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Presentation and Management of Urea Cycle Disorders Outside the Newborn Period

GUEST EDITOR
Marshall L. Summar, MD

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Nutritional Management of Urea Cycle Disorders

Rani H. Singh, PhD, RD[a,*], William J. Rhead, MD, PhD[b], Wendy Smith, MD[c,d], Brendan Lee, MD, PhD[e], Lisa Sniderman King, MSc[f], Marshall Summar, MD[g]

[a]*Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30032, USA*
[b]*Department of Pediatrics and Pathology, Medical College of Wisconsin, Madison, WI, USA*
[c]*Department of Genetics, The Barbara Bush Children's Hospital, Maine Medical Center, Portland, ME, USA*
[d]*Department of Pediatrics, Division of Genetics, Maine Pediatric Specialty Group, Portland, ME, USA*
[e]*Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA*
[f]*Department of Pediatrics, Divison of Genetics and Development, University of Washington, Seattle, WA, USA*
[g]*Center for Human Genetic Research and Division of Medical Genetics, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA*

A cardinal principle of urea cycle disorder (UCD) management is the restriction of protein intake to minimize the flux of nitrogen through the urea cycle. However, the calculation of tolerated protein intake is neither simple nor static. Tissue protein is constantly being synthesized and catabolized, and ammonia detoxification needs vary according to enzyme deficiency, growth rate, activity level, and the patient's developmental and health status. During growth, increased protein intake is necessary to prevent catabolism. Careful protein management is also essential during hospital treatment when a patient may receive only parenteral nutrition and is subjected to long intervals of bed rest, which can contribute to breakdown of tissue protein. Administration of essential and other amino acids must also be considered in the nutritional equation, as should the appropriate titration of nitrogen-scavenging medications, energy intake, and vitamin and mineral supplements. In addition, the patient's own eating behaviors, lifestyle, and life events may often confound even the most carefully balanced prescription.

In both acute and long-term situations, close monitoring and calibration of the relevant factors are critical to preventing metabolic decompensation. This, in turn, is essential to maintaining existing neurologic status and providing the patient (and patient's family) with a reasonable quality of life. This paper presents two case histories and a series of recommendations outlining the nutrition management of urea cycle disorders. It also identifies difficulties that arise in the course of treatment, and suggests practical solutions for overcoming them.

Case 1

Inducing anabolism

Medical history

After an uneventful birth and successful breastfeeding for the first 2 days of life, a 3-day-old white girl exhibited lethargy and refusal to suck. Enzyme values reflecting liver function were mildly increased and her plasma ammonia concentration at 5 days of life was significantly elevated at >500 μmol/L.

Further findings included abnormal urine lactic and pyruvic acids caused by shock and poor perfusion; elevated plasma amino acid concentrations, specifically citrulline (2694 μmol/L), glutamic acid, glutamine, alanine, methionine, lysine, and histidine; and excessive urine orotic acid. A diagnosis of citrullinemia (argininosuccinate synthetase [ASS] deficiency) was made.

Treatment

Treatment was started on day 5 at which time the patient's plasma ammonia concentration was 518μmol/L. To maximize caloric intake, the child received hyperalimentation via umbilical artery catheter. The regimen included dextrose 25% in water at 18 mL/hr, fat emulsion (Intralipid) 20% at 0.75 mL/hr (1 g/kg/d) as an energy source, and insulin 0.05 u/kg/d to promote nutrient use. In addition, she was given L-arginine HCL 10% 500 mg/kg/d, an amino acid

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Complete financial disclosure information for each author is provided in the frontmatter of this supplement on page iii.

* Corresponding author. Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30032.

E-mail address: rsingh@genetics.emory.edu (R.H. Singh).

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that becomes conditionally essential because of the decreased rate of synthesis by the urea cycle (in all urea cycle disorders except L-arginase deficiency). This prescription offered 112 kcals/kg/d and 0 g/kg/d of protein. Nitrogen scavenging was provided by sodium phenylacetate and sodium benzoate (Ammonul) 500 mg/kg/d. Within 24 hours, the plasma ammonia concentration had decreased to 80μmol/L.

On the ninth day of life (day 4 of treatment), the patient began transitioning to oral feeds and hyperalimentation fluids and intravenous medications were decreased. Starting with a hyperalimentation regimen of dextrose 25% in water 18 mL/hr, insulin 0.02 u/kg/d, essential and nonessential amino acid mixture (TrophAmine) 0.5 g/kg, fat emulsion (Intralipid) 20% 1g/kg/d, and L-arginine HCL 10% 500 mg/kg/d, she was gradually advanced to full oral feeds, including amino acid modified medical food with iron (Cyclinex-1) 25 g, protein-free diet powder with iron (ProPhree) 3 g, L-arginine base 27 mL (66.6 mg/mL) (after intravenous arginine was discontinued), and the oral nitrogen scavenger sodium phenylbutyrate (Buphenyl) 500 mg/kg/d.

Although her plasma citrulline concentration did not change significantly (Table 1), the patient showed general improvement in other important parameters. The plasma glutamine concentration decreased substantially and fell below the lower limit of the reference range. The other plasma essential amino acids, which include the branched chain amino acids, were in the reference ranges, although both leucine and isoleucine were near the lower end of the range. The patient was discharged when she was 12 days old.

Table 1
Plasma amino acid concentrations (μmol/L)

Amino acid	Patient at diagnosis	Patient after treatment	Patient at discharge	Reference range
Taurine	124	200	175	38–227
Aspartic acid	15	9	5	0–28
Threonine	83	75	299	50–248
Serine	127	53↓	95	90–209
Glutamic acid	209 ↑	67	52	10–189
Glutamine	2079 ↑	811	172↓	246–984
Proline	349	54↓	106	88–417
Glycine	253	16	265	125–497
Alanine	578 ↑	197	262	124–573
Citrulline	2694 ↑	1856 ↑	2260 ↑	6–52
Valine	195	97	153	67–299
Cystine	42	7	40	4–65
Methionine	160 ↑	26	49	17–49
Isoleucine	40	20	35	20–96
Leucine	108	47	63	29–151
Tyrosine	111	8↓	71	24–129
Phenylalanine	63	60	71	37–86
Ornithine	32	168	183 ↑	19–173
Lysine	464 ↑	77	224	43–243
Histidine	152 ↑	63	68	38–145
Arginine	26	258	16	20–149

Discharge regimen

It was imperative in the weeks and months following discharge that the infant ingest sufficient protein, energy, and other essential nutrients to ensure growth, but not so much protein that elevated ammonia levels or vomiting would result. With the advent of nitrogen scavenging medications, protein intake did not need to be as restricted as in the past. Care required a carefully calibrated diet, written instructions for ongoing management and dietary modifications during illness, and rigorous education of the parents regarding the necessity to adhere to the diet, the value of nasogastric feeds as needed, and the need for a rapid response to any signs of decompensation.

An age-appropriate diet was prescribed. The diet consisted of medical foods and infant formula which provided 1.9 g/kg/d of protein (54% protein from medical foods and 46% from Enfamil [Mead Johnson & Company, Evansville, Indiana]), 123 kcal/kg/d of energy, and 500 mg/kg/d of L-arginine base. This regimen supplied about 24 kcal/fluid ounce. Additional water (100 to 150 mL/d) was to be offered.

Parents were instructed how to insert a nasogastric tube in the event of a poor suck. In this case, formula was to be given every 3 hours, and sodium phenylbutyrate was to be administered every 6 hours. The parents were also provided with a letter at discharge that detailed the regimen to be used to prevent decompensation during periods of metabolic stress associated with infections and fevers. Symptoms they were instructed to look for included refusal to suck, labored breathing, lethargy, and excess sleepiness. Should the child appear ill, they were told to temporarily decrease or eliminate protein intake from food and substitute a special metabolic formula that would provide increased calories from non-protein sources, as well as necessary vitamins and minerals. They were also instructed to continue sodium phenylbutyrate, and to administer antiemetic medication and nasogastric feeding, if required. In the event that feeding was disrupted, the child was to be taken to the emergency room (ER) where the staff should be given a copy of the "emergency letter."

At age 2, a gastrostomy tube (g-tube) was placed to overcome the child's mild anorexia.

Outcome data

With sodium phenylbutyrate and diet management, plasma ammonia concentrations have been maintained in treatment range. As reflected in Table 2, the patient's protein and energy intake have been within the recommended guidelines throughout her life. Because a reduction in whole dietary protein alone does not usually offer adequate nutrients for growth, her diet has consistently provided about 50% of protein through supplementation with medical foods. This has not only provided higher concentrations of essential amino acids to take advantage of their lower nitrogen density, but also provided a source of vitamins and minerals, and additional calories from fats and carbohydrates. Such high essential amino acid protein sources

Table 2
Recommended daily nutrient intake in urea cycle disorders

	Nutrient				
Age	Patient protein intake* (g/kg)	Protein (g/kg)	Patient energy intake* (kcal/kg)	Energy (kcal/kg)	Fluid (mL/kg)
Infants					
0 to <3 mo	2.1–1.4	2.20–1.25	150–101	150–125	160–130
3 to <6 mo	1.5–1.2	2.00–1.15	100–80	140–120	160–130
9 to <12 m	1.2–1.1	1.60–0.90	80–75	120–110	130–120
Girls and boys	(g/day)	(g/day)	(kcal/day)	(kcal/day)	(mL/day)
1 to <4 yr	18.6–12.5	8–12	800–1040	945–1890	945–1890
4 to <7 yr	21.0–19.0	12–15	1196–1435	1365–2415	1365–2445
7 to <11 yr	22.0–24.0	14–17	1199–1693	1730–3465	1730–3465
Women					
11 to <15 yr		20–23		1575–3150	1575–3150
15 to <19 yr		20–23		1260–3150	1260–3150
≥19 yr		22–25		1785–2625	1875–2625
Men					
11 to <15 yr		20–23		2100–3885	2100–3885
15 to <19 yr		21–24		2200–4095	2200–4095
≥19 yr		23–32		2625–3465	2625–3465

* Data are for Case 1 patient.
Modified from Acosta PB, Yannicelli S. Nutrition support protocols. Columbus, OH: Ross Products Division, Abbott Laboratories; 2001; with permission.

have helped meet all essential amino acid requirements. At 10 years of age, the child's growth continues to be satisfactory: height 25th percentile and weight 50th percentile.

Case 2

Onset of hyperammonemia

Medical history

A 10-year-old African-American female presented to a tertiary care ER with ataxia, disorientation, and mild hemiplegia. She had no known prior encephalopathic or other unusual episodes. She may have mildly self-restricted protein intake. She had reached menarche just 2 months before presentation. Her initial plasma ammonia concentration was 330μmol/L. A presumptive diagnosis of a urea cycle disorder was made and she was treated with intravenous sodium benzoate and sodium phenylacetate (Ammonul), L-arginine, and substantial IV and enteral carbohydrate intake. The plasma ammonia concentration dropped some 100 μmol/L in 2 hours, and soon returned to normal. However, it spiked twice over the next 5 days for no apparent reason, eventually tapering to normal. The girl suffered no intellectual deficit and was initially discharged on a regimen of protein restriction at 1.0 g/kg/d, sodium phenylbutyrate (Buphenyl) 308 mg/kg/d (20 g/d), and citrulline 108 mg/kg/d (7 g/d), the latter two dose levels represent the usual maximum adult dosage for her weight of 65 kg. She was later identified as a symptomatic carrier for ornithine transcarbamylase (OTC) deficiency; she had an affected male cousin in the maternal line.

Clinical course

Ten months later, the patient became progressively disoriented over 24 to 48 hours, shortly after her menses began. Upon admission, she exhibited a reduced level of consciousness. Her initial plasma ammonia concentration was between 200 and 225 μmol/L (Fig. 1). It was reduced to a normal concentration within 24 hours following administration of IV sodium benozoate and sodium phenylacetate (Ammonul) and L-arginine as before; the patient was then

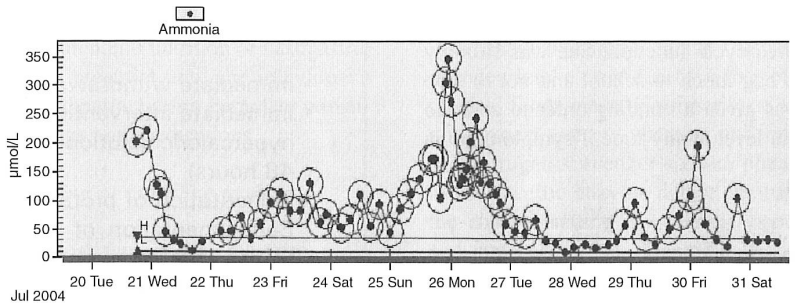

Fig. 1. Plasma ammonia concentrations following admission for disorientation.

fed orally and given oral sodium phenylbutyrate and citrulline. Several days later she showed a nighttime spike in plasma ammonia concentration to 350 μmol/L, followed by a fall to120μmol/L, and then another spike to 250 μmol/L. High-carbohydrate total parenteral nutrition was resumed and insulin was administered to block tissue catabolism. These measures reduced plasma ammonia concentration and were followed by progressive reinitiation of food and oral medication. Three more spikes in the patient's ammonia level were seen on three successive nights. Ultimately she stabilized and was discharged.

During the last 4 days of hospitalization, the patient was not encephalopathic; she was clinically well and normoammonemic every morning. However, she had a regular re-elevation of her ammonia level nightly. There was no evidence for an infectious etiology. During this period she was inactive and confined to bed, which might have led to the mobilization of muscle mass, and resulted in significant quantities of nitrogen that had to be processed. Moreover, the girl was an adolescent with an irregular dietary pattern: she would eat breakfast and then skip food until dinner. It is also possible that she was experiencing asymptomatic hyperammonemic spikes quite frequently at home.

In this young lady's case, it is also quite possible that the cyclic anabolism and catabolism associated with her normal menstrual cycles played a role in triggering her hyperammonemic episodes, although these potential confounding and complicating effects have not been addressed systematically in the urea cycle disease literature. Anecdotal evidence suggests that menstruation may provoke crises in a minority of symptomatic OTC females and is presumably most problematic in those individuals with marginal hepatic urea synthesizing capacity. In females where this pattern is pronounced, instituting a "sick day" dietary regimen for the premenstrual or menstrual period would seem reasonable.

Discharge regimen

To minimize hyperammonemic spikes, the patient was placed on a regular diet limited to 50–60 g/d of high quality natural protein (although her dietary recall suggested that she was already self-restricting her protein intake to 40–50 g/d). She was also prescribed 6 tbsp/d amino acid-modified medical food (Cyclinex-2) at bedtime to enhance essential amino acid nutrition, 20 g/d sodium phenylbutyrate to promote urinary nitrogen excretion, and 7 g/d citrulline to optimize residual urea cycle function. She was strongly encouraged to bring a bag lunch to school and not to skip her noon meal. She was given a standing order to come to our ER for an ammonia level at any time if symptomatic in any way.

Outcome data

The patient is currently 13 years old and postpubertal, 5 feet 5 inches tall, mildly obese at 82 kg, and exhibits high mental development and excellent school performance. Although she does get her ammonia checked when she is experiencing headache or feeling "off" (about every 2 months), she has not had any hyperammonemic episodes since the admission described above. The long-term diet issues have largely involved reasonable spacing of the patient's food and protein intake throughout the day.

Discussion

Nutrition management: acute therapy

Nutrition management of urea cycle enzyme deficiencies is divided into acute and chronic therapy and depends on the specific enzyme defect. The general strategy for acute therapy is outlined in Box 1 and amplified below.

Immediate withdrawal of protein

During the hyperammonemic episode, external nitrogen sources must be eliminated. Thus dietary protein should be temporarily withdrawn and adequate energy intake provided from non-protein sources.

Immediate intervention with non-protein hypercaloric solutions

Start infusion of dextrose 10% solution and fat emulsion (Intralipid) 20% (beginning at 2 g/kg/d) to be administered as peripheral parenteral nutrition. Sufficient energy cannot be delivered through this route to meet long-term nutritional needs. Thus, if a patient requires parenteral nutrition (PN) for longer than 48 hours, a central venous catheter should be placed to provide a higher concentration of non-protein calories (dextrose 12%–30%). Also, sodium and potassium salts can be added initially or as part of PN to meet the body's salt requirements. Once the vital signs are stable, the sensorium is clear, and the emesis has ceased, every effort should be made to use nitrogen-free enteral feeds made with protein-free formulas. Recommended energy intake guidelines are shown in Table 2. If not tolerated, antiemetic medication should be administered to transition to enteral feeds. If the patient cannot take nutrients by mouth, institute nasogastric or g-tube feeds by constant per-

Box 1. Acute therapy strategy

- Immediate withdrawal of protein
- Immediate intervention with non-protein hypercaloric solutions (for the first 24–48 hours)
- Reinstitution of protein and oral nutrition
- Supplementation of L-arginine or citrulline to use alternative pathway
- Fluid management
- Nitrogen scavenging medication

fusion. Total volume of the formula prescribed will depend on the intracranial pressure. Should problems arise with administering the entire volume enterally, a combination of enteral and parenteral feedings can be provided, which may be advanced to total parenteral nutrition (TPN) if necessary. As illustrated in Case 1, the latter should be a high-energy solution consisting primarily of dextrose 25% in water and fat emulsion 20%.

Reinstitution of protein and oral nutrition

As plasma ammonia concentration reverts toward normal, there is a transitional period of PN plus some oral feeds. During this time, protein content is slowly increased. After 24–48 hours of protein-free energy intervention, reinstitution of protein is begun with approximately 25%–50% of the prescribed amounts, slowly advancing to tolerance. It is essential to meet protein and energy requirements to prevent catabolism. Several different amino acid solutions are currently available as protein sources to be offered as a component of TPN. If a patient is partially tolerant of enteral feeds, some protein may be supplied by carefully measured infant formula or human milk obtained by pumping breast milk. However on-demand breast feeding is rarely feasible because of uncontrolled volume and protein intake.

In the recovering younger patient who has been in a hyperammonemic coma, it often takes a day or two for the individual to awaken sufficiently to feed. Nevertheless, it is important to initiate some form of gastric feeding as early as possible. For those who have not had placement of a nasogastric or nasojejunal tube, introduction of such an aid, even while the patient is still on dialysis, allows formula to be dripped into the gut to prepare it for full enteral feeding. In the older patient, a potential impediment to recovery from an acute hyperammonemic episode is prolonged and fluctuating degrees of obtundation. When coupled with anorexia, common in the recovery phase, this situation can substantially complicate feeding and reestablishment of positive nitrogen balance, as well as the transition to orally administered ammonia scavenger medication. Prolonged inflammatory effects from a lingering viral infection coupled with catabolism of muscle mass from bed rest may likely complicate the recovery period as well. And, although it does not seem to have been studied in detail, the timing of both protein feeding and administration of ammonia scavengers can also be a confounding factor. Provision of positive energy balance using total parenteral nutrition or nasogastric or g-tube pump feedings is essential until the individual's level of consciousness and appetite permit complete reinstitution of normal oral feedings and medications.

Supplementation of L-arginine or citrulline to use alternative pathway

An interesting biochemical fact is that the urea cycle not only makes urea, but also L-arginine. This amino acid becomes conditionally essential in the absence of a functioning urea cycle, and, in fact, the body triggers protein catabolism to produce L-arginine when supplies are low. Thus, L-arginine supplementation is a very important concept in nutrition management of these disorders. Administration of L-arginine base at 100–500 mg/kg/d enhances nitrogen loss by increasing citrulline and argininosuccinic acid excretion in ASL and ASS deficiencies [1]. L-arginine can be given in the IV form if the patient cannot tolerate oral feeds. Citrulline 100–170 mg/kg/d is used in carbamyl phosphate synthetase and OTC deficiencies [1], because additional nitrogen is used in the synthesis of L-arginine from citrulline.

Clinicians should bear in mind that excessive amounts of L-arginine intake can lead to hyperargininemia and the formation of argininosuccinate, and may generate a hepatotoxin [2]. Treatment-induced hyperargininemia is toxic and can lead to spasticity. This may be of particular concern in aberrations in the proximal urea cycle enzymes. Treatment must be individualized because all patients react differently.

Fluid management

Adequate hydration is important to promote excretion of metabolic waste. Give water to supply a minimum of 1.5 mL/kcal or give 1–1.5 times the normal amount of maintenance fluids to meet minimum fluids needs.

Nitrogen scavenging medication

The pharmacologic management of hyperammonemia is discussed elsewhere in this supplement by Summar and coworkers and Smith and colleagues. Management of hyperammonemia during acute episodes is best managed by aggressive nutrition intervention in conjunction with a pharmacologic approach to provide alternative methods of waste nitrogen excretion. In the presence of significant plasma ammonia elevations, any delays in aggressive nutrition therapy may result in the need for dialysis, which only compounds the nutrition problem. Because dialysis removes nutrients, energy and nutrient requirements may be increased by as much as 20%. This in turn may exacerbate catabolism caused by decreased protein synthesis and increased proteolysis [3]. Nutrition interruptions should be minimized and coordinated with the nutritionist.

Nutritional management: chronic therapy

Chronic nutritional therapy usually consists of limited nitrogen intake provided by a mix of intact dietary protein, medical foods made up primarily of essential amino acids or non-protein energy, vitamins and minerals, fluids, and the oral nitrogen scavenger sodium phenylbutyrate. In addition to the specific enzyme defect, appropriate protein intake in the chronic setting is generally dependent on growth rate and state of health. Recommended ranges of protein that may be tolerated by patients of different ages are presented in Table 2. As illustrated by the case reports, many factors may complicate protein requirements. Precise minimum pro-

tein requirements for infants and children are difficult to calculate because of the large variability in growth. In general, the most widely accepted recommendations are those published by the Food and Agriculture Organization and the World Health Organization, which define safe intake for most individuals. However, the recommendations shown in Table 2 are specific for urea cycle disorders based on clinical observations. The discussion below anticipates some of the more common management problems and offers a guide to minimizing them.

Maintain positive nitrogen balance

The key to successful nutrition management for patients who have urea cycle defects is to maintain positive nitrogen (N) balance: protein synthesis must be greater than protein catabolism. As infant growth slows, usually around 6 months of age, protein requirement declines per kg of body weight [4]. During the prepubertal growth spurt, protein requirement increases considerably.

Maximum tolerated protein should be prescribed, with approximately 50% to 60% supplied by essential amino acids. When ingestion of intact protein is low, essential amino acids fail to meet recommendations. Thus medical foods (amino acids, in either liquid or solid form, that yield a protein equivalent calculated as grams of N × 6.25) are required to help prevent growth failure. When medical food supplies 50% to 60% of prescribed protein, it assures that adequate amounts of minerals, trace minerals, and vitamins are provided [5]. As suggested for acute therapy, infants may obtain the remainder of protein by carefully measured infant formula or human milk obtained by pumping breast milk. Again, on-demand breast feeding is rarely feasible because of uncontrolled volume and protein intake.

Provide adequate essential amino acids

Scaglia and coworkers [6] and Lee and coworkers (elsewhere in this issue) suggest that patients with a urea cycle enzyme defect who are treated with protein restriction and sodium phenylbutyrate may develop low concentrations of branched-chain amino acids (BCAAs). Because abnormally low concentrations of plasma BCAAs can reduce the threshold for protein catabolism in patients with a UCD, these patients may fluctuate between protein insufficiency and sufficiency, making them difficult to control. Hypothetically, increased intake of BCAAs in conjunction with sodium phenylbutyrate could possibly allow greater restriction of protein for improved control and less likelihood of catabolism. As noted in Table 3, all the medical foods supply greater amounts of BCAAs than human milk, whole cow's milk, or whole egg, and use of medical foods in the proportion suggested assures appropriate supplies of these nutrients.

Table 3 compares the protein, essential amino acid, and energy content per gram of protein of milk, egg, and various

Table 3
Comparison of nutrient content of protein sources (per gram of protein)

				Amino acid modified medical foods						
Nutrient	Human milk (per 98 g)	Whole cow's milk (per 31 g)	Whole egg (per 8 g)	Cyclinex -1 (per 13 g)	Cyclinex -2 (per 6.7 g)	Essential amino acid mix (per 1.3 g)	WND-1 (per 15.4 g)	WND-2 (per 12.2 g)	UCD-1 (per 1.79 g)	UCD-2 (per 1.49 g)
Energy, kcal	69	19	12	68	32	4	77	34	4.5	4.3
Protein equiv, g	1	1	1	1	1	1	1	1	1	1
Amino acids, mg										
Alanine	35	32	59	0	0		0	0	0	0
Arginine	42	23	65	0	0		0	0	0	0
Aspartic Acid	80	73	106	0	0		0	0	0	0
Carnitine	N/A	N/A	N/A	25	25				0	0
Cystine	19	5	22	40	40	49	31	21	55	0
Glutamic acid	165	201	134	0	0		0	0	0	0
Glycine	25	23	34	0	0		0	0	0	0
Histidine	23	23	25	48	48	49	68	45	55	54
Isoleucine	55	51	54	170	170	135	152	103	136	133
Leucine	93	82	87	289	289	210	308	205	229	224
Lysine	67	43	73	148	148	172	191	129	161	159
Methionine	21	23	30	45	45	49	39	25	55	106
Phenylalanine	45	46	54	120	100	74	103	69	95	210
Proline	80	106	41	0	0		0	0	0	0
Serine	42	33	78	0	0		0	0	0	0
Taurine	N/A	N/A	0	5	4				0	0
Threonine	45	44	44	100	100	148	131	88	107	106
Tryptophan	17	23	13	37	37	31	60	40	39	42
Tyrosine	52	47	40	117	117	123	123	83	116	0
Valine	62	60	68	190	190	189	152	103	161	159

Data from Acosta PB, Yannicelli S. Nutrition support protocols. Columbus, OH: Ross Products Division, Abbott Laboratories; 2001, and U.S. Department of Agriculture, Agricultural Research Service. USDA national nutrient database for standard reference, release 17. Available at: http://www.nal.usda.gov/fnic/foodcomp. Accessed June 8, 2005.

medical foods [7,8]. Cyclinex-1, for example, provides considerably more energy per gram of protein equivalent (N × 6.25) than other protein sources. Human milk is similar to amino acid modified medical food with iron (Cyclinex-1) in energy content per gram of protein, but distinctly lower in total protein content than cow's milk. That is why an infant with a mild urea cycle enzyme defect may not present until the transition from human milk to proprietary infant formula or whole cow's milk. Amino acid modified medical foods used for older patients (Cyclinex-2, WND-2, UCD-2) provide a higher protein-to-energy ratio.

To offset restricted protein intake, non-protein energy intake must be increased to meet requirements for physical activity and growth. If not, energy, the first requirement of the body, will be supplied by protein catabolism. Additional non-protein energy sources not only help prevent catabolism of body protein and decompensation, they maximize use of amino acids for protein synthesis, a phenomenon called "protein sparing effect." In general, energy intake must match resting energy expenditure plus an additional percentage (usually about 25%) to cover these needs. Although energy requirement per kilogram of body weight decreases with age, the total amount of energy required increases (Table 2).

Energy is obtained from medical food, intact protein (cereals, vegetables, and modified high-protein foods such as low-protein cheeses, peanut butter, and other products), protein-free energy sources such as the protein-free diet powder (Product 80,056; Mead Johnson), protein-free diet powder with iron (ProPhree), and very low protein foods (a variety of sources including popsicles, juices, and fruits). The percentage of energy supplied as medical food or intact food varies depending on the extent of each individual's food intake.

Individuals and families may not always report intake accurately, either out of inadvertence or active misrepresentation. Clinical experience would suggest that active misrepresentation of dietary protein intake would be more prominent in older children and adolescents as opposed to infants, toddlers and young children. In either case, such discrepancies must be taken into account when calculating calorie, protein, and medication prescriptions.

Manage fluids

Dehydration is often a trigger for hyperammonemia and proper fluid supplementation is often overlooked by parents and caregivers in the chronic setting. Water (fluid) intake by the infant should be at least 1.5 mL/kcal. After the first year of life through adulthood, fluid requirements decrease to about 1.0 mL/kcal.

Titrate the phenylbutyrate dose to maximize protein tolerance

Phenylbutyrate dosing up to a maximum of 500 mg/kg/d or 20 g/d allows the addition of increased amounts of intact protein. The prescription of age-appropriate protein intake containing as much intact protein as possible improves diet compliance and quality of life.

Assess dietary intake

Monitoring nutrient consumption allows for the titration of protein intake with sodium phenylbutyrate, coordination of medications and foods, and evaluation of nutrient adequacy. Protein and energy intake should be correlated with plasma amino acid concentrations. The adequacy of both macro- and micro-nutrient intake should also be watched. Some medical foods do not contain all required nutrients, and the amount of tolerated protein usually fails to provide adequate micro-nutrients. For example, there are no vitamins and minerals in the essential amino acid mixture by Scientific Hospital Supplies (Gaithersburg, Maryland), and selenium is missing in UCD-1 and UCD-2 by Mead Johnson.

Appropriate monitoring requires a 3-day diet record. A 1-day dietary history is of little use because intake in infants and children, even normal children, is very erratic.

Monitor potassium levels and include high potassium foods in diet

A retrospective chart review of six patients with ASL deficiency over the course of 36 months revealed frequent plasma potassium concentrations below the lower limit of reference ranges. This was particularly common in association with hospital admission for acute management, which normally includes high intakes of dextrose and insulin, driving potassium with glucose into the cell. The reason for hypokalemia in these patients is uncertain. Potassium supplements should be given if potassium from diet sources is inadequate to maintain plasma potassium concentrations in reference ranges.

Consider devices to assist enteral feeding

In chronic management, placement of a g-tube can contribute significantly to dietary regimen adherence and is strongly recommended for very young patients if prescribed intake is an ongoing challenge. A g-tube relieves the stress associated with a child who eats poorly. Even parents who are initially resistant to the idea of inserting a g-tube will often accept it when they understand that it will help keep their child out of the hospital. Nevertheless, these devices are not free of problems. Their insertion requires a knowledgeable and skilled surgeon and nursing team. Revision is frequent, since patients must be refitted over time with a larger-diameter device to provide a tight fit. Minor infections are frequent as well. Ironically, there may also be some reluctance to remove the g-tube once the patient has acclimated to it.

Reagent strips for urinalysis (Ketostix) are also helpful devices. Primarily designed for diabetics, they are useful for determining when a patient is becoming catabolic, or when energy balance is inadequate for reasons such as nausea, fever, infection, or increased activity.

Facilitate compliance in school-age children

Flavor additives such as Hershey syrup, unsweetened Kool-Aid, and other protein-free flavoring agents may be used to improve the palatability of medical foods. Lunch period at school, where kids want to "fit in," is a challenge for any dietary regimen. One choice is for the child to bring lunch from home. However, choosing items from the school lunch menu is also possible with appropriate forethought and preparations. Most cafeterias now have a salad bar, so if the child brings his/her medical food mixture, they can go through the lunch line with friends. A discussion with the school nutritionist may uncover suitable items among the standard selections, which can be monitored by the kitchen staff or a teacher. There is also the possibility of a parent or nutritionist working with the lunch staff to cook and freeze appropriate lunches in single servings beforehand. The patient then selects other allowable items from the regular menu (fruit, grains, vegetables, etc), and picks up the prepared low-protein entrée at the same time other students are choosing their entrée. Of course, children with a UCD must be educated about the dangers of Bac-O bits in salads and other "hidden" protein.

Birthday parties at school or someone's home, where everyone gets cake or a cupcake, can also pose problems. It is important to have an acceptable alternative available.

The situation has actually become easier among teens with the advent of fad diets, particularly among girls. Few teenagers eat a regular meal at school; they are either restricting energy carbohydrates or fat intake. So a low-protein diet is just one more variation on the diet theme. Furthermore, there are sports energy drinks that fit in with a protein-restricted diet and are considered "cool."

Educate regarding lifestyle choices

In OTC deficient heterozygotes and mild urea cycle disorders, where patients may be less brittle and the diet less severe, a slight dietary latitude may be indulged to the point of metabolic difficulties. Typical problems are dieting, bingeing or other erratic eating patterns, and hangovers from mild hyperammonemia. Patients frequently sneak bolus protein loads: "I had a 'Big Mac' attack," "Can I eat my whole week's protein on Friday night"? or "I thought vegetable protein was safer than animal protein." Sunburn and athletic training (eg, "making weight in wrestling") can also contribute to metabolic stress and thus protein catabolism. Patient and family education should be emphatic and should anticipate these problems.

Provide a "sick-day" regimen

Menarche, menses, pregnancy, childbirth, postpartum, and menopause, as well as medical events such as immunizations, influenza, trauma, surgery, chemotherapy, and the use of glucocorticoids place additional demands on the body and can precipitate a hyperammonemic episode [9–11]. A sick-day diet regimen with additional energy may be required before or following these events (Box 2). For example, energy requirements are increased during infection by some 12% for each centigrade of elevated temperature [12]. Following childbirth, protein intake may require further restriction because of catabolism, while energy intake may need to be increased for up to 2 weeks [10]. Families should be provided in advance with a sick-day prescription.

Box 2. Sick-day diet regimen

- Decrease protein intake 50% to 100% for 24 to 48 hours
- Increase non-protein calories by 25% to 50%
- Ensure fluid intake from 1× to 1.5 × normal maintenance levels
- Maximize sodium phenylbutyrate dose temporarily if prescription is not already at age-appropriate maximum
- Give nausea medication as required
- Aggressively treat the underlying illness
- If symptoms do not disappear within 24 to 48 hours, report (or take patient) to ER
- Bring emergency letter provided for ER personnel
- Contact on-call member of the genetic team

Certain other medical events may have unanticipated effects on patients with a urea cycle disorder and require appropriate caution. Total parenteral nutrition that contains protein and is used as nutrition support during stressful events like surgery has been reported to trigger hyperammonemic coma in women with heterozygous OTC defect [13]. Valproic acid, an anticonvulsant used to treat epilepsy, has been reported to cause hyperammonemia in patients both heterozygous and homozygous for UCD [14–18]. As with all patients, valproate also affects carnitine metabolism, resulting in its deficiency [19]. Therefore, levels of this fat transporter should be evaluated.

Summary

Nutritional management of patients with urea cycle disorders is one of the most challenging tasks in clinical nutrition. The degree to which protein intake should be restricted in urea cycle disorders requires complex calculations which depend on many variables such as specific enzyme defect, age-related growth rate, current health status, level of physical activity, amount of free amino acids administered, energy intake, residual urea cycle function, family lifestyle, use of nitrogen-scavenging medications, and the patient's eating behaviors. The key to successful nutrition management is maintaining a positive nitrogen balance (protein synthesis > protein catabolism). This involves balancing intake of intact protein and medical foods that contain essential amino acid to help prevent growth failure. It also requires increased energy intake to prevent

the body from supplying energy via protein catabolism. Supplementation of the urea cycle intermediates arginine and citrulline is also involved. Nutritional support measures that may help prevent common triggers of metabolic decompensation include use of a nasogastric or gastrostomy tube to assist enteral feeding, facilitation of proper food choices in school-age children, proactive patient and family education, and design and careful implementation of a higher-energy "sick-day" regimen for demanding life changes and medical events.

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