At a Glance
Urea Cycle Disorders (UCD)

Deficient enzyme: NAGS- N-acetylglutamate synthetase
CPS1- Carbamoyl phosphate synthetase
OTC- Ornithine transcarbamylase
ASS- Argininosuccinic acid synthetase (citrullinemia)
ASL- Argininosuccinic acid lyase (also referred to as ASA-argininosuccinic aciduria)
ARG1 - Arginase (argininemia)
Deficient transporter: Citrin (*note: nutrition treatment is very different and not covered here*)
ORT1 – Ornithine translocase (HHH Syndrome)

Toxic Metabolites: Ammonia
Argininosuccinic acid- in ASL deficiency
Arginine- in arginase deficiency
Mode of Diagnosis: clinical presentation, family history, newborn screening (for ASS, ASL, ARG1, HHH Syndrome)

Clinical presentation in untreated patients: hyperammonemia caused neurotoxicity, poor feeding, growth failure, vomiting, seizures, lethargy, liver dysfunction, coma, death; late identified adolescents/adults- chronic neurological symptoms and dietary history of self-restricting dietary protein

Treatment: prevent catabolism, limit intact protein and provide essential amino acid medical food, supplement citrulline or arginine (except in arginase deficiency), provide nitrogen scavenging medications; degree of treatment varies based on residual enzyme activity/clinical presentation

Goal Treatment Range*: Ammonia- normal (<35 µmol/L; <60 mcg/dL)
Plasma glutamine- <900 µmol/L
Plasma essential amino acids- maintain all within normal range
Plasma arginine (in ARG1)- <300 µmol/L
Plasma arginine (all other UCD)- 70 – 120 µmol/L[2]

Nutrient Needs by Age[1]

Age	Intact Protein g/kg/d	Essential Amino Acid (medical food; g/kg/d)	Total Protein g/kg/d
0-1 yr	0.8-1.1	0.4-1.1	1.2-2.2
1-7 yr	0.7-0.8	0.3-0.7	1.0-1.2
7-19 yr	0.3-1.0	0.4-0.7	0.8-1.4
>19 yr	0.6-0.7	0.2-0.5	0.8-1.0

Starting a Diet

1. Determine goals for total protein (g) and percentage to be provided by intact protein vs essential amino acids (medical food). Consider 30-50% from essential amino acids for initial diet.
2. Calculate amount of intact protein source (breast milk, infant formula, food) and amount of medical food required to meet total protein (g) goal.
3. Calculate energy (kcals) provided by intact protein and medical food sources to ensure DRI for energy needs are met. Consider addition of protein-free calorie modular as needed to meet energy needs.
4. Consider use of enteral nutrition support in this population as anorexia is a common complication.
5. Patients with severe forms of UCD may require placement of a gastrostomy tube.

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Medical Food Therapy

	Abbott abbottnutrition.com	Mead Johnson hcp.meadjohnson.com	Nutricia NutriciaMetabolics.com	Vitaflo www.VitafloUSA.com
Infant (0-1 yr)	Cyclinex®-1	WND 1		
Toddler & Young Children	Cyclinex-1® Cyclinex-2	WND 1 WND 2	UCD Anamix® Junior Essential Amino Acid Mix	UCD trio™ EAA supplement™
Older Children & Adults	Cyclinex-2	WND 2	UCD Anamix Junior Essential Amino Acid Mix	UCD trio EAA supplement
Protein Free Modular	Pro-Phree®	PFD Toddler PFD 2	Duocal® Polycal™	S.O.S™ 25

Supplementation [1]

L-Citrulline (OTC and CPS-1 deficiency): 100-200 mg/kg/d

L-Arginine (ASS and ASL deficiency): 100-300 mg/kg/d (100 mg/kg/d may be sufficient in ASL deficiency)

Medical Therapy [1]

Nitrogen scavenging medications – use alternative pathways to remove nitrogen to prevent hyperammonemia while allowing for greater protein tolerance. Monitor branched chain amino acids.

Sodium Benzoate- binds with glycine to form hippurate, removes one nitrogen atom, then is excreted in urine

Sodium Phenylbutyrate- binds with glutamine to form phenylacetylglutamine, removes two nitrogen atoms, then is excreted in urine, 450-600 mg/kg/day or 9.9-13.0 g/m2/d when >20kg, generic available

- Buphenyl ® (Amgen- www.amgen.com)
- Olpruva ™ (Zevra Theraputics- zevra.com)
- Pheburane ® (Medunik USA- www.medunikusa.com)

Glycerol Phenylbutyrate- same mechanism of action as sodium phenylbutyrate but on a glycerol backbone, 4.5-11.2 mL/m2/d

- Ravicti® (Amgen- www.amgen.com)

Sodium Phenylacetate + Sodium Benzoate (IV only)

- Ammonul® (Ucyclyd Pharma, Inc- www.ucyclyd.com)

Carglumic acid- a synthetic form of N-acetylglutamate synthase approved for NAGS deficiency, generic available (www.etonpharma.com)

Laboratory Monitoring

Plasma Amino Acids [A] (especially glutamine)
Ammonia [A]
Ferritin, iron, folate, zinc, vitamin B12 [B]
25-OH Vitamin D [B]
CBC [B]
CMP [B]

A Weekly in infancy, 1-3 months thereafter
B At least annually or as indicated

References

1. MacLeod, E. Nutrition Management of Urea Cycle Disorders. In LE Bernstein, F Rohr, S van Calcar (Eds.) *Nutrition Management of Inherited Metabolic Diseases* (2nd Edition). Springer: 2021
2. Häberle J, et.al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019 Nov;42(6):1192-1230. doi: 10.1002/jimd.12100. Epub 2019 May 15. PMID: 30982989.