birth for HCU, but newborn screening tests do not currently detect all of the cases and this type of screening is not available in all countries. If HCU is diagnosed from a positive newborn screening test, treatment is easier to implement and prevention of all the recognised complications becomes a realistic goal.

If a baby is not diagnosed during newborn screening, over the following years they may end up seeing many different medical specialists before a diagnosis is made.

The effects on the eye and skeleton resemble those seen in Marfan syndrome and patients are often misdiagnosed with this condition. Currently, about half the individuals with HCU are misdiagnosed at first and the majority will see three or more doctors (some seeing significantly more) before HCU is finally diagnosed. It takes an average of 4.5 years from the time of the original consultation to obtain a formal HCU diagnosis.[10]

Understanding the tests

HCU diagnosis is based on clinical presentation (signs and symptoms) and laboratory (biochemical and genetic) tests. Once the doctor thinks (or has a 'clinical suspicion') that HCU could be present they use biochemical tests of the urine and blood to confirm the levels of the different amino acids involved in the metabolism of homocysteine and methionine (figure 2).

HCU is very likely if there are:

- **High levels of homocysteine in blood and urine**
- **High levels of methionine in blood**

Blood plasma samples are usually tested for the presence of high homocysteine levels. Plasma is the liquid part of the blood that remains after the red blood cells, white blood cells and platelets are removed by centrifuging unclotted whole blood. The total homocysteine (tHcy) concentration is measured; tHcy is the sum of the all the free and protein-bound forms of homocysteine found in plasma.[2] Just testing for free homocysteine (fHcy) is no longer recommended as only small amounts of the amino acid exist as fHcy, and the test is considered insensitive and unreliable.[2] Plasma, rather than whole blood, samples are used because free homocysteine is released from blood cells and can artificially increase tHcy levels.

The normal (reference) range of tHcy in blood plasma is generally between 10 and 15 µmol/L, although it can vary with age and the test method.[2] The untreated severe form of HCU will typically have tHcy concentrations above 100 µmol/L.[2]

Newborn screening for HCU is usually done by testing a few drops of blood from a heel prick when a baby is about 2-5 days old. The drops of blood are soaked up by a special card, dried and tested – this is called a dry blood spot test. HCU is suspected if the baby's blood is found to have higher than normal levels of methionine and further tests are needed to confirm the diagnosis (as other conditions can also cause high levels of methionine in blood). Newborn screening has its own set of testing problems and not all HCU cases can be picked up at this point, especially the milder cases of the disease.

HCU diagnosis can be masked in people with a mild form of the disease if they are taking vitamin B6 (pyridoxine) or pyridoxine-fortified multivitamins and foods. This is why your doctor may ask you not to take any pyridoxine supplements, fortified foods or drinks for at least 2 weeks before testing.[2]

The initial biochemical tests are normally followed by confirmatory tests (enzyme or DNA analysis). If one of these techniques does not confirm the diagnosis in someone with unusual blood results, then the other test should be carried out as well – to double check.[2] This is particularly important if the disease is a mild form of HCU and there is more uncertainty over the diagnosis.

DNA (molecular genetic) analysis of the CBS gene is helpful for:[2]

- Confirming the diagnosis of HCU
- Confirming someone is a carrier of the mutated gene (but does not have the disease)
- Prenatal testing during pregnancy if both parents are carriers. Preimplantation Genetic Diagnosis (PGD) is also possible: this is where an embryo is tested prior to implantation when in vitro fertilisation (IVF) is used.

When someone has HCU and they are the first person in their family to be diagnosed, they are called the index case. Other family members who are at risk of having the disease should be offered screening to check if they too are affected. This is usually done by biochemical testing.[2]

Testing for vitamin B6 responsiveness

Two forms of HCU have been identified:

- **A 'milder' form that responds to vitamin B6 (pyridoxine) supplements**
- **A more 'severe' vitamin B6 non-responsive form**

It is recommended someone with HCU is tested to see if they are responsive to vitamin B6 – that is they are able to achieve close to normal homocysteine levels with only vitamin B6 supplements.

Vitamin B6 is given to the test person each day for 6 weeks with at least two homocysteine measurements before and 2-3 measurements during the testing period. If the individual is vitamin B6 responsive the homocysteine levels should fall by more than 20%.[2] The test should be done when the person is stable, on a normal protein diet with folate supplements and after any vitamin B12 deficiency is corrected.[2]

A response to vitamin B6 is very rarely seen when HCU is detected by newborn screening. In this situation, to avoid delaying effective treatment, the guidelines recommend using a higher dose of vitamin B6 for a shorter period of time (2 weeks).[2]

Some people are only partially responsive to vitamin B6 and need this supplement plus some extra treatment such as a low protein diet.

What's next?

Once HCU has been diagnosed the next step is to develop a treatment plan with your medical care team that aims to:

- **Prevent all the complications associated with the condition – in early-diagnosed HCU**
- **Prevent further complications developing – in late-diagnosed HCU**

TREATMENT PLANNING

Although there is no cure for HCU, it is a treatable condition.

When HCU is diagnosed early and there is good compliance with the recommended dietary treatments, prevention of all the recognised HCU complications is a realistic goal.[2]

The dietary treatment should not affect growth or nutrition and should allow people to function normally and to have a family if they wish.[2]

For those people who have been diagnosed with HCU later in life, the main aim of HCU treatment is to prevent further complications.

Behavioural and intellectual improvement has been reported in some studies,[11] but the main goal is to prevent blood clotting (thromboembolic) problems, such as strokes, which can be fatal and are the most commonly seen 'late' HCU complication.[2]

Biochemical targets

The aim of HCU treatment is to keep homocysteine concentrations in the body at safe levels (as normal as possible) while maintaining the body's normal growth and nutrition.

Vitamin B6 responsive HCU – the recommended target level for homocysteine in the blood is less than 50 µmol/L. Not everyone will be able to achieve this target, particularly if they are only partially responsive to vitamin B6.[2]

Some people who are partially-responsive to vitamin B6 may be able to achieve their target level if they are also on a low-methionine diet, while for other people it is just not a realistic goal even on a restricted diet. If methionine in the diet is restricted too much (so that the methionine concentrations in the blood are sometimes below the normal range of about 15-40 µmol/L) normal growth and development in children may be affected.

Vitamin B6 non-responsive HCU – the current recommended target level for homocysteine* in the blood is less than 100 µmol/L.[2]

If dried blood spots are used for monitoring homocysteine* the target level should be adjusted to below about 30 µmol/L in vitamin B6 responders and below 60-70 µmol/L in non-responders (depending on the method used), as homocysteine concentrations are lower in the blood spots compared to blood plasma used in the other testing methods.[2]

Remember that keeping homocysteine concentrations at exactly the right level can be tricky – if they are okay most of the time that is fine – occasional low or high levels are bound to occur.

Dietary management

The current HCU recommended treatment involves low-methionine (protein) diets with additional dietary supplements.

Dietary management should be considered for all those people who are vitamin B6 non-responsive (i.e. cannot control homocysteine levels with only vitamin B6 supplements), and as an additional treatment in individuals who are partially vitamin B6 responsive.[2] Some patients will combine dietary treatment with the drug, betaine (discussed below). HCU cannot be cured so treatment must continue for the whole of the individual's life.

* Total homocysteine (tHcy) in blood plasma

• Methionine-restricted diet (low protein plus a methionine free amino acid supplement)

The amino acid methionine cannot be made by the body and is contained in the foods we eat. Methionine is found in all foods that contain protein, particularly protein-rich foods such as nuts, meat, fish, legumes and dairy products (see also page 4).

If the amount of methionine in the diet is reduced, the amount of homocysteine produced by the body is also reduced (because homocysteine is only be made in the body from methionine – figure 2).

The strictness of the methionine (protein) restriction required will vary from person to person and is worked out by first checking and then rechecking the levels of homocysteine and methionine in the blood (this is usually done by a metabolic dietitian).

Methionine is essential for normal growth and development (particularly in children) so close monitoring of methionine levels and growth are needed when HCU is severe and a low-methionine diet is recommended.

Most people with vitamin B6 non-responsive HCU can only reach the recommended homocysteine targets if their diet is very low in foods containing protein, so low that they need supplements of a methionine-free amino acid mixture to avoid protein malnutrition.

The amino acid, cysteine, is normally formed when homocysteine is broken down (figure 2), so people with HCU may have low levels. To avoid this, cysteine is included in the methionine-free amino acid supplement in the form of cystine.

The different amino acids and metabolites with similar sounding names can be confusing when you start learning about HCU. Cystine is made from two cysteine molecules joined together. This reaction occurs spontaneously but the body can convert cystine back to two cysteine molecules. (Similarly, homocystine is formed from two homocysteine molecules joined together).

Even if a restricted diet is recommended it should still be nutritionally complete and contain all the nutrients and energy requirements the body needs. For example, most amino acid supplements contain vitamins and minerals and many now also contain long-chain polyunsaturated fatty acids as low-methionine (protein) diets may not provide enough.

• Vitamins

Vitamin B6 (pyridoxine)

If HCU is vitamin B6 responsive the amount of supplement taken each day should be the lowest possible to achieve the recommended homocysteine targets. Partially responsive individuals may need higher doses of vitamin B6 and additional treatment. There is no evidence that taking long-term vitamin B6 supplements helps non-responsive forms of HCU.[2]

The guidelines recommend using doses of vitamin B6 of up to 10 mg/kg/day with a maximum for adults of 500 mg/day. Some problems, including peripheral nerve damage (neuropathy), can occur when very high doses of vitamin B6 (greater than 900 mg/day) are taken for long periods.[2]

Vitamin B12 and folate

People with HCU may not have enough vitamin B12 or folate – this can be due to the disease itself or because of a restricted diet. These two vitamins, along with vitamin B6, play important roles in the metabolism of homocysteine and methionine (figure 2). It is important that our bodies have enough so everything functions properly.

The guidelines recommend that everyone with HCU is given low-dose folate supplements and that vitamin B12 should be monitored and supplemented only if needed.[2] Vitamin B12 and folate supplements are generally included in methionine-free amino acid supplements so, if you are taking one of these, additional supplements may not be needed.

• Betaine treatment

Betaine is a chemical that can convert homocysteine back into methionine (figure 2). It is sometimes added to the diet if homocysteine levels are above the targets goals.

Betaine doses need to be optimised for each person. The guidelines recommend:[2]

- For children – a starting dose of 50 mg/kg taken twice a day
- For adults – a starting dose is 3 g taken twice a day.

The dose (and frequency of the dose) are then adjusted according to how your homocysteine levels respond to the treatment, but no extra benefit is likely with doses of more than 150-200 mg/kg/day.[2]

Some people think betaine has a fishy smell or do not like the taste, which can put them off taking the treatment. Betaine can also further increase the high methionine blood levels. Very rarely a side effect called cerebral oedema (brain swelling) occurs when methionine levels are too high. The current recommendation is to keep methionine levels below 1000 µmol/L when betaine is added to the diet.[2]

• Monitoring

It is important to monitor blood samples for homocysteine, other amino acids including methionine, folate and vitamin B12 regularly during treatment – how often will depend on things like how severe the HCU is, the type of treatment being used, as well as the age and medical condition of the individual.[2] People on dietary treatments will also need regular nutritional assessments to check all their nutritional needs are being met.

Regular blood tests and regular attendance at a metabolic clinic, therefore, play an important part in the treatment plan. The HCU recommended monitoring assessments are summarised in table 1, which gives an idea of the range and frequency of tests needed. Some assessments or tests will be done every time you visit the clinic, while others may only require annual checks.[2]

• Special management issues

There are times when special attention to dietary and other treatments may be necessary. For example, having surgery, being ill or being immobilised (not moving for a period of time) all have their own particular issues.

Treatment compliance

Compliance means correctly following medical advice. For HCU, good treatment compliance is very important for the best long-term health results.

An early HCU diagnosis followed up with the recommended treatments can prevent damage to the eyes, brain, skeleton and the vascular system developing – but the treatment has to be routinely followed throughout life.[2]

Getting adolescents and young adults to take supplements and stick to their required dietary changes can be difficult. It is very important that they fully understand the serious consequences of not following treatments and not keeping homocysteine levels within their target range – however boring or difficult they think the treatments are!

It can also be challenging to start (and stick with) dietary restrictions when HCU is diagnosed late. But, being persistent and sticking to the recommended treatments can reduce the risk of further complications developing and even help reduce some symptoms, for example, seizures and behaviour may improve.[2]

Table 1: Recommended type and frequency of monitoring for HCU.[2]

Type of Monitoring	Frequency of Monitoring
• Height • Weight	• Every clinic visit
• Dietary intake analysis	• Every clinic visit (when on dietary treatment)
• Homocysteine levels • Methionine levels	• Depends on age and disease severity
• Vitamin B12, folate • Blood count, albumin, plasma amino acid, ferritin, zinc, vitamin D • Selenium, essential fatty acids	• At least annually (everyone) • At least annually (when on dietary treatment) • Only if they are thought to be a problem
• Clinical examination • Neuroimaging	• Annually • Only if there are new CNS symptoms
• Eye examination	• At least annually
• IQ testing	• At least every 5 years during childhood
• Clinical psychology or psychiatric assessment	• If required
• Bone density scan (DEXA)	• Every 3-5 years from adolescence (unless needed earlier)
• Lipid profile, cardiovascular risk review	• Once in childhood, annually in adulthood

CNS = central nervous system; DEXA = dual-energy X-ray absorptiometry

Surgery

Undergoing surgery and having a general anaesthetic can cause problems when you have HCU. High homocysteine levels can increase the risks of blood clots forming (thromboembolism). To minimise these risks, homocysteine levels need to be optimised before any surgery and special attention needs to be paid to dietary treatments and nutrition.[2]

The guidelines also recommend that other standard anti-thrombotic measures, such preventing dehydration, wearing elastic stockings, using leg compression systems and early mobilisation, are used during and after surgery. Heparin (an anticoagulant) may also be used to prevent blood clots if you are unable to move about after surgery.[2]

Nitrous oxide, which is sometimes used to sedate and relax people during surgery and dentistry, affects vitamin B12 causing homocysteine levels to rise and should usually be avoided (discuss this with your doctor or dentist).[2]

Illness

Minor illnesses, such as colds or flu, can cause homocysteine levels to increase. This should not be a problem if the illness is short and homocystinuria treatments need not be stopped. When homocysteine levels are higher than they ought to be over weeks or months, long-term health complications could become a problem and more frequent nutritional monitoring may be needed.[2]

Because HCU increases the risk of blood clots, it is important not to become dehydrated when you are ill (for example, through diarrhoea and vomiting) or to stay in bed (immobilised) for too long.

Travelling

There have been no published studies on what precautions to take when travelling with HCU. However, standard precautions are recommended to minimise the risk of blood clots: keep as mobile as possible while travelling (for example, flexing muscles or periodically walking around airplane cabins) and stay well hydrated.[2]

If you have had a blood clot or have a high risk of one forming, your doctors may recommend taking heparin as a preventative while travelling.

Many doctors may not have come across HCU before, so carrying some information that helps explain the rare condition may be useful when you are travelling. For longer periods away from home, your medical care team may be able to suggest a local doctor that could help supervise your care.

LIVING LIFE

The key to improving outcomes

An accurate diagnosis is the first step to improving the care and outcomes for those living with a rare disease such as HCU. The second step is following the recommended long-term treatment.

In HCU the loss of biochemical control, at any age, can lead to serious complications that may be life-threatening.[2] These complications can be prevented with long-term treatment, but once the damage has occurred it usually cannot be reversed. However, treatment can prevent existing complications getting any worse and other problems occurring. This means people, teenagers and young adults in particular, who may not follow recommended treatments put their health at risk.

When HCU is detected early and treated appropriately, children are able to reach their full potential. The risk of complications occurring (and their severity) is related to the age at which HCU is diagnosed, how well treatment is followed and whether it responds to vitamin B6.

In the more severe, vitamin B6 non-responsive form of HCU the best outcomes are achieved when the disease is identified by newborn screening and treatment is started soon after birth.

HCU complications

The major complications of untreated HCU affect four parts of the body: the eyes, the skeleton, the brain, and the vascular system. All four of the systems can be affected or only one of them. Complications can vary from mild to severe – but are progressive unless HCU is diagnosed and treated.

• The EYES

Eye problems (ophthalmological complications) are common in untreated HCU. The earliest sign is severe and rapidly worsening short-sightedness (myopia) at an early age. Dislocation of the lens away from the centre of the eye (ectopia lentis), is another sign of HCU and it is often this that leads to diagnosis of the disease. It is very rare in children under 2 years but, without treatment, most vitamin B6 non-responsive children (85%) will have dislocated lenses by the time they are 12 years old.[2]

Other complications include glaucoma (loss of vision due to increased pressure in the eye causing optic nerve damage), and retinal detachment (separation of the layer of nerve cells lining the back of the eye). 'Quivering' or 'trembling' of the coloured part of the eye (iridodonesis) occurs with early dislocation of the lens.

Following diagnosis, regular check-ups with an ophthalmologist are recommended. Physical activity is important for everyone's health and well-being and many activities can be safely incorporated into your daily routines. However, because of the risk of lens dislocation contact sports, such as rugby and boxing, should be avoided.

• The SKELETON

Problems with how bones form and grow (skeletal complications) are also common in untreated HCU. Skeletal problems are not seen at birth and they are very rarely seen in infants or very young children. Early signs of untreated HCU may include rapid growth.[2]

Knock knees and highly arched feet are usually the first skeletal problems to appear. Arms and legs start to appear overly long compared to the body around puberty, the chest may become sunken or protrude and curvature of the spine can occur. Overcrowding of teeth and a high arched palate can make the upper teeth stick out more and change how the face looks. The appearance of older people with untreated HCU can be very similar to people with Marfan syndrome.[2]

Osteoporosis (bone weakening), especially of the spine, is the most consistently seen skeletal complication and bone density scans are recommended every 3-5 years from adolescence.[2] If low bone density becomes a problem, vitamin D and dietary calcium levels may need checking and weight-bearing exercise may be recommended to help improve bone health.

• The BRAIN AND NERVOUS SYSTEM

HCU problems linked to the brain and nervous system (psychological and neurological complications) in untreated people may include: developmental delay, intellectual disabilities, seizures, strokes, psychiatric and behavioural problems, as well as movement disorders.[2]

Developmental delay is sometimes the first symptom noticed by parents or doctors. Children with untreated HCU may take longer than normal to reach developmental milestones such as sitting, standing, walking and speaking. About 1 in 5 children with untreated HCU will develop seizures by the time they are 12 years old.[2]

Many untreated people develop psychological issues which can include depression, anxiety, obsessive-compulsive disorder, personality disorders and psychotic episodes.[12]

• The VASCULAR SYSTEM

The vascular (circulatory) system is made up of arteries, veins and capillaries that carry blood around our bodies. HCU increases the risk of blood clots (thrombi) developing.

These blood clots can occur at any age and symptoms will depend on which blood vessel becomes blocked. Veins are commonly affected in HCU with 50% of vascular complications being deep vein thrombosis (DVTs). Sometimes some of the clot can break off and travel in the blood till it blocks an artery in the lungs (pulmonary embolism). About a third of vascular complications are strokes where the blood flow in the brain is affected.[2]

In HCU, strokes (particularly in young people) are caused by a blood clot blocking a vein that stops blood draining out of the brain (sagittal sinus thrombosis). This is unusual as most strokes are caused by abnormalities of arteries carrying blood into the brain.

Vascular complications are common in untreated or poorly controlled HCU. Dehydration can increase the risk of blood clots forming, particularly in children, and it is important to always stay well hydrated.[2]

• OTHER COMPLICATIONS

Other rarer complications include pancreatitis (inflammation of the pancreas), spontaneous pneumothorax (collapsed lung), discoloration of the skin (hypopigmentation), rashes on the cheeks (malar flushing) and tears in the abdominal wall (inguinal hernia).[2,13]

Fertility, pregnancy and contraception

HCU does not appear to affect fertility, so some form of contraception will be needed if you are not planning to start a family.

Women should avoid any contraceptives containing the hormone oestrogen as it increases the risk of blood clots (thrombosis).

Where possible, a pregnancy should be planned so care can be provided before and after conception. By sticking to the recommended treatments, complications can usually be prevented and there have been many successful pregnancies and births reported.

Once you fall pregnant, having HCU does not appear to increase your risk of miscarrying (if metabolic control is good) or increase the risk of birth defects.[2] HCU does, however, increase the risk of blood clots during pregnancy, at delivery and for a few weeks after the birth.

Anticoagulant therapy (with heparin) is recommended during pregnancy to help prevent blood clots. This is usually recommended during the last part of the pregnancy (the third trimester) and a 6-week period after the birth.[2]

Frequent biochemical monitoring and dietary assessments, during pregnancy and after the birth, are important to help maintain the mother's energy and protein needs, as well as making sure homocysteine targets are met. Betaine has been used in pregnancy without adverse effects.[2]

MAKING DECISIONS

Making decisions or expressing opinions about different treatments, sharing information and feelings, and accepting health team instructions are all part of the HCU journey – a process that aims to support people to stay well and manage their own conditions better.

It is important to find out as much as possible about HCU and its treatment, so you can talk over any problems or concerns you have with your medical care team.

A metabolic disorder is not something you can manage on your own – it is a team effort and with support things can seem a little less daunting.

Asking questions and being informed means you are in a better position to make the best decisions for you or your child. It is often helpful to write down any questions you want to ask and take them to your next appointment.

Questions that may be helpful include:

- What is your experience of HCU?
- What does the diagnosis mean for me/my child/our family now and in the future?
- What further screening/testing/follow-up appointments are there?
- How long will the test results take to come through?
- Can you go through the test report (again) with me?
- What does each treatment option require of me?
- If my child were to have a child of their own, would they also have HCU?
- Do I and my partner need testing? Will other members of the family need testing?
- How/when do we explain HCU to our child?
- Are there any other medical problems associated with HCU?
- What services am I likely to need?
- Where can I go for support?

Finding help and support

• HCU Organisations

European Network and Registry for Homocystinurias and Methylation Defects (EHOD)
Website: http://www.e-hod.org

HCU Network America
Email: hcunetworkamerica@gmail.com
Website: http://www.hcunetworkamerica.org

HCU Network Australia
Email: info@hcunetworkaustralia.org.au
Website: http://www.hcunetworkaustralia.org.au

• Rare Diseases and Research Organisations

Australian Society for Inborn Errors of Metabolism (ASIEM) – a special interest group of the Human Genetics Society of Australia (HGSA)
Website: https://www.hgsa.org.au/asiem

Canadian Organization for Rare Disorders
Website: http://www.raredisorders.ca

EURORDIS - Rare Diseases Europe
Website: https://www.eurordis.org

GARD (Genetic and Rare Diseases Information Center – USA)
Website: https://rarediseases.info.nih.gov

Genetic Alliance Australia
Website: http://www.geneticalliance.org.au

Genetic Alliance UK
Website: http://www.geneticalliance.org.uk

Genetic Alliance USA
Website: http://www.geneticalliance.org

Global genes
Website: https://globalgenes.org

Metabolic Dietary Disorders Association
Website: https://www.mdda.org.au

Metabolic Support UK
Website: https://www.metabolicsupportuk.org

New Zealand Organisation for Rare Disorders
Website: https://www.nzord.org.nz

NORD (National Organisation for Rare Diseases - USA)
Website: http://www.rarediseases.org

Rare Diseases South Africa
Website: http://www.rarediseases.co.za

Rare Diseases Sweden
Website: http://www.sallsyntadiagnoser.se

Rare Voices Australia
Email: info@rarevoices.com.au
Website: https://www.rarevoices.org.au

Unique the Rare Chromosome Disorder Support Group
Website: http://www.rarechromo.org

• Rare Diseases Reference Databases

Orphanet
Website: http://www.orpha.net

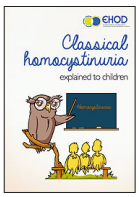
Rare Disease Connect
Website: https://www.rareconnect.org

• Dietary support

The ASIEM Low Protein Handbook for Homocystinuria
ASIEM have produced several dietary handbooks to help dietitians and families treat different metabolic disorders, including HCU, and are available at:
https://www.hgsa.org.au/resources/asiem-resources-for-parents-and-families/asiem-dietary-handbooks

Dietitians Association of Australia (DAA)
Website: https://daa.asn.au

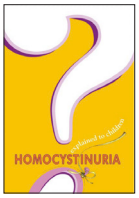
• Information for children



An information booklet designed to explain HCU to children is available in English and eight other languages from the EHOD website:
http://www.e-hod.org/information-for-children

An information booklet designed to explain HCU to parents, patients and families is also available in English and eight other languages from the EHOD website:
http://www.e-hod.org/information-for-adults-parents-carers

The Medical Genetics Service of Hospital de Clinicas de Porto Alegre, Brazil have also prepared a children's information booklet on classical homocystinuria. It is available in English, Spanish and Portuguese from the HCU Network Australia website:
https://www.hcunetworkaustralia.org.au



Orphan Europe together with CLIMB has prepared an information booklet on homocystinuria for children. It is available from the Orphan Europe website in English and six other languages:
http://www.orphan-europe.com/patients-and-families/homocystinuria

Any information provided by the above sources should be discussed with your medical care team and should not replace their advice. This is not a complete list of HCU information sources.

GLOSSARY

Amino Acids – are the basic building blocks of proteins.

Anticoagulants – are medications, such as heparin, that are used to help prevent blood clots forming.

Catalyst – is a substance that helps speed up a chemical reaction but is not permanently changed in the process.

Cerebral oedema – or brain swelling, is the build-up of fluids in the tissues of the brain.

Chromosome – is a structure in our cells that is made up of a very long strand of DNA. A chromosome can contain thousands of our of genes and is involved in the transmission of heredity information.

Clinical presentation – the physical signs and symptoms associated with a particular disease that are used to help diagnosed the condition.

Cobalamin – is another name for vitamin B12.

Cystathionine – is an amino acid that is an intermediate stage in the production of cysteine. Methionine is metabolised into homocysteine, which combines with serine to form cystathionine which is then converted to cysteine.

Cystathionine beta-synthase – also known as CBS, is an enzyme that catalysts the conversion of the amino acids homocysteine and serine into cystathionine.

Cysteine – is a non-essential amino acid that is produced in the body from the essential amino acid methionine; cysteine may become semi-essential when methionine intake is limited.

DNA – or deoxyribose nucleic acid, is a long molecule that contains our unique genetic code (the instructions needed to make all the proteins in our bodies required for us to develop, live and reproduce).

Ectopia lentis – dislocation of an eye lens.

Enzyme – is a protein that acts as a catalyst within living cells and helps speed up a chemical reaction.

Essential amino acids – are amino acids that cannot be made (synthesised) within our bodies and need to be provided by our food.

Folate – also called vitamin B9 or folic acid.

Genes – are the basic units of heredity and act as instructions to make all the body's proteins. Genes are made up of small sections of DNA and are located in our chromosomes.

Gene mutation – is a permanent change in the DNA sequence that makes up a gene and can affect a single DNA building block or a large part of a chromosome that includes many genes.

Genu valgum – is another name for knock knees (where the knees angle in and can touch each other when the legs are straightened).

Glaucoma – is a condition that affects the optic nerve connecting the eye to the brain and is often caused by increased pressure in the eye. Glaucoma can lead to permeant vision loss.

Homocysteine – is an amino acid which is an intermediate in the metabolism of methionine and cysteine.

Index case – is the first person to be identified in a group of related cases of a communicable or heritable disease.

Iridodonesis – is the vibration or trembling motion of the iris (coloured part of the eye) when the eye moves. It is a sign of the total or partial dislocation of the lens (ectopia lentis)

Marfan syndrome – is a genetic disorder of the body's connective tissue and can affect the heart, eyes, skeleton and lungs.

Metabolic disorder – occurs when the normal metabolic processes in the body fail and causes either too much or too little of particular substances needed to stay healthy.

Metabolic pathway – is a linked series of chemical reactions that occur in a cell that either lead to the production or breakdown of particular substances.

Metabolism – is the many different chemical reactions going on continuously inside our bodies that allow us to live and function normally.

Metabolites – are the substances that are produced during metabolism or that take part in a metabolic process.

Methionine – is one of nine essential amino acids we need to have in our diet. It is metabolised to form homocysteine.

Myopia – is another name for short-sightedness.

Neuropathy – is damage or disease that affects nerves.

Newborn screening – is where a newborn baby is tested for certain harmful or potentially fatal disorders that are not otherwise apparent at birth.

Non-essential amino acids – are amino acids that can be made by our bodies and are not 'essential' in our diet.

Ophthalmologist – is a doctor who has specialist training in the diagnosis and management of disorders of the eye and visual system.

Osteoporosis – is a condition that affects bones causing them to become weak and more likely to break.

Pectus carinatum – a protruding chest.

Pectus excavatum – a sunken chest.

Pes cavus – is a foot with a high instep or arch.

Prenatal – is something occurring before birth.

Prognosis – is the opinion, based on medical experience, of the likely course of a medical condition.

Pyridoxine – is another name for vitamin B6.

Scoliosis – is a sideways curvature of the spine.

Thrombus – is a blood clot (plural: thrombi).

Thromboembolism – is when a blood vessel becomes blocked by a blood clot that has become dislodged from another blood vessel and travelled through the circulationary system.

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Notes:

Notes:

For more information about classical homocystinuria or patient support please visit **www.hcunetworkaustralia.org.au.**
HCU Network Australia is a Health Promotion Charity established in 2014, with the vision "to be a driving force in the journey to a cure, improving quality of life along the way". Our aim is to improve individual outcomes through education, research and support.
If you would like to contact HCU Network Australia, please send us an email at **info@hcunetworkaustralia.org.au**.

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