

ONLINE APPENDIX: DIET PRESCRIPTION

The diet recommendations below are intended as a starting point only. A physician and dietitian familiar with the dietary management of inborn errors of protein metabolism should be central in the implementation and monitoring. Determination of actual nutrient needs, including protein, lysine, calories, and micronutrients, must be individually ascertained via careful monitoring of growth and pertinent laboratory values, particularly plasma lysine.

Initiation of the lysine-restricted diet:

1. Provide explanation to patient, parents and caregivers regarding the goal of the diet and its general principles.
2. Assess patient nutritional status and growth parameters.
3. Perform baseline blood work according to Table 1 in the monitoring protocol.
4. Assess the patient's current lysine intake using resources listed below.
5. Determine lysine prescription based on patient age (according to Table A).

Age (yr)	Lysine^{b,c} (mg/kg)	Protein^{d,e} (g/kg)	Energy (kcal/kg)
0.0 < 0.5	70-100	2.75-3.50	125-145
1.0 < 1.0	55-70	2.50-3.25	140-115
			kcal/day
1 < 4	50-80	1.80-2.60	900-1800
4 < 7	40-70	1.60-2.00	1300-2300
7 < 11	35-65	1.55-1.85	1600-2800
Female			
11<15	35-40	1.50-1.80	1500-2800
15 < 19	33-40	1.45-1.75	1200-2800
> 19	30-40	1.45-1.75	1400-2400
Male			
11 < 15	35-40	1.45-1.75	2000-3200
15 < 19	33-45	1.45-1.75	2100-3200
> 19	30-40	1.45-.175	2000-3000

- a- These guidelines are based on the guidelines published for GA-I by Kölker et al (2011) and Yanicelli et al (2010), and adapted for PDE by the Consortium based on experience.
- b- The lysine/protein ratio varies considerably in natural food: thus natural protein intake in children on a low lysine diet is dependent on the natural protein source. The natural protein intake is relatively high the predominant sources of natural protein have a low lysine content.
- c- The continued chronic damage model in PDE requires as low as reasonably possible -chronic lysine levels. This contrasts with GA1, where currently the focus is on preventing damage

during acute episodes. In some cases, this translates into lower intakes in PDE than currently recommended in GA1.

- d- Tryptophan restriction is not needed in the management of PDE, in contrast to GA-I. Lysine free-amino acid formulas developed for managing GA-I are often low in tryptophan. The individual’s diet should be assessed for tryptophan adequacy and, if inadequate, should be supplemented.
- e- Lysine-free amino acid mixtures should be supplemented with minerals and micronutrients necessary to maintain normal levels. Adequate intake of essential amino acids is provided by natural protein and lysine-free amino acid supplements. The amount of amino acid supplementation is adjusted to meet 130% of the patient’s age-appropriate DRI (Table C).

Table B: Converting grams of protein to milligrams lysine (Values in table calculated using the USDA Database 2013; http://ndb.nal.usda.gov/)		
Food	%lysine	mg lysine/g protein
Fish	9%	90 mg
Meat	8%	80 mg
Milk	7%	70 mg
Eggs	6%	60 mg
Potatoes	6%	60 mg
Soy	6%	60 mg
Nuts	8.5%	85 mg
Vegetables	5%	50 mg
Fruits	4%	40 mg
Cereals/Baked goods with egg or milk	5%	50 mg
Bread, Pasta without egg/milk	3%	30 mg
Rice, Barley, Oats	4%	40 mg

Table B shows that the lysine content per gram of protein varies widely depending on the source of protein, i.e., from 2 – 4% lysine/gram protein in cereals to 9% lysine/gram protein in fish. Nutrition databases are available that provide (an estimate of) lysine contents of many foods. If the lysine content of a specific food cannot be found in a database, the estimated percentage lysine for that food group can be used. Alternatively, an average estimate of 40 mg lysine/gram of protein can be substituted as it is unlikely that high lysine content protein sources will be used

6. Ensure adequate protein intake.

Dietary Reference Intakes (DRIs) for protein are a starting point to determine total protein needs but must be individually assessed for adequacy.

Table C: Dietary Reference Intake for Protein (Table adapted from the DRI Report: Dietary Reference Intakes for Energy & Macronutrients (2002). (www.nap.edu)	
Age	RDA (g/kg/day)
Infants	
0-6 mo	1.52
7-12 mo	1.2
Children	
1-3 yrs	1.05
4-8 yrs	0.95
Males	
9-13 yrs	0.95
14-18 yrs	0.85
19-30 yrs	0.8
31-50 yrs	0.8
50-70 yrs	0.8
> 70 yrs	0.8
Females	
9-13 yrs	0.95
14-18 yrs	0.85
19-30 yrs	0.8
31-50 yrs	0.8
50-70 yrs	0.8
> 70 yrs	0.8
Pregnancy & Lactation	
< 18 yrs	1.3
19-30 yrs	1.3
31-50 yrs	1.3

The daily lysine prescription determines the amount of natural protein that is allowed in the patient's diet. Lysine-free amino acid formulas should be used to provide additional protein intake to meet individual total protein needs. Examples of commercially available lysine-free formulas developed for the use in GA-1 are: Glutarex-1, Glutarex -2 (Abbott Labs); GA-Gel, GA Express15 (VitaFlo, N.A.); XLys, Xtrp Analog; XLys; Xryp Maxamaid; Xlys; Xtryp Maxamum; Glutarade Junior; Glutarade GA1 amino acid blend N.A.); GA (Mead Johnson); and Lys1, Lys 2 prima (Milupa, Germany). These formulas are designed to meet the specific needs of different age groups. It is essential to use the age-appropriate formula.

For patients who require an amino acid based formula for the majority of the protein intake, it is generally recommended to aim for 130 – 135% of DRI for total protein intake.

A source of high-biological value protein can be incorporated into the diet by using part of the lysine allowance as cow's milk, particularly for the younger patient. Cow's milk may be added to the lysine-free formula or given separately, depending on the formula chosen and patient preferences.

During the first year of life, mothers should be encouraged to breastfeed. Nutritional values in human breast milk vary; on average the lysine content is 68-86 mg lysine per 100 ml (www.bls.nvs2.de; <http://www.ars.usda.gov/nutrientdata>). Therefore, only a moderate restriction will be necessary in a breastfed infant. In analogy to the management of PKU,³ this can be achieved by prescribing a defined amount of lysine free formula administered before breastfeeding. In contrast, infant formula may contain significantly higher amounts of lysine.

Regular monitoring of growth, pre-albumin, albumin, and plasma amino acids will help determine individual protein needs compared to the daily age-appropriate DRIs for protein.

7. Ensure adequate tryptophan intake.

Tryptophan restriction is not needed in the management of PDE, in contrast to GA-I. Lysine free-amino acid formulas developed for managing GA-I are often low in tryptophan. The individual's diet should be assessed for tryptophan adequacy and if inadequate, should be supplemented.

Age	Tryptophan (mg/kg/day)
0-5 years	9.5
1-2 years	6.4
3-10 years	4.8
11-14 years	4.8
15-18 years	4.5
>18 years	4.0

Age	Tryptophan (mg/kg/day)
1 month	29
2 months	21
3	19
4 months	17
6 months	16

8. Monitor adjusted diet for adequacy of vitamins, minerals, essential fatty acids and calories.

Careful assessment of the individual diet is required. Lysine-free amino acid formulas are often supplemented with vitamins and minerals and may provide adequate or significant intakes of these nutrients. Where amino acid formulas are not used, vitamin and mineral supplement preparations can be added. A diet analysis tool such as MetabolicPro® <https://metabolicpro.org/> is useful.

9. On-going monitoring of nutritional status of an individual on a lysine-restricted diet should include:

- monitoring of growth (weight, length or height, weight for length, BMI, head circumference)
- frequent monitoring of plasma lysine
- monitoring of other nutrition labs: see protocol
- assessment of food records for compliance

10. Useful resources

Nutrient Databases:

Canadian Nutrient File: www.hc-sc.gc.ca/fn-an/nutrition/fiche-nutri-data/index-eng.php

USDA Data Base: http://www.ars.usda.gov/main/site_main.htm?modecode=12-35-45-00

Bundeslebensmittelschlüssel II3: www.bls.nvs2.de

Taiwan: <http://consumer.fda.gov.tw/Food/TFND.aspx?nodeID=178>

Ross Nutrition Protocol 2001– Lysine content of foods, pp 179 - 191

Low Protein Food List for PKU, Virginia E. Schuett, 2010

PKU News <http://www.pkunews.org/diet/BabyFoodsList.htm>

Germany: Glutaric aciduria type I guideline http://www.awmf.org/uploads/tx_szleitlinien/027-018I_S3_Glutarazidurie_Typ_I_2011-05_01.pdf

Diet Analysis Tools

MetabolicPro: http://www.gmdi.org/index.php?option=com_tienda&view=products&filter_category=5:metabolicpro&Itemid=8

Sources of low protein foods

Cambrooke Foods: www.cambrookefoods.com

Dietary Specialties: www.dietspec.com

Ener-G-Foods: www.ener-g.com

Glutino Foods: www.glutino.com

LoProfin Products: www.shsna.com

Med Diet: www.med-diet.com

Pane Riso Foods: www.canbrands.ca

PKU Perspectives: www.pluperspectives.com

Special Products Distribution Center: www.bcchildrens.ca/spdc

Specialty Food Shop: www.specialtyfoodshop.com

Taste Connections: www.tasteconnections.com

iv) Websites for low protein recipes and support groups

www.cambrookefoods.com

www.depts.washington.edu/pku

www.cookforlove.org

References

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National Research Council (1989) **Recommended Dietary Allowances.** 10th ed., Washington D.C.: National Academy Press.

Kölker S, Christensen E, Leonard JV et al (2011) **Diagnosis and management of glutaric aciduria type I--revised recommendations.** J Inherit Metab Dis **34**:677-694.

Yanicelli S (2010) **Nutrition management of patients with inherited disorders of organic acid metabolism.** In: P. B. Acosta (Ed). Nutrition management of patients with inherited metabolic disorders. Boston: Jones and Bartlett publishers, 314