Clinical Guideline for the Dietary Management of Paediatric 3-hydroxy-3-methylglutaryl CoA lyase Deficiency (HMG-CoA lyase deficiency) Clinical Support and Imaging CMG Nutrition and Dietetic Service	University Hospitals of Leicester NHS NHS Trust **Trust Reference Number C31/2016**

1. Introduction and Who Guideline applies to

These guidelines have been developed to ensure that dietetic advice given to patients with HMG-CoA lyase deficiency and their families is consistent and follows current scientific evidence and consensus.

These clinical guidelines are intended for use by Senior Specialist Paediatric Dietitians and Senior Paediatric Dietitians 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.

HMG-CoA lyase deficiency is a rare autosomal recessive disorder of the biosynthesis of ketones (ketogenesis). Ketones are an important fuel source, which can be used by all tissues and more importantly by the brain during periods of prolonged fasting. Around 30% of patients with this disorder will present by day 5 of life after a short initial symptom free period. Most other patients present in the first year of life after an infection or when fasted. A few patients remain asymptomatic for a number of years and very occasionally patients will present in adulthood (Morris 2012).

Typical features at presentation include vomiting, hypotonia, lethargy, hyperammonaemia, metabolic acidosis and hypoglycaemia and in some cases encephalopathy, which is associated with high mortality. With appropriate treatment most patients will recover from their metabolic decompensation. Unfortunately, a number suffer neurological sequelae including epilepsy, intellectual handicap, hemiplegia, particularly after neonatal hypoglycaemia.

Diagnosis is made by measuring plasma acylcarnitines (increased C5OH and C6DC acylcarnitine) and urinary organic acid profile (high level of 3-hydroxy-3-methylglutaric acid, 3-hydroxy-isovaleric acid, 3-methylglutaconic acid and 3-methyglutaric acid).

2. Guideline Standards and Procedures

HMG-CoA lyase deficiency occurs when an enzyme, called “HMG CoA lyase”, is either missing or not working properly. This enzyme has two roles. The first is to help break down leucine, a branched chain amino acid. The second is to help the body to make ketones from stored fat. There is very little published information on the dietary management of this disorder. Prolonged fasts should be avoided and the provision of adequate energy is important. There are no published guidelines on safe fasting times in this disorder, however in general the same fasting times recommended for Medium Chain Acyl CoA Dehdrogenase Deficiency (MCADD) are advised (Table 1).

Table 1 Recommended “Safe” fasting times for the well child

Age	Time in hours
Positive screening to 4 months	6
From 4 months	8
From 8 months	10
From 12 months	12

Source British Inherited Metabolic Disease Group (BIMDG)

1.1 Diet when well

In UHL patients are treated with a high carbohydrate, moderate protein restriction (to limit leucine) usually around 1-2g/kg per day (Thompson, Chalmers and Halliday 1990) ensuring that the safe level of protein intake for age is met to provide adequate protein for growth (Appendix 1) and with a fat restriction of 20-25% of energy.

Infants and children should have regular feeds / meals, with infants having feeds during the night to ensure that they do not go beyond the safe fasting time (Table1). A starch containing bedtime snack and breakfast are essential meals to minimise the duration of the overnight fast in toddlers and children. Missed meals should be replaced by a suitable snack or milky drink and if this is refused, be replaced with a sugary or glucose polymer-based drink, the appropriate amount and concentration is dependent on age (see Emergency Regimen, Appendix 2).

Infants will require manipulation of their feeds to ensure that they do not have too much fat and protein in their diet (see Appendix 3 for an example of a modified feed). Weaning takes place at normal age (minimum 17 weeks for term infants or 17 weeks corrected for a preterm) onto a diet of free fruit and vegetables alongside their modified milk recipe. At the next stage of weaning parents and carers will be taught to use an exchange system for fat and protein containing foods (Appendix 4). The diet can be supplemented with prescription low protein products to add bulk to the diet.

Parents and carers will be given an individualised plan for their child which is reviewed regularly in line with growth, it is therefore very important that regular contact is maintained with the family to ensure that the child is growing well and to try to overcome any difficulties quickly. Over time parents and carers will be taught to read labels and encouraged to plan meals to allow them greater flexibility.

As the child gets older the diet becomes less restrictive due to the larger quantities of protein and fat that can be consumed. The list of exchanges will also become more extensive. In those children who take part in prolonged sporting activities it is prudent to give a starchy carbohydrate snack before and after exercise.

1.2 Diet during illness

During illness, or if the child has a reduced appetite, the standard Emergency Regimen (ER) appropriate for age should be given without delay. This consists of a regimen of very frequent feeds, day and night, of a specific concentration and volume of glucose polymer dependent on age (Appendix 2). This helps to minimise lipolysis and endogenous protein catabolism in particular the ketogenic amino acid leucine, which can lead to the production of toxic metabolites. Provision of glucose will also help to prevent hypoglycaemia. Blood glucose monitoring is not recommended as a marker of metabolic status since hypoglycaemia is a relatively late finding and treatment should be initiated before this develops. Parents are given detailed information as to how to make up and

administer the feeds (Appendix 3). The ER should be used for up to a maximum of 48 hours at home. As the child improves, the normal

diet can be resumed but extra ER drinks should be given, particularly during the night, until the child is fully recovered and eating well.

If the ER is not tolerated i.e. the child will not take the ER or vomits on two successive occasions then the child should be taken to the Children's Emergency Department at Leicester Royal Infirmary so that either a nasogastric tube can be placed to administer the ER if refused, or if the child is vomiting a 0.45% saline 10% glucose with additives can be started immediately by the medical team.

Patients are advised to bring their oral ER and any written information to hospital with them to avoid any delays. Medical staff should follow the guidelines that can be accessed from the BIMDG website www.bimdg.org.uk.

If for any reason a child needs to be started on a specialist feed during the recovery phase it should not contain medium chain triglyceride (MCT) as this may be of potential harm due to its ability to be converted rapidly to ketones once it is absorbed (Dixon et al 2015).

1.3 Levocarnitine (L-carnitine)

L-carnitine supplementation is prescribed to facilitate the removal of potential toxic metabolites and to prevent secondary carnitine deficiency. It should be used under medical supervision, see British National Formulary (BNF) for children for dosing advice (Levocarnitine).

1.4 Vitamin and mineral supplementation

This necessary due to the dietary protein and fat restrictions. Paediatric seravit can be used in infancy and with older children and can be added to any feeds or drinks.

1.5 Monitoring

- Weight and height should be measured at each clinic visit and fortnightly by the health visitor in infants.
- A diet history should be taken to establish with compliance and understanding of the diet at each visit and a food diary should be requested at least once a year.
- Fasting times and current ER should be checked at each clinic visit
- Serum monitoring should take place at least annually in clinic but more frequently if there are concerns
    - Acyl carnitine profile
    - Serum amino acids
    - Vitamin and mineral status including Vitamins A & D, B_{12} folate, zinc, calcium, copper, iron and selenium
    - LFTs
    - Bone
    - U&Es
    - FBC

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. Dietitians should also ensure that they meet the Health and Care Professional Council (HCPC) standards for continuing professional development (CPD).

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Monitoring of weight, height and BMI* * above 2 years	Recorded on clinic proforma. Growth chart completed for each clinic appointment	Senior Specialist Paediatric Dietitian	Each clinic appointment	Clinic notes
Nutritional bloods reviewed at least annually or more frequently if concerns. To include quantitative plasma amino acids, albumin, full blood count, plasma zinc, copper, selenium, ferritin, folate, vitamin B12, vitamin D	Recorded on proforma	Senior Specialist Paediatric Dietitian	At least annually	Clinical notes and discussion at MDT
Appropriate Emergency Regimen for age	Recorded on clinic proforma at each clinic appointment.	Senior Specialist Paediatric Dietitian	At appropriate ages <12months, 1 yr, 2 yrs, 10 yrs	Clinic notes
Knowledge of correct ER and fasting time	Patient and or parent asked and recorded on clinic sheet	Senior Specialist Paediatric Dietitian	Each clinic appointment	Clinic notes

5. Supporting References

Dixon M, Stafford J, White F, Clayton N and Gallagher J (2015) 'Disorders of Mitochondrial Energy Metabolism, Lipid Metabolism and Other Disorders', in Shaw (ed.) Clinical Paediatric Dietetics 4th Edition, London, Wiley Blackwell

Morris AAM (2012) 'Disorders of ketogenesis and ketolysis' in Saudubray, van den Berghe and Walter (eds.) Inborn Metabolic Diseases Diagnosis and Treatment 5th Edition, Berlin, Springer- Verlag

Thompson GN, Chalmers RA, Halliday D. The contribution of protein metabolism to metabolic decompensation in 3-hydroxy-3-methylglutaric aciduria. *Eur J Pediatr.* 1990;149:346-350

Useful websites

British Inherited Metabolic Disease Group http://www.bimdg.org.uk The Screening, Technology And Research in Genetics (STAR-G)

www.newbornscreening.info/Parents/organicaciddisorders/HMGCoA.html#1

British National Formulary for Children https://bnf.nice.org.uk/guidance/prescribing-in-children.html

Useful reading

Shaw (ed) 2015 Clinical Paediatric Dietetics 4th Edition, London, Wiley Blackwell Chapter 17 and 19

6. Key Words

List of words, phrases that may be used by staff searching for the Guidelines on PAGL. If none – state none.

Emergency Regimen, 3-hydroxy-3-methylglutaryl CoA lyase deficiency, HMG-CoA lyase deficiency, ketogenesis, HMG

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Moira French Senior Specialist Paediatric Dietitian	**Executive Lead**
Details of Changes made during review: Addition of preterm can wean 17 weeks corrected at the earliest Updated Emergency Regimens added.	

Safe level of Protein Intake for Infants, Children and Adolescents

Age	Safe level (g protein/kg/day)
For infants<6 months of age (months)	
1	1.77
2	1.5
3	1.36
4	1.24
6	1.14
For weaned infants (sexes combined) (years)	
0.5	1.31
1	1.14
1.5	1.03
2	0.97
3	0.9
4	0.86
5	0.85
6	0.89
7	0.91
8-9	0.92
10	0.91
Girls	
11	0.9
12	0.89
13	0.88
14	0.87
15	0.85
16	0.84
17	0.83
18	0.82
Boys	
11	0.91
12-13	0.90
14	0.89
15	0.88
16	0.87
17	0.86
18	0.85

Source Clinical Paediatric Dietetics Chapter 17 Shaw (Ed) 4th Edition

Emergency Regimen Appropriate to Age

Age	Concentration of glucose polymer	Volume
0-6months	10%	Aim 150-200ml/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%	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%	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%	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

Example of a Modular Feed Calculation

6kg infant EAR 120kcal/kg feeding Cow and Gate (C&G) first prior to diagnosis

Aim 720kcal/day 2g protein/kg/day= 48kcal 25% energy as fat = 180kcal = 20g

C&G first (liquid)= 66kcal; 3.4g fat; 1.3g protein; 7.4g CHO per 100ml

Fat from feed 20 ÷3.3 = ~6 Therefore use 600ml of C&G (liquid)

	kcal	Protein (g)	Fat (g)	CHO (g)
600ml C&G1	396	7.8	20.4	44.4
5g Protifar (2 scoops)	18.4	4.4	-	-
5g Paediatric seravit	13.4	-	-	6.7
75g Polycal (15 scoops)	285	-	-	72
Totals	712.8	12.2	20.4	123.1
%		6.8	25.7	65.6

Provides 150ml/kg of fluid.

Aim 12g protein

Sp need (12-7.8)g = 4.2g

Protifar 2.5g scoop =2.2g protein

Therefore 2 x 2.5 = 4.4g protein

Additional vitamins required – use 5g scoop paediatric seravit

13.4kcal and 6.7g CHO

Need additional CHO to make up the kcalories (720-(396+18.4+13.4))= 292kcal

Each 5g Polycal scoop is 19kcal therefore 292-19 = 15.3 ~ 15 scoops of Polycal or 75g Each component rounded for ease of measurement.

Add cooled boiled water to make up to a total volume of 900ml. Divide between 6 or 8 feeds and refrigerate.

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EMERGENCY REGIMEN (ILLNESS PLAN) FOR CHILDREN – FACT SHEET
Give with the appropriate age information

What is the Emergency Regimen (ER) (Illness Plan)?
This is a special plan whereby drinks that are high in sugar (glucose polymers) are given regularly during the day and night when your child is unwell and unable to eat properly. The purpose of giving these drinks is to keep your child safe by providing them with energy to help prevent them from breaking down their fat stores. Glucose polymers, e.g. Polycal, Maxijul, Vitajoule and S.O.S are available on prescription from your GP.

When should I give the Emergency Regimen (Illness Plan)?
Anytime your child is not eating well, e.g. during illness.

Step1: If you are unsure if your child is unwell, continue with normal medicines, give the sugary drink and continue to review.
Step 2: If your child is definitely unwell, start the full illness plan of frequent sugary drinks. If your child wants to eat this is fine – try to give them starchy foods such as pasta, potatoes or cereal.
Step 3: If you child is not getting better, not tolerating or refusing to take the sugary drinks you should bring your child to the Children's Emergency Department.

If you go to hospital take your information pack, glucose polymer and scoops if you have them.

Vomiting - Use this rule to assess when to start the emergency regimen:

1 vomit - Start the full Emergency Regimen and monitor (you may find that your child is able to take the 2 or 3 hourly amount as small frequent sips). If your child is able to eat a little but not the usual amount then continue to top with regular sugary drinks.
2 vomits - Continue the Emergency Regimen and bring your child to the Children's Emergency Department immediately.
Your child will need IV glucose if they are unable to tolerate their Emergency Regimen orally or by a nasogastric tube.

How do I give the sugary drinks?
Give glucose polymer drinks every 2 or 3 hours, both **day and night**. If you child is vomiting give the drinks volume needed over the 2-3 hours as small frequent sips.

When can I stop giving the sugary drinks?
When your child starts eating again you can give less sugary drinks but continue some night drinks. The drinks can be stopped once your child is eating normally again. Try to do this within 48 hours or starting the sugary drinks.

Diarrhoea

If your child is feeding normally then do not worry but make sure you give him/her plenty of fluids. You may need to use an oral rehydration solution such as dioralyte particularly if they have profuse diarrhoea.

If you are using the Emergency regimen then add the sachet of dioralyte to the glucose polymer before making up (see the recipes overleaf).

Should I contact the Hospital doctor if my child is on the Emergency Regimen (Illness Plan)?

If you are concerned and want advice then please telephone a member of the Metabolic Team during normal working hours. You should contact the Metabolic Team if you feel that your child may need their Emergency Regimen for more than 48 hours because they are not eating.

Glucose Polymer recipes for children age under 1 year (10% carbohydrate)

20g or 4 scoops* of Polycal (glucose polymer)
Make up to 200ml with cooled boiled water

*always use level unpacked scoops

OR 1 S.O.S 10 sachet (Vitaflo) made up to 200ml with cooled boiled water

How to give the drinks

Age	Carbohydrate solution	Polycal + Water Dilution	S.O.S10	Daily Volume
0-3 months	10%	2 scoops up to 100ml	1 sachet made up to 200ml	60mls every 2 hours or 90mls every 3 hours **Aim for 700-750 in 24 hours**
3-6 months	10%	2 scoops up to 100ml		75ml every 2 hours or 115ml every 3 hours **Aim 800 – 1000ml in 24 hours**
1 year	10%	2 scoops up to 100ml		85ml every 2 hours or 125ml every 3 hours **Aim 1000 – 1100ml in 24 hours**

Dioralyte (oral rehydration solution) recipe

1 sachet of Dioralyte
Add 20g **or** 4 scoops* of Polycal **or** one sachet of S.O.S 10
Make up to 200ml with cooled boiled water

Fluid volume as in the table.

*always use level unpacked scoops

Please show this information to any Doctor who has to see your child.

For further information contact the Metabolic Team:

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Childrens Emergency Department
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Glucose Polymer recipes for children age over 2 years (20% carbohydrate)

40g or 8 scoops* of Polycal (glucose polymer)
Make up to 200ml with water

*always use level unpacked scoops

OR 1 S.O.S 20 sachet (Vitaflo) made up to 200ml with water

How to give the drinks

Age	Carbohydrate solution	Polycal + Water Dilution	S.O.S 20	Daily Volume
2 years	20%	4 scoops up to 100ml	1 sachet made up to 200ml	100ml every 2 hours or 150ml every 3 hours **Aim 1200ml in 24 hours**
3 and 4 years	20%	4 scoops up to 100ml		110ml every 2 hours or 170ml every 3 hours **Aim 1300-1400ml in 24 hours**
5 and 6 years	20%	4 scoops up to 100ml		125ml every 2 hours or 190ml every 3 hours **Aim 1500ml in 24 hours**
7 and 8 years	20%	4 scoops up to 100ml		140ml every 2 hours or 210ml every 3 hours **Aim 1700ml in 24 hours**
9 years	20%	4 scoops up to 100ml		150ml every 2 hours or 220ml every 3 hours **Aim 1800ml in 24 hours**

Your child may tolerate the 2 or 3 hourly volume given as small frequent sips rather than the full volume given in one go.

Dioralyte (oral rehydration solution) recipe

1 sachet of Dioralyte
Add 40g **or** 8 scoops* of Polycal **or** one sachet of S.O.S 20
Make up to 200ml with water

The daily fluid volume is the same as in the table.

*always use level unpacked scoops

Please show this information to any Doctor who has to see your child.

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Glucose Polymer recipes for children age over 10 years (25% carbohydrate)

50g or 10 scoops* of Polycal (glucose polymer)

made up to 200ml with water.

*always use level unpacked scoops

OR 1 S.O.S 25 sachet (Vitaflo) made up to 200ml with water

How to give the drinks

Age	Carbohydrate solution	Polycal + Water Dilution	S.O.S 25	Daily Volume
10 and 11 years	25%	5 scoops up to 100ml	1 sachet made up to 200ml	160ml every 2 hours or 240ml every 3 hours **Aim 1900ml in 24 hours**
12 and 13 years	25%	5 scoops up to 100ml		170ml every 2 hours or 250ml every 3 hours **Aim 2000ml in 24 hours**
14 and 15 years	25%	5 scoops up to 100ml		200ml every 2 hours or 300ml every 3 hours **Aim 2400ml in 24 hours**
16 and 17 years	25%	5 scoops up to 100ml		210ml every 2 hours or 310ml every 3 hours **Aim 2500ml in 24 hours**

Dioralyte (oral rehydration solution) recipe

1 sachet of Dioralyte

Add 50g **or** 10 scoops* of Polycal **or** one sachet of S.O.S 25
Make up to 200ml with water

The daily fluid volume is the same as in the table.

Please show this information to any Doctor who has to see yourchild

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