16 Nutrition Management of Urea Cycle Disorders

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Contents

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Core Messages

- Urea cycle disorders (UCD) differ widely in their presentation and severity.
- Correcting hyperammonemia is the priority in treating UCD.
- Dietary protein is restricted in UCD. The amount of protein provided as intact protein versus medical food protein (essential amino acid) varies.
- Preventing catabolism by providing sufficient energy is a critical part of nutrition management.
- Medications that remove nitrogen by alternative pathways help to prevent hyperammonemia and increase protein tolerance.
- Outcomes are guarded and depend on severity of the disease.
- Liver transplantation is recommended for infants with severe forms of the disorder.

Box 16.1: Principles of Nutrition Management in UCD

Restrict:	Protein
Supplement:	Essential amino acids, arginine in ASS and ASL, citrulline in OTC and CPS.
Toxic:	Ammonia in all UCD Argininosuccinic acid (ASA) in ASL deficiency Arginine in arginase deficiency

16.1 Background

Urea cycle disorders (UCD) are caused by a deficiency in any one of six enzymes or two transporters in the urea cycle [1] (Fig. 16.1). In addition, a new disorder has recently been described which causes hyperammonemia (and hyperlactatemia), carbonic anhydrase VA (CA-VA [2]. Management of CA-VA will not be reviewed here. Collectively, UCD are relatively common, with an incidence of 1:35,000 births [3]. Apart from ornithine transcarbamylase deficiency (OTCD), which is x-linked, all UCD are inherited in an autosomal recessive pattern [1]. While a secondary role of the hepatic urea cycle is to produce arginine, the primary function is to remove nitrogen that is produced from amino acid metabolism to prevent accumulation of ammonia. Waste nitrogen is produced when protein intake exceeds the amount needed for protein synthesis or when endogenous protein stores are broken down to produce energy (catabolism). Nitrogen is cleaved from an amino acid and the remaining molecule is used as a source of energy (if needed) or stored as fat. Excess nitrogen is normally converted to ammonia, which enters the urea cycle and through a series of enzymatic reactions, is converted to urea and excreted (Box 16.1).

Ammonia is neurotoxic [4, 5]. The pathophysiology of UCD and the cause of neurotoxicity is complex. It involves not only ammonia, but also the effect of ammonia and excess production of glutamine on astrocytes, causing brain edema [6]. The acute effects of hyperammonemia include poor feeding, vomiting, seizures, and lethargy that can rapidly progress to coma and death. Chronic effects of mild elevations of ammonia are less well understood but may be a cause of impaired neurocognition seen in children with UCD [7]. The potential consequences of increased ammonia concentrations are presented in Table 16.1. Note that ammonia concentrations may be expressed as μmol/L or mcg/dL.

UCD can be differentiated based on the pattern of citrulline, arginine, and ornithine on plasma amino acid analysis.

UCD can present at any age [1, 9, 10]. Typically, a neonate with a severe form of UCD will present with rapidly progressive symptoms of hyperammonemia within the first few days of life. In infants and children, presenting symptoms may include failure to thrive, cyclic vomiting, liver dysfunction, seizures, and developmental delay [1, 11, 12]. Children and adults may present after the newborn period and have a milder clinical course [10]. In some cases, adults are diagnosed with UCD after encephalopathic crises

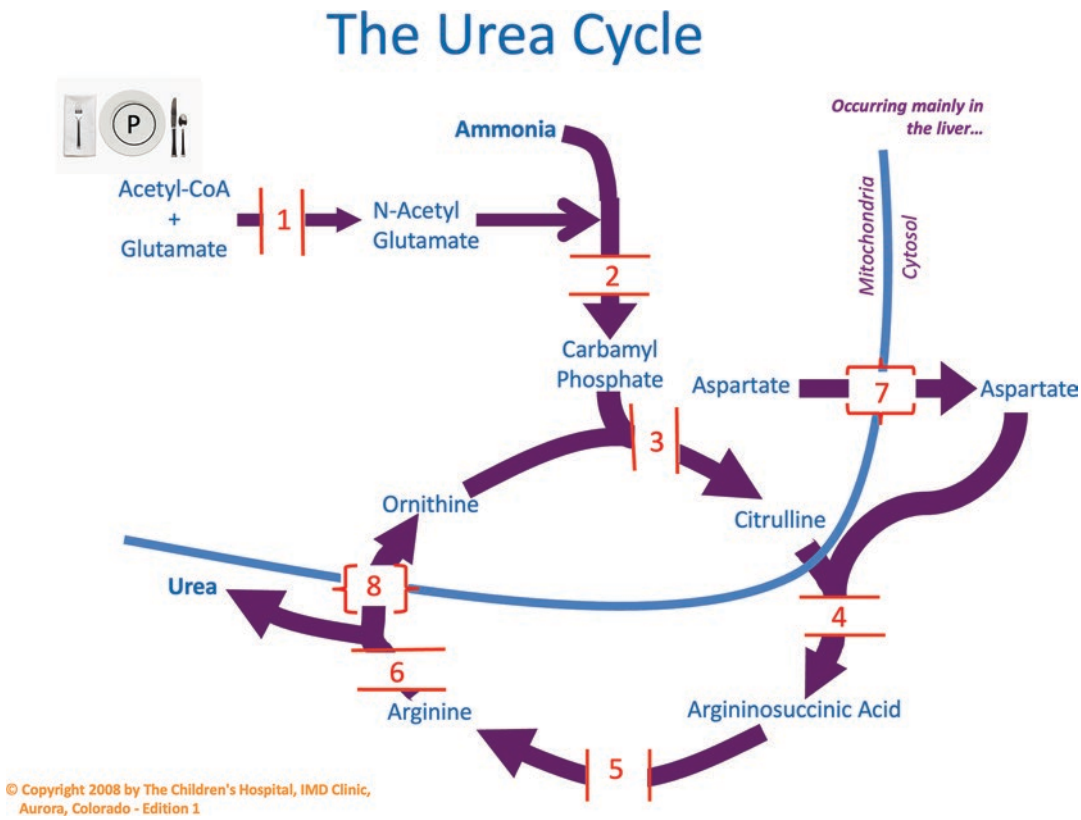

Fig. 16.1 Metabolic pathway of urea cycle disorders. The urea cycle contains six enzymes: 1. *NAGS* N-acetylglutamate synthase – activates CPS. 2. *CPS* Carbamoyl phoshate synthetase – adds bicarbonate to ammonia to form, along with a phosphate group, carbamoyl phosphate, starts the urea cycle. 3. *OTC* Ornithine transcarbamylase combines carbamoyl phosphate with ornithine to produce citrulline. 4. *ASS* Arginiosuccinate synthetase – combines citrulline and aspartate to form arginosuccinic acid. 5. *ASL* Argininosuccinate lyase – breaks down argininosuccinic acid into arginine and fumarate. 6. *Arginase* – cleaves arginine to form urea and ornithine which then feeds back into urea cycle. 7. *Citrin* – transports aspartate from the mitochondria to the cytosol. 8. *ORNT1 Ornithine translocase* – transports ornithine between the mitochondria and the cytosol, deficiency causes hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome

Table 16.1 Ammonia concentrations and potential consequences

Ammonia concentration		Interpretation and symptoms
µmol/L	mcg/dL	
<35	<60	Normal concentration[a]
36–60	60–100	Mild elevation; not always associated with symptoms
61–200	150–350	Elevation: poor feeding, vomiting, irritability, lethargy, confusion
>250	>350	Hyperammonemic crisis; potentially leading to coma

[a]In newborns normal ammonia concentrations are 64–107 µmol/L (90–150 mcg/dL) and in infants age 0–2 weeks 56–92 µmol/L (79–129 mcg/dL).

Note: Norms for ammonia concentration may vary according to laboratory used. Individual symptoms may vary – some patients are more sensitive to elevations in ammonia than others. Therefore, treatment should not be based solely on ammonia concentration and needs to consider patient history, clinical, and laboratory assessments.

Ref. [8]

following catabolic stress, including infection, surgery, pregnancy, and the postpartum period [13, 14]. Finally, females who are carriers for OTC deficiency may be diagnosed following the diagnosis of a more severely affected child. Females who are carriers for OTC deficiency can still exhibit neurocognitive deficits in executive functioning and approximately 15% require treatment [1, 15]. Adolescents and adults who are diagnosed with UCD often have a history of chronic neurological and/or psychiatric symptoms [1] as well as a diet history indicating avoidance of high protein foods.

Not all individuals with UCD come to attention clinically. Some may be identified through newborn screening (NBS) [3, 11]. NBS detects high concentrations of metabolites in the blood; therefore, ASS and ASL can be identified because these disorders result in increased concentrations of citrulline and arginase deficiency because of high concentrations of arginine. However, OTC, the most common UCD, is not identified through most NBS programs because in OTC the metabolite citrulline is lower than normal. The Association of Public Health Laboratories NewSTEPS website (newsteps.org) can be accessed for state-specific screening profiles. For individuals who come to attention through NBS, the challenge is to determine how aggressively to treat infants who are flagged by NBS but who remain asymptomatic. For those who have been confirmed through biochemical testing (and in some cases molecular testing as well) but maintain normal plasma glutamine, treatment with medical foods and ammonia scavengers may not be needed, though patients should continue to be followed, supplemented with citrulline/arginine when needed, and treated conservatively when ill. Algorithms for guidance in diagnosing specific UCD are available [11].

Table 16.2 presents the 6 enzymes and 2 transporters of the urea cycle and the disorder associated with a deficiency of each. Proximal UCD, or those in the mitochondria, (NAGS, CPS, OTC) tend to be associated with marked elevations in ammonia, whereas UCD that are more distal

Table 16.2 Urea cycle disorders, associated enzymes, and altered laboratory values

Disorder	Enzyme	Abbreviation	Ammonia concentration	Plasma amino acid findings[1]
NAGS deficiency	N-Acetylglutamate synthetase	NAGS	Markedly elevated	Markedly low citrulline Low arginine
CPS deficiency	Carbomoyl phosphate synthetase	CPS	Markedly elevated	Markedly low citrulline Low arginine
OTC deficiency	Ornithine transcarbamylase[2]	OTC	Markedly elevated	Markedly low citrulline Low arginine
ASS deficiency; Citrullinemia I	Argininosuccinic acid synthetase	ASS	Elevated	Markedly elevated citrulline Low arginine
Citrin deficiency	Citrin	Citrin	Elevated	Elevated citrulline Elevated arginine
ASL deficiency; Argininosuccinic aciduria (ASA)	Argininosuccinic acid lyase[3]	ASL	Elevated	Mild elevation in citrulline Low arginine
Arginase deficiency; Argininemia	Arginase	ARG	Rarely elevated	Elevated arginine
Hyperornithinema-hyperammonemia- homocitrullinuria (HHH) syndrome	Ornithine translocase	ORNT1	Elevated	Elevated ornithine Low citrulline

[1] Plasma glutamine typically elevated in in all UCD, elevations are associated with higher risk of hyperammonemia
[2] Urine orotic acid is also present and is pathognomoic for OTC deficiency
[3] Urine argininosuccinic acid will be elevated in mild ASL deficiency even if blood level is normal

(ASS, ASL, ARG, HHH) are less likely to result in severe hyperammonemic episodes; however, all individuals with UCD are at risk of developing hyperammonemia, especially if stressed by infection and/or poor energy intake leading to catabolism of endogenous protein [16]. Although proximal UCD often have a more severe clinical course and higher risk of hyperammonemia events, there is debate about the severity of neurocognitive outcomes between the two groups [7, 9, 17].

Overall, outcomes in UCD are improving due to newborn screening for several disorders, advances in medications and nutrition management, and liver transplantation [18–20]. Traditionally, however, outcomes have been suboptimal and characterized by early mortality, growth failure, chronic liver disease, and poor development [9]. Survival rates are better for those with late onset (11% mortality) compared to neonatal onset (24% mortality) [20]. Because of shortcomings of traditional therapies, liver transplantation is becoming a more viable and attractive option for many patients with UCD [21, 22].

16.2 Nutrition Management

16.2.1 Chronic Nutrition Management

Treatment of UCD includes limiting dietary protein, providing sufficient energy to prevent catabolism, supplementing with specific amino acids, and using nitrogen-scavenging drugs [11, 14, 23–26] (Box 16.2). These strategies are typically used in combination depending on the severity of the disease. In an infant who presents with a severe form of UCD, for example, a male with OTC deficiency, emergency management is indicated [11, 27] (Sect. 16.2.2).

The goals of nutrition management are to prevent the accumulation of ammonia, normalize plasma amino acids and promote normal growth and development. The treatment of UCD differs from other metabolic disorders with respect to protein intake. In UCD, total protein is limited, unlike in many other metabolic disorders where total protein is not limited but is provided as medical food without the offending amino acid(s). The steps to initiating a diet in a newborn are presented (Box 16.3). Feeding from the breast and/or the use of pumped breast milk should be

Box 16.2: Components of Management of UCD

- Limit protein
- Prevent catabolism
- Use nitrogen scavenging drugs
- Supplement amino acids

Box 16.3: Initiating Nutrition Management in an Infant with UCD

(For the infant who is medically stable and ready to start feeding)

Goals:

- Prevent hyperammonemia
- Normalize plasma amino acids
- Promote normal growth and development

Step-by-Step:

1. Establish goals for total protein intake and (essential amino acids) (Table 16.3).
2. Determine amount needed to meet goal in step 1 and which medical food to use.
3. Determine amount of intact protein needed to meet the protein goal in step 1 and whether the source will be breast milk or standard infant formula
4. Determine if DRI for energy is met by the combination of medical food and standard infant formula/ breast milk. If not, add a protein-free energy source to meet needs.
5. Determine how much water to add to make a volume of formula that will meet the infant's fluid needs and have a caloric density of 20–25 kcal/oz.

See Sect. 16.7 Example Diet Calculation

Table 16.3 Recommended nutrient intakes for patients with UCD

Age (year)	Total protein[1] (g/kg/day)	Protein from medical food (essential amino acids) [2] (g/kg/day)	Intact protein (g/kg/day)
0–1	1.2–2.2	0.4–1.1	0.8–1.1
1–7	1.0–1.2	0.3–0.7	0.7–0.8
7–19	0.8–1.4	0.4–0.7	0.3–1.0
>19	0.8–1.0	0.2–0.5	0.6–0.7

Intakes for energy, vitamins, and minerals should meet the DRI [28] and fluid requirements [11, 29] and R.H. Singh Nutritional Management of UCD [30]

[1] Total protein goals should be considered the minimum protein required, some individuals may tolerate more total protein

[2] For some with mild disease supplementation with essential amino acids may not be required. If supplementation is needed, provide 30–50% total protein from medical food

Table 16.4 Energy and protein content of medical foods (essential amino acids) for the treatment of UCD (per 100 g powder)[1]

Medical food	Energy (kcal)	Protein (g)
Cyclinex®-1[2]	510	7.5
Cyclinex®-2[2]	440	15
EAA Supplement™[3]	288	40
Essential Amino Acid Mix[4]	316	79
UCD Anamix® Junior[4]	385	12
UCD Trio™[3]	393	15
WND® 1[5]	500	6.5
WND® 2[5]	410	8.2

[1] Available in the US (2022)

[2] Abbott Nutrition (Columbus, OH; abbottnutrition.com)

[3] Nutricia North America (Rockville, MD; nutricia-na.com)

[4] Vitaflo USA, (Alexandria, VA; vitaflousa.com)

[5] Mead Johnson Nutrition (Evansville, IN; meadjohnson.com)

encouraged as breast milk contains less total protein when compared to standard infant formula. Breast milk may need to be supplemented with a protein-free energy module to ensure energy needs are met in infants with poor feeding.

Sources of protein in the diet for infants with UCD include intact protein (breast milk or standard infant formula in infancy, baby food, table foods) and medical foods containing essential amino acids. Some patients with mild forms of UCD can be treated with breastmilk/standard infant formula (with or without protein-free energy supplement) and followed with a vegetarian diet, though continued follow-up and monitoring are required.

Practice varies widely with respect to the balance between intact protein and medical food protein. Current European guidelines suggest following FAO/WHO/UNU 2007 guidelines for protein requirements [31] and supplementing with essential amino acids with metabolic instability or use of ammonia scavengers [11]. A cross-sectional study of those enrolled in the European Registry and Network for Intoxication Type Metabolic Diseases [25] found that essential amino acid medical food was given in 32% of individuals with a UCD and provided 28–32% of total protein intake. This is congruent with previous recommendations that 20–30% of protein requirements be given as essential amino acids [14]. However in some centers, protein restriction alone (without the use of medical foods containing essential amino acids) is used [32, 33] while others recommend that approximately half of the total protein allowance be given as essential amino acids and half as intact protein [34]. Protein restriction without essential amino acid supplementation may lead to chronic protein insufficiency [35] and when intact protein is low, EAA supplementation may improve plasma branched-chain amino acid concentrations [25]. Once the current severity status of the individual patient is determined and diet goals are established, the amount of medical food and the amount of breast milk or standard infant formula necessary to meet these goals is calculated. Medical foods for the treatment of UCD are listed in Table 16.4. They provide essential amino acids as the protein source but differ in energy, vitamin, and mineral profiles.

Providing sufficient calories often necessitates the use of special protein-free medical foods, such as Pro-Phree® (Abbott Nutrition, Columbus, OH), PFD (Mead Johnson, Glenview, IL), Polycal™ (Nutricia North America, Gaithersburg, MD), Duocal® (Nutricia North America, Gaithersburg, MD), S.O.S™ (Vitaflo USA, Alexandria, VA) or Solcarb® (Solace Nutrition, Pawcatuck, CT). Nutrition education and counseling should be provided on low protein calorie-dense food options.

Preventing catabolism Catabolic stress is a major source of waste nitrogen. Episodes of

hyperammonemia are often precipitated not by an overconsumption of protein, but rather by an acute infectious illness coupled with inadequate energy and protein consumption. Although a recent study found energy intakes of patients with UCD often meet recommended requirements [36], it can be challenging to provide sufficient calories to some patients with UCD as appetites at baseline can be poor. The reason for anorexia in UCD is multifactorial. Elevated blood glutamine concentrations often seen in patients with UCD, cause high brain glutamine concentrations. In the brain, glutamine is a carrier for tryptophan, which is a precursor for serotonin, the neurotransmitter that is associated with a feeling of satiety [37]. Also, patients with UCD have been shown to have higher than normal concentrations of the hormone peptide tyrosine tyrosine (also referred to as Peptide YY or PYY) that is associated with feelings of satiety [38]. It is also likely that patients with UCD have food aversions because they have been conditioned to associate intake of high protein foods with episodes of vomiting, headaches, and/or lethargy. In one study, half of the patients with UCD had feeding problems including poor appetite, food refusal, protein aversion or vomiting [39]. Given the tendency to self-restrict protein, patients with UCD need nutrition education on appropriate amounts and types of protein in the diet, particularly if EAA supplementation is not given. It is common for children with UCD, especially those with severe forms, to require nasogastric or gastrostomy tubes (G-tubes) in order to provide sufficient calories. G-tubes are especially helpful for providing medications and extra calories, especially during illness when appetites may be further diminished [11].

Use of nitrogen scavenging drugs Although there are several medications available, they remove nitrogen by one of two pathways (Fig. 16.2). Sodium benzoate binds with glycine and forms hippurate and is excreted in urine. This

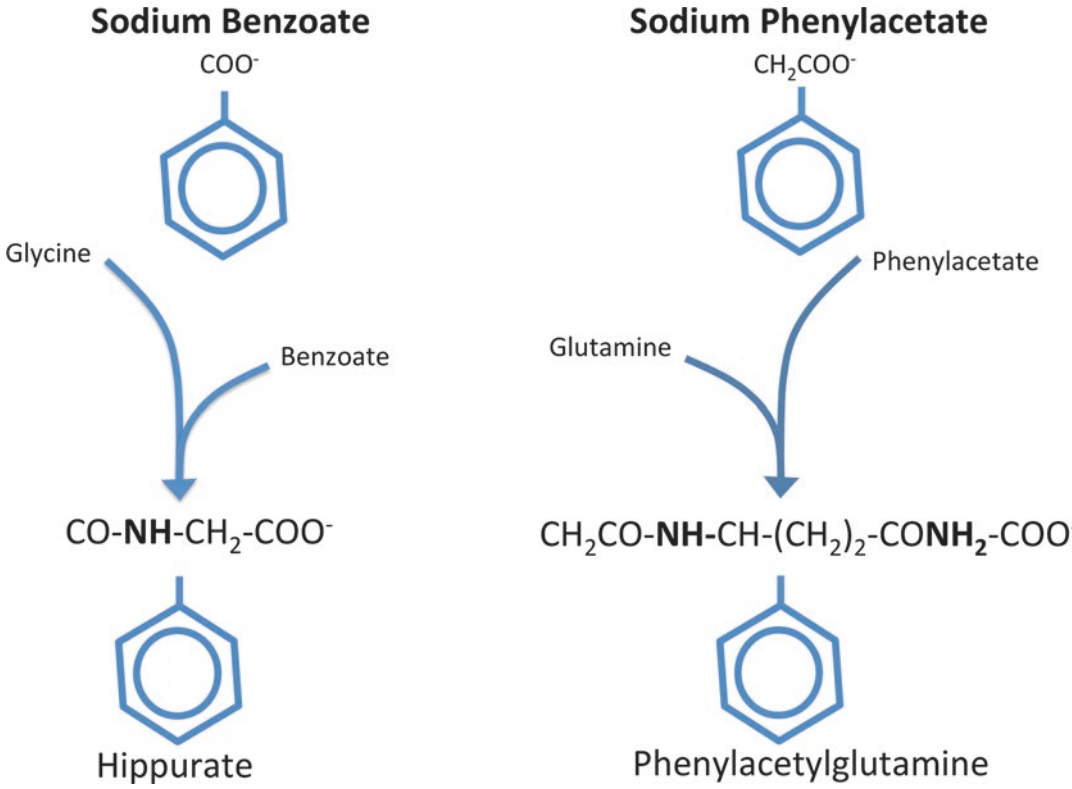

Fig. 16.2 Alternate pathways for the removal of nitrogen using sodium benzoate or sodium phenylacetate. Sodium phenylbutyrate (Buphenyl®) and glycerol phenylbutyrate (Ravicti®) are both converted to sodium phenylacetate in the liver

reaction removes one nitrogen atom. Similarly, in the second reaction, sodium phenylacetate binds with glutamine and forms phenylacetylglutamine that is excreted. In this reaction, two nitrogen atoms are bound and excreted. The pro-drug to sodium phenylacetate, sodium phenylbutyrate, is available as Buphenyl® (Hyperion Therapeutics Inc., Brisbane, CA) as well as a generic form (PAR Pharmaceuticals and Simapharm Laboratories, LLC). Glycerol phenylbutyrate (Ravicti®, Hyperion Therapeutics Inc.) works by the same mechanisms as sodium phenylbutyrate and some find it easier to administer because the dose is lower and taste is better than sodium phenylbutyrate [40]. Sodium phenylbutyrate has the secondary effect of activating branched-chain ketoacid dehydrogenase, which often results in low plasma branch chain amino acid concentrations [41]. Ammonul® (Ucyclyd Pharma, Scottsdale, AZ) is an IV form of nitrogen scavenging medication that contains a combination of sodium phenylacetate and sodium benzoate.

Carglumic acid (Carbaglu®, Recordati Rare Diseases Inc., Lebanon, NJ) is a medication for treating deficiency of the first enzyme of the urea cycle, NAGS deficiency, but it is not a nitrogen-scavenging drug. Carglumic acid is chemically analogous to N-acetylglutamine, which activates CPS. In a study of 20 patients receiving carglumic acid, 12 had NAGS deficiency and their hyperammonemia resolved [42]. Patients with NAGS deficiency receiving carglumic acid can quickly transition to a normal diet with no protein restriction. A carglumic acid trial should also be considered for all patients with CPS1 deficiency as some have been shown to have improvements in urinary nitrogen excretion and may result in increased intact protein tolerance [43].

Supplemental amino acids For all UCD except arginase deficiency, arginine becomes an essential amino acid. Arginine or citrulline supplements are given to replace the arginine that is normally produced by the urea cycle. Often, L-arginine is used in ASS and ASL deficiency whereas L-citrulline is used in CPS and OTC deficiency because it has the advantage of incorporating aspartate into the pathway and removing one additional nitrogen molecule [44]. The goal in supplementing amino acids is to keep plasma concentrations within the normal range and the doses vary for an individual as higher amounts are prescribed in acute illness [11, 27]. The typical maintenance dose of L-citrulline in OTC and CPS is 100–200 mg/kg/day [11] and should be adjusted based on plasma concentrations of citrulline. Current European guidelines recommend 100–300 mg/kg/day (2.5–6 g/m^2/d if >20 kg) L-arginine for ASS and ASL deficiency [11]. In ASL, there is evidence that lower dose arginine supplementation (100 mg/kg/day) results in lower accumulation of ASA and perhaps improved outcome since ASA may contribute to the liver and neurological disease [45]. L-arginine supplementation should be adjusted based on plasma concentrations of arginine and glutamine. The typical maintenance dose of L-citrulline in OTC and CPS is 100–200 mg/kg/day [11] and should be adjusted based on plasma concentrations of citrulline.

16.2.2 Acute Nutrition Management

16.2.2.1 Nutrition Management During Hospitalization

A hyperammonemic crisis is treated as a medical emergency whether it is in a sick neonate or an older child/adult with an acute illness. All patients should have an emergency protocol [46] to ensure they receive prompt and proper treatment. If hospitalized with hyperammonemia, protein feeds should be discontinued and IV access obtained for administration of nutrition support and medications including the nitrogen-scavenging drug, Ammonul®, and arginine. If possible, plasma amino acids should be ordered for stat analysis. In a known patient, analysis of amino acids can help to determine if hyperammonemia is due to acute illness or may be secondary to excess protein intake. If multiple essential amino acids are low on plasma amino acid analysis, essential amino acid supplementation should be given quickly to prevent further catabolism.

In severe cases of hyperammonemia, dialysis is usually required to normalize ammonia concentrations. Often patients are not able to tolerate

Box 16.4: Example of Parenteral Nutrition for a Patient with UCD in Hyperammonemic Crisis[a]

Glucose infusion rate: 10–12 mg/kg/min
Intralipid: 2–3 g/kg/d (up to 3–4 g/kg/d in neonate)
Amino acids: (after 24 h or if dialyzed):
0.25 – 0.5 g/kg/d and advanced as tolerated
Arginine HCl: 210 mg/kg/d
[a]Management in conjunction with metabolic physician

enteral feedings and parenteral nutrition (PN) is required. The PN solution focuses on providing as much energy as possible by using 20% dextrose solution and 2–3 g/kg Intralipid® and eliminating or severely restricting protein intake (Box 16.4). Goal calories should provide 120% of the DRI for age and if hyperglycemia occurs, insulin can be provided [11]. Whenever possible, enteral feeds should be utilized, even for small amounts of essential amino acids. If the patient is to be dialyzed, a limited amount of an IV amino acid solution is given, since dialysis will remove amino acids as well as ammonia, and the infant runs the risk of becoming catabolic. PN solutions that contain only essential amino acids can be ordered but may not be readily available. If enteral feeds cannot be used for EAA, standard PN solutions can be utilized to prevent further catabolism associated with inadequate protein intake. Catabolism is reversed faster when some amino acids are provided in the diet in addition to adequate energy (through glucose and/or intralipids) [47].

In a patient who is not dialyzed, protein should be eliminated for no more than 24 hours to prevent further catabolism [27]. Essential amino acids can be provided during an acute illness in order to prevent branched-chain amino acid deficiency that can occur with hyperammonemia and be further exacerbated by nitrogen scavenging medications [35, 41]. There is no consensus on how long to eliminate protein and essential amino acids in acutely ill patients with UCD and the decision is made by the medical team depending on the patient's ammonia, plasma amino acids, nutritional intake and neurological status. Enteral sources of protein can be reintroduced slowly, starting with half of the patient's intact protein needs and advancing as tolerated.

Once a neonate who presented with hyperammonemia is stabilized, he or she will usually experience a period of metabolic stability or "honeymoon period" [20]. During this time, the infant is growing rapidly and has a relatively higher protein tolerance. The diet is less complicated in the first few months since solid foods have not been introduced and protein does not yet have to be counted. The infant also has innate immunity and often limited exposure to infections. Depending on severity and desire of the family, infants with UCD can be breastfed from the breast or given pumped breast milk in combination with essential amino acids and/or a protein-free calorie supplement.

16.2.2.2 Nutrition Management During Illness at Home

Intercurrent illness is the most common cause of hyperammonemia outside of the newborn period and prompt treatment can prevent catabolism and be lifesaving [20]. Patients should have a Medic Alert® bracelet (MedicAlert, Turlock, CA). Those with mild illnesses may be managed at home if the metabolic team assesses that it is safe to do so. In such cases, ensuring adequate supplemental calories and hydration should be the focus. Given the tendency to self-restrict protein, ensuring that the patient has not been consuming less protein than recommended needs to be assessed. In some cases, the percentage of EAA to intact protein can be adjusted to ensure minimum protein needs are met during illness. Sick day plans that reduce intact protein should be given on a case-by-case basis depending on the degree of illness, how well the child has been managed at home in the past, distance to clinic, and diet history (Sect. 16.7). However, medical food containing EAA is still provided in sick day formulas as well as additional energy from fat and/or carbohydrate. If a sick day diet is prescribed, it should be used for no more than 24–48 hours [14, 23]. Its necessity beyond that requires an evaluation from the medical team.

Because fluid and energy needs are higher than normal during illness, patients need to eat more when they often feel like eating less. For patients who do not have G-tubes, getting sufficient energy and fluids by mouth may not be possible and admission for IV fluids and calories is often needed.

16.3 Monitoring

Nutrition monitoring includes assessment of anthropometrics, dietary intake, and laboratory parameters (Box 16.5). Nutrition goals should be individualized to laboratory measures and growth parameters as there may be some differences in resting energy expenditure for those with a UCD [48]. Routine laboratory measurement includes ammonia and plasma amino acids, particular attention is paid to glutamine, branched-chain amino acids, alanine, and glycine. Both ammonia and glutamine are markers for neurocognitive outcomes [20]. Collection of an accurate ammonia sample can be challenging as it must be taken from free-flowing blood and immediately placed on ice and analyzed. Ammonia measurements from send-out labs should not be considered accurate and an elevated concentration that does not coincide with the patient's clinical picture should be repeated [49].

Box 16.5: Nutrition Monitoring of Patients with UCD

- Routine assessments including anthropometrics, dietary intake, physical findings
- Laboratory Monitoring
  - Diagnosis-specific
    - Ammonia
    - Plasma amino acids, including
      - Glutamine
      - Arginine
      - Citrulline
      - Argininosuccinic acid (in ASA lyase deficiency)
      - BCAA (often low if on sodium (glycerol) phenylbutyrate therapy)
  - Nutrition laboratory monitoring of patients on protein-restricted diets may include markers of:
    - Protein sufficiency (plasma amino acids)
    - Nutritional anemia (hemoglobin, hematocrit, MCV, serum vitamin B_{12} and/or MMA, total homocysteine, ferritin, iron, folate, total iron binding capacity)
    - Vitamin and mineral status (25-hydroxy vitamin D, zinc, trace minerals)
    - Others as clinically indicated

16.3.1 Plasma Amino Acids Related to Dietary Intake

Glutamine is often a harbinger of high ammonia because it is a reservoir for ammonia, as glutamine is synthesized in the liver from glutamate and ammonia. A recent report found 20–30% of patients with UCD had low branched-chain amino acids [25] though, anecdotally, this rate could be higher. Regardless of the cause (either as a consequence of dietary restriction or sodium phenylbutyrate therapy) [50], low branched-chain amino acids indicate the need for more protein. This can be given as intact protein if the patient can tolerate it, essential amino acid medical food, or specific branched-chain amino acid supplements [11]. Low plasma branched-chain amino acids in those with a UCD have been associated with lower linear growth velocity [18, 36]. Linear growth may be related to the ratio of intact protein to energy [36, 51], and those with early-onset UCD, in particular, are at risk for poor linear growth [52]. Plasma amino acids can further be used to assess caloric intake as elevated alanine may occur if energy intake is insufficient and elevated glycine is often seen in catabolism [1].

16.3.2 Additional Plasma Amino Acids to Evaluate Based on Diagnosis

Depending on the diagnosis, analysis of an amino acid profile can help to guide management.

Arginine and citrulline should be monitored for those on L-arginine or L-citrulline supplementation as an indication of compliance or necessity of dose adjustment. Plasma citrulline will always be elevated in those with citrullinemia; however, citrulline alone is not toxic and elevations in the presence of normal glutamine is not concerning. Some labs report argininosuccinic acid (ASA) on plasma amino acid profile. For diagnosis, patients with mild ASL may only have argininosuccinic acid elevated in urine amino acids. Beyond diagnosis, ASA concentrations have not been associated with changes in dietary protein or disease outcome. Plasma arginine should be monitored in arginase deficiency with a goal to achieve concentrations as close to normal as possible [53]. Although hyperammonemia is less common in arginase deficiency, a greater restriction of intact protein may be required to achieve ideal plasma arginine concentrations [11].

Periodic laboratory monitoring to ensure that the patient is receiving adequate protein, vitamins, and minerals is recommended. Evaluation of vitamins and mineral status is of particular importance in those on a protein-restricted diet without a complete medical food supplement. Finally, compliance with nitrogen scavenger medications can be assessed using ratios of phenylacetate to phenylacetylglutamine [54]. A ratio less than 0.6 is associated with elevated plasma glutamine and may be related to suboptimal intake of nitrogen scavenger rather than excessive intake of dietary protein.

16.4 Transplantation

In patients with severe UCD outcomes are poor despite treatment and liver transplantation is often the treatment of choice [21]. The Urea Cycle Disorders Consortium and the recent European guidelines recommend that patients with UCD, other than those with NAGS, who have absent or very low enzyme activity be stabilized, aggressively managed, and placed on the liver transplant list as early as is practical [11, 20]. Even in arginase deficiency, liver transplantation has been shown to halt the progression of neurological damage [55].

Earlier United Network for Organ Sharing (UNOS) data found higher mortality when patients with UCD were transplanted before age 2 years [22]. This may be explained by the fact that, historically, only the most severely affected patients were referred for transplantation; however, current recommendations state that transplants should occur at the earliest possible time [11, 20]. Transplantation outcomes in patients with UCD have been good. In a study of 23 patients (none of whom had arginase deficiency), there was 100% patient survival and 96% graft survival [56]. Developmental outcomes were stable or improved following transplant.

Prior to liver transplantation, the goal is to maintain good metabolic control and nutritional status. Better surgical outcomes are correlated to pretransplant weight and protein status both of which can be difficult to attain on a protein-restricted diet. A minimum weight of 5 kg is usually recommended before transplantation can be performed [11]. Maintaining metabolic control is of paramount importance in order to preserve neurocognition because transplantation does not reverse neurocognitive damage [20, 57].

Pre- and postoperative nutrition protocols vary. At one center [56], patients with UCD continued to receive their usual protein-restricted diet up to approximately 6 hours prior to surgery. During surgery, patients are typically given 10% dextrose with electrolytes and Intralipid® (2 g/kg/d). After surgery, intravenous amino acids (1.5–2 g/kg/d) are added to the parenteral nutrition. After transplantation, patients with UCD no longer require a protein-restricted diet, medical food or nitrogen-scavenging drugs [56]. While a normal diet can be followed, it may be difficult for patients who have not had high protein foods in the past to readily accept unfamiliar foods. Nutrition education and guidance should be provided to expand patients' palates and introduce new foods in a healthful way.

Most patients still require L-arginine or L-citrulline supplementation, with decreased dose based on plasma amino acid concentrations. Follow-up of liver transplant patients by the metabolic dietitian in collaboration with the transplant dietitian is best. The transplant dietitian can

best address issues common to all transplant patients, including possible nutrition-related side effects of anti-rejection medication, food safety concerns, and prevention of obesity, which is common in pediatric patients who have undergone liver transplantation [58].

16.5 New Treatment Options

Currently, multiple new therapies are in clinical trials for the treatment of UCD. These include targets to reduce ammonia production in the gut, supplementation of nitric oxide for ASL, enzyme replacement therapy for ARG1, and gene therapy for OTC deficiency [59]. These new treatment modalities have the potential to improve overall management and outcomes of patients with UCD as well as potentially allow for safe diet liberalization. The role of the metabolic dietitian is essential for patients who embark on these new treatment options to ensure nutrition requirements are met in a healthful way.

16.6 Summary

The primary function of the urea cycle is the removal of waste nitrogen produced during protein metabolism. Deficiency in the activity of any of the 6 enzymes or 2 transporters in the urea cycle may result in the accumulation of ammonia, often to toxic concentrations. Treatment includes restricting dietary protein, preventing catabolism, supplementing amino acids that are normally produced by the urea cycle, and promoting the excretion of nitrogen via alternative pathways. Outcomes are guarded and appear to be better for patients identified by NBS compared to patients identified clinically. Liver transplantation is a treatment option, especially for patients with a severe form of the disorder.

16.7 Diet Calculation Example

Example 1 Infant male with OTC deficiency weighing 2.9 kg who presented acutely and is ready to transition from parenteral nutrition to enteral feedings.

Patient Information	Nutrient Intake Goals
Age: 3-week-old male with OTC deficiency Weight: 2.9 kg Presented acutely with hyperammonemia Treated with dialysis Ammonul and parental nutrition Currently tolerating 1 g protein PN and ready to transition to enteral feeding	Energy: 120 kcal/kg Protein: 1.5 g/kg (half as whole protein and half as essential amino acids) Diet prescription summary for sample calculation of UCD diet

Diet prescription summary for sample calculation of UCD diet

Diet	Amount	Protein, total (g)	Protein, intact (g)	Protein, medical food (g)	Energy[1] (kcal)	Fluid[2] (mL)
Goals		4.4	2.2	2.2	348	290
Cyclinex-1 powder[3]	29 g	2.2	0	2.2	148	
Similac powder[3]	20 g	2.2	2.2		108	
Pro-Phree powder[3]	18 g		0	0	92	
Totals		4.4	2.2	2.2	348	
Total per kg		1.5	0.76	0.76	120	
Add water to make:	14–17 ounces					420–510 mL

[1] Dietary Reference Intake [28]
[2] Fluid requirement [29]
[3] Abbott Nutrition (Columbus, OH; abbottnutrition.com)
Note: Check manufacturer's website for the most up-to-date nutrient composition

Example 2 Modification of usual well-day diet during a mild illness treated at home for a 6-year-old female with ASA deficiency, weighing 24 kg (Table 16.5).

Table 16.5 Usual full protein diet prescription (when well) and sick-day modifications to diet prescription for half intact protein or no intact protein

Diet	Amount	Protein, intact[1]	Protein, medical food[1]	Energy (kcal)
Diet prescription: Usual full protein		0.7 g/kg (17 g)	0.5 g/kg (12 g)	1600[2]
Anamix Junior[3]	100 g	0	12	385
Duocal®[3]	80 g	0	0	394
Add water to make	28 oz			
Food/beverages		17 g	0	807
Diet prescription: Half intact protein, 20% more energy		0.35 g/kg (8 g)	0.7 g/kg (17 g)[5]	1900
Anamix Junior[3]	140 g	0	17	539
Duocal®[3]	140 g	0	0	689
Add water to make	44 oz[4]			
Food/beverages		8 g	0	672[6]
Diet prescription: No intact protein, 20% more energy[7]		0	0.5 g/kg (12 g)	1900
Anamix Junior[3]	100 g	0	12	385
Duocal®[3]	200 g	0	0	984
Add water to make	48 oz[4]			
Food/beverages		0 g		531[5]

[1] Singh 2007 [11, 23]
[2] Dietary Reference Intake [28]
[3] Nutricia North America (Rockville, MD; nutricia-na.com)
[4] Total amount of fluid provided in the formula is greater than usual diet in order to maintain caloric density similar to usual diet and because additional fluid is required during illness
[5] If intact protein is decreased, consider increasing EAA supplement to meet DRI for protein
[6] If patient is not able to consume sufficient amounts of food or fluids to reach energy goal, additional Pro-Phree®/Duocal and water may be added to the formula instead
[7] A sick day plan which provides less than the DRI for protein should only be given for 24–48 hours and followed up closely to ensure further decompensation does not occur at home due to catabolism

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