Dietary Management of Paediatric Urea Cycle Disorders (UCDs) UHL Dietetic Guideline	University Hospitals of Leicester NHS NHS Trust **Clinical Support and Imaging CMG** **Nutrition and Dietetic Service** **C70/2019**

1. Introduction and Who Guideline applies to

These clinical guidelines have been developed to ensure that dietetic advice given to paediatric patients with UCDs and their families is consistent. These conditions are very rare and the management of these patients are based around our current practice and suggested guidelines for the management of urea cycle disorders (Haberle et al 2019).

The guidelines are intended for use by Senior Specialist Dietitians (Paediatric) and Senior Dietitians (Paediatric) within the Nutrition and Dietetic Service, University Hospitals of Leicester NHS Trust. Ideally dietitians using the guidelines should have had relevant clinical training and clinical supervision from the Senior Specialist Dietitian in Inherited Metabolic Disorders. They may be used as a point of reference for other Health Care Professionals involved in the care of patients with UCDs but detailed dietetic advice should only be provided by a Senior Specialist Dietitian or Senior Dietitian.

Urea Cycle disorders (UCD) are a group of Inherited Metabolic Disorders that occur due to a defect in one of the enzymatic reactions of the urea cycle. The urea cycle has two key functions; to convert toxic ammonia from waste nitrogen compounds to form non- toxic urea for excretion by the kidneys and the formation of arginine to form important metabolites such as nitric oxide, creatine and glutamate. Deficiencies of enzymes involved in the reactions of the urea cycle cause a build-up of toxic ammonia which can cause severe encephalopathy and glutamine which can contribute to central nervous toxicity (Shaw et al 2015).

UCDs can present at any age. In the neonatal period, the infant will display poor feeding and often respiratory distress, seizures and collapse. The outlook in the newborn period is poor, particularly if ammonia levels are >1000μmol/l. Symptoms on presentation in older children include loss of appetite, neurological abnormalities and developmental delay.

UCDs are treated using dietary intervention in addition to a group of medicines called nitrogen scavengers such sodium benzoate and either glycerol phenyl butyrate, or sodium phenylbutyrate that encourage excretion of waste nitrogen via alternative pathways. The aims of dietary intervention are to decrease the load on the urea cycle by reducing protein intake, whilst maintaining nutritional adequacy. Prompt management of illness with a Dietary Emergency Regimen is also important to prevent accumulation of ammonia and glutamine through protein catabolism. Emergency information can be accessed via the BIMDG website and used to support the medical teams.
http://www.bimdg.org.uk/site/index.asp

2. Guideline Standards and Procedures

The guidelines will cover the following:

1. Aims of Dietetic Treatment
2. Dietetic Management of newly diagnosed patients
3. Dietetic Management of established patients
4. Management of Illness and Acute Decompensation
5. Resources
6. References

2.1. Aims of Dietetic Treatment

The aims of dietary intervention are to decrease the load on the urea cycle by reducing protein intake, whilst maintaining nutritional adequacy. Prompt management of illness with an Emergency Regimen is also important to prevent accumulation of ammonia and glutamine through protein catabolism.

2.2 Dietetic Management of Newly Diagnosed Patients

Infants

Infants may present in the first few days of life as an in-patient usually with severe hyperammonaemia. Initially protein-containing feeds will be stopped and the infant should be started on a 10% glucose infusion intravenously (IV) until blood ammonia levels are within an acceptable range. The infant may require haemofiltration depending upon the severity of the hyperammonaemia. Once enteral feeds can commence, liaise with the Metabolic Consultant for advice regarding feeding and whether protein can be restarted. The typical procedure is as follows but will be dependent on the clinical picture of the patient and the advice given by the Metabolic Consultant.

1. Start a high energy, protein free feed in order to prevent catabolism
   - This should be given as a continuous nasogastric feed or 2 hourly boluses if tolerated. Energivit (Nutricia Metabolics) is the feed of choice due to it's kcalorie content and the fact that it contains vitamins and minerals.
   - If Energivit is not tolerated, use a 10% glucose polymer solution e.g. polycal (Nutricia Metabolics)
   - Liaise with the Metabolic Consultant and /or the Intensivist regarding fluid allowance. Enteral fluids should be titrated with the IV fluids.
   - If further kcalories are required intravenous lipid can be given up to 3g/kg. Liaise with the paediatric pharmacist for advice.
   - An energy source alone must not be continued for long periods of time as this can lead to catabolism. Following improvement of hyperammonaemia, protein re-introduction should not be delayed beyond 24-48 hours (Haberle et al, 2019)

2. Introduce protein (usually when ammonia levels reach 100µmol/l).
   - Introduce 0.5g protein/kg as expressed breast milk (EBM) or infant formula with added Polycal to make a total carbohydrate content of 10%. The remainder of the of fluid allowance can be be given separately, using Energivit or 10% Polycal/ SOS10.
   - Increase by 0.5g protein/kg daily, or as tolerated, aiming for 1.5- 2.0g protein/kg. Adjust Energivit / Polycal volume accordingly.
   - If ammonia levels increase during protein re-introduction, essential amino acid mixture can be considered to replace some or all of the natural protein. (See the section below).
   - For patients who are struggling to tolerate enteral feeds containing protein an intravenous source of amino acids should be considered by the Specialist Dietitian at the request of the Metabolic Consultant. Vaminolact contains 63.5g of amino acids per 1000ml. (0.6g of amino acids is equivalent to 0.5g of protein), this can be used alongside IV dextrose and lipids. This should only be used short term as it does not contain vitamins and minerals. At the earliest opportunity and for longer term use a bespoke PN bag with **only** the desired amount of protein in the form of amino acids should be used. Liaise with the

paediatric pharmacist via the pharmacy satellite by 9.30 am each weekday that PN is required.

3. Once the infant is metabolically stable, the protein allowance may be further relaxed. This will be dependent upon the results of monitoring bloods (plasma amino acids and ammonia levels) in consultation with the Metabolic Consultant. The nutritional adequacy of long term feeds should always be considered. For composite or modular feeds it is advisable to check the nutrition adequacy using a dietary analysis tool.

Children

The principles of initial dietary treatment are the same as in infants. A protein free, high energy diet should be started upon diagnosis and protein reintroduced to a safe level over 3-4 days once the patient is stable (Shaw et al, 2015). Recommended carbohydrate concentrations in relation to age can be found in the table below. Safe levels of protein intake can be found in the next section.

Age	**CHO concentration required in total feed until metabolically stable**
0-1 year	10%
1-2 years	15%
2-10 years	20%
10 years +	25%

Table 1 Carbohydrate content of initial protein free feed

2.3. DIETETIC MANAGEMENT OF ESTABLISHED PATIENTS

2.3.1 Protein

The low protein diet should provide *at least* the safe levels of protein intakes set by WHO (2007) and outlined in table 2 below:

Age	**Safe level of protein intake sexes combined (g/kg/day)**
1 month	1.77
2 months	1.5
3 months	1.36
4 months	1.24
5 months	1.14
6-12 months	1.14 -1.31
12 months	1.14
2 years	0.97
3 years	0.9
4-6 years	0.87
7-10 years	0.92
11-14 years	0.89
15-18 years	0.84

Table 2 Safe level of protein intake with age

Potein allowance is decided between the Dietitian and Metabolic Consultant and will be adjusted depending on:

- Growth
- Severity of disease
- Medication
- Episodes of Illness/ metabolic decompensation
- Plasma ammonia levels
- Plasma amino acid levels

High biological value (HBV) proteins such as meat, fish and cheese provide a better protein quality as less waste nitrogen is produced but are unlikely to be allowed in large quantities. In practice, a combination of HBV and low biological value protein which provide higher energy content, should contribute to the overall natural protein allowance. More HBV in milder defects should be encouraged as the protein allowance is greater. The daily protein allowance should be divided as equally as possible throughout the day. Patients carers should be educated so that they are able to calculate the protein content of foods using food labels.

For patients with a very restricted natural protein allowance, an essential amino acid supplement may be necessary to achieve the safe level of protein intake (see below).

2.3.2 Essential Amino Acids

Essential Amino Acid (EAA) supplements can provide part of the total protein allowance. The supplement does not contain non-essential amino acids and so decreases the demand on the urea cycle. In theory they promote waste nitrogen to be recycled for synthesis of non-essential amino acids, however this has never been proven clinically (Shaw, 2015).

Essential amino acid supplements may be advocated when

- the natural protein tolerance is too low to achieve optimal growth and metabolic stability
- plasma quantitative essential amino acids are low.

Suitable EAAs include *Essential Amino Acid AA mix* (Nutricia Metabolics), *Dialamine* (Nutricia Metabolics) or *EAA supplement* (Vitaflo). They differ in suitable age range, carbohydrate, vitamin and mineral quantity. The choice of supplement should be considered on an individual basis. The dose prescribed will be decided between the Dietitian and Metabolic Consultant and will depend on the reason for administration.

2.3.3 Energy

It is difficult to achieve adequate energy intakes on a low protein diet. Kcalorie intakes should aim to meet the Estimated Average Requirement (EAR) for the patient's age and gender in order to maintain adequate growth and metabolic control. This may need to be adjusted on an individual basis dependent on the child's activity levels.

Along with the protein allowance, dietary energy can be provided by:

- 'Free Foods', those naturally low in protein, such as sugar, fats, fruit and vegetables.

- Protein free energy supplements, including *Energivit (*Nutricia Metabolics*)*, glucose polymers and fat emulsions.
- Specially manufactured low protein foods e.g. bread, cereals, pasta, which are ACBS approved and available on prescription.

Long fasts should be avoided so a starchy bedtime snack must be encouraged.

2.3.4 Vitamin and Mineral Supplements

The patient may be at risk of vitamin or mineral deficiencies due to poor dietary intake on assessment or poor nutritional biochemical/haematological status. They may also be at risk of essential fatty acid (EFAs) or long-chain polyunsaturated fatty acid (LCPUFAs) deficiencies. Supplementation is decided upon discussion with the Metabolic Consultant. Suitable supplements include comprehensive preparations such as *Paediatric Seravit (*Nutricia Metabolics*)*, *Phlexyvits* (Nutricia Metabolics) (>11 yrs), *Fruitivits (Vitaflo*) (>3 yrs) or single vitamin/mineral/EFA/LCPUFA preparations to correct particular deficiencies noted from dietary assessment or biochemistry.

2.3.5 Individual amino acid supplementation

Arginine, Citrulline or Ornithine supplements are often prescribed depending upon the type of urea cycle disorder in order to reduce the build-up of toxic waste products, but this is dictated and prescribed by the Metabolic Consultant.

2.3.6 Feeding difficulties

Patients with UCD may experience feeding difficulties related to their neurological disease. These should be dealt with according to severity, from thickened fluids for weakened swallow to complete PEG or jejunal feeds in more developmentally-affected patients. Energy and protein requirements should be calculated as stated in previous sections, but these patients may rely more on energy supplements, EAAs and vitamin/mineral supplementation to achieve a nutritionally adequate intake on a restricted protein diet.

2.3.7 Practical Suggestions when managing the Low Protein Diet

Infant Feeding

Breast feeding is possible in some cases, but ammonia levels must be closely monitored and it may be advisable to give a measured amount or protein-free formula prior to a demand breast feed. For formula-fed babies, a measured amount of infant formula (sometimes in combination with essential amino acids) is given followed by demand protein-free formula at each feed. Some, more complex patients may require a modular feed

Weaning

Tolerance to solid foods may differ greatly between patients. Once the patient is ready to be weaned, low protein fruits and vegetables can be offered as per standard weaning practice. Once established, gradually replace breast milk or infant formula with protein-containing solid food by one gram of protein at a time (Haberle 2019). The changeover from milk feeds to solid food can be a difficult time and requires close supervision and monitoring. Additional resources may be required e.g. pictorial guides/ interpreters where

there are language barriers. If the child becomes well established on solid foods, the need for vitamin and mineral supplementation should be considered as this group of patients often have feeding difficulties.

2.3.8 Fasting

There is no published information regarding safe fasting times for patients with urea cycle disorders when well. It is essential that patients are not compromised metabolically. At UHL we advise that patients safe fasting times follow the same duration for patients with Medium chain acyl-CoA dehydrogenase deficiency.

Age	Time in hours
0-4months	6
From 4 months	8
From 8 months	10
From 12 months	12

Table 3 “Safe” fasting times for the well child

Source British Inherited Metabolic Disease Group (BIMDG)

2.4 MANAGEMENT OF ILLNESS AND ACUTE DECOMPENSATION

During periods of illness or poor appetite, it is important to avoid metabolic decompensation where the body starts to break down protein stores causing a build-up of toxic metabolites. The aim is to minimise protein intake temporarily whilst providing enough energy to meet metabolic demands (Haberle 2019). All patients are given a Metabolic Dietary Emergency Regimen (ER), which encourages regular (2-3hrly) drinks/feeds of high energy, protein-free feed. A specialist protein-free formula such as Energivit (*Nutricia Metabolics*) supplemented with a glucose polymer powder e.g. Polycal (*Nutricia*) to the age appropriate concentration of carbohydrate is usually the basis for the drinks/feeds. If this is not tolerated then the glucose polymer alone at the age appropriate concentration should be tried aiming to give a total volume equivalent to their normal fluid requirements. All patients must be given a Metabolic Dietary Emergency Regimen on diagnosis.

If the Dietary Emergency Regimen is not tolerated, or the patient is vomiting or unconscious, they must be taken to hospital straight away for assessment or further treatment. Due to the vulnerable nature of these patients it is imperative that the medical team act immediately and follow the UHL Children’s Hospital Guideline (Metabolic Conditions UHL- Children’s Medical Guideline E3/2020 via Insite) in conjunction with

information from the BIMDG website. The Metabolic Team must be informed immediately. Out of normal working hours the oncall metabolic consultant at Sheffield Children's Hospital or Manchester Children's Hospital should be contacted for advice.

3. Education and Training

Senior Specialist Paediatric Dietitians/ Senior Paediatric Dietitians with appropriate training ideally having undertaken the British Dietetic Association Masters Level Module 4 Dietetic Management of Inherited Metabolic Disorders, Plymouth University.

Ongoing clinical supervision (1:1 and group) should be accessed regularly n.b. contract of employment states x 4 times per rolling 12 months.

4. Monitoring Compliance

What will be measuredto monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Nutritional adequacy of the diet	Monitoring of nutritional bloods.To include quantitative plasma amino acids, albumin, full blood count, plasma zinc, selenium, ferritin, folate, vitamin B12, vitamins A,D& E	Senior Specialist Paediatric Dietitian and Consultant Inherited Metabolic Disease	At least annually	Clinic proforma Medical notes
Growth	Monitoring of weight, height and BMI at eachclinic appointment	Senior Specialist Paediatric Dietitian Inherited Metabolic Disease	Bi-annually	Clinic proforma Medical notes
Metabolic stability	Blood ammoniaPlasma amino acids	Consultant Inherited Metabolic Disease	Bi-annuallyMore frequently in unstable Patients	Medical notes

5. Supporting References

Haberle et al (2019) Suggested Guidelines for the Diagnosis and Management of Urea Cycle Disorders Journal of Rare Diseases First Review

https://doi.org/10.1002/jimd.12100 last accessed July 2022

Shaw, V and Lawson, M. (Eds) (2015) Disorders of amino acid metabolism, Organic acidaemias and Urea Cycle Disorders Clinical Paediatric Dietetics 5th edition. Blackwell Publishing 587-594.

WHO (2007) Protein and amino acid requirements in human nutrition. *Report of a joint WHO/FAO/UNU Expert Consultation.*

Useful further reading

Clinical Paediatric Dietetics 5th Ed. Edited by Vanessa Shaw Chapter 28

Metabolic Support UK www.metabolicsupportuk.org

Inborn Metabolic Diseases Diagnosis and Treatment 5th Ed. Edited by J. Saudubray, G. van den Berghe and J. Walter

6. Key Words

Urea cycle disorders, UCD, ammonia,

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Moira French Senior Specialist Paediatric Dietitian	**Executive Lead** Chief Nurse
Details of Changes made during review: Paediatric added to the title Paragraph 3 additional information re purpose of the urea cycle added Referred to the Suggested guidelines for the diagnosis and management of urea cycle disorders: First Updated reference to medical management from Insite Minor grammatical changes	

APPENDIX 1

Higher kcalorie Emergency Regimen for patients with Urea Cycle Disorders

Age	Percentage Carbohydrate	Recipe	Volume
0-6months	10%	3 scoops of Energivit made up to 100ml with cooled boiled water	Aim150-200ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 75ml every 2 hours or 115ml every 3 hours
6-12months			Aim 120-150ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 85ml every 2 hours or 125ml every 3 hours
12-18 months	15%	3 scoops of Energivit plus 1 scoops of polycal made up to 100ml with water	Aim 100ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 85ml every 2 hours or 125ml every 3 hours
18-24 months			Aim 100ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 100ml every 2 hours or 150ml every 3 hours
2-6 years	20%	3 scoops of Energivit plus 2 scoops of polycal made up to 100ml with water	Aim 1200-1600ml in 24 hours; offer 100 – 130ml every 2 hours or 150 – 200ml every 3 hours
7-9years			Aim 1500-1800ml in 24 hours; offer 135-150ml every 2 hours or 210- 220ml every 3 hours
10 and 11 years	25%	3 scoops of Energivit plus 3 scoops of polycal made up to 100ml with water	Aim 1900ml in 24 hours; offer 160ml every 2 hours or 240ml every 3 hours
12 and 13 years			Aim 2000ml in 24 hours; offer 170ml every 2 hours or 250ml every 3 hours
14 and 15 years			Aim 2250ml in 24 hours; offer 190ml every 2 hours or 280ml every 3 hours
>16 years			Aim 2500ml in 24 hours; offer 210ml every 2 hours or 310ml every 3 hours

Use the scoops provided in the products.
Energivit scoop = 5g Energivit
Polycal scoop = 5g Polycal

APPENDIX 2

Standard Emergency Regimen consisting of glucose polymer only

Age	Concentration of glucose polymer	Recipe	Volume
0-6months	10%	4 scoops of polycal or 1 sachet of S.O.S 10 made up to 200ml with cool boiled water	Aim150-200ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 75ml every 2 hours or 115ml every 3 hours
6-12months			Aim 120-150ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 85ml every 2 hours or 125ml every 3 hours
12-18 months	15%	6 scoops of polycal or 1 sachet of S.O.S 15 made up to 200ml with water	Aim 100ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 85ml every 2 hours or 125ml every 3 hours
18-24 months			Aim 100ml/kg in 24 hours split into 8 feeds 3 hourly or 12 feeds 2 hourly Average amount 100ml every 2 hours or 150ml every 3 hours
2-6 years	20%	8 scoops of polycal or 1 sachet of S.O.S 20 made up to 200ml with water	Aim 1200-1600ml in 24 hours; offer 100 – 130ml every 2 hours or 150 – 200ml every 3 hours
7-9years			Aim 1500-1800ml in 24 hours; offer 135-150ml every 2 hours or 210-220ml every 3 hours
10 and 11 years	25%	10 scoops of polycal or 1 sachet of S.O.S 25 made up to 200ml with water	Aim 1900ml in 24 hours; offer 160ml every 2 hours or 240ml every 3 hours
12 and 13 years			Aim 2000ml in 24 hours; offer 170ml every 2 hours or 250ml every 3 hours
14 and 15 years			Aim 2250ml in 24 hours; offer 190ml every 2 hours or 280ml every 3 hours
>16 years			Aim 2500ml in 24 hours; offe every 2 hours or 310ml ever

Use the scoops provided in the product.
Polycal scoop = 5g Polycal