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REVIEW

Nutritional management of patients with urea cycle disorders

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Summary The nutritional management of patients with urea cycle disorders (UCDs) involves restriction of dietary protein along with provision of adequate protein-free energy, essential amino acid supplements, and vitamins and minerals in combination with nitrogen-scavenging drugs. The present paper discusses nutrition therapy for a range of circumstances: during an acute hyperammonaemic episode and at hospital discharge; before, during, and after surgery; and for lifelong chronic management of UCDs.

Abbreviations

ARG	arginase deficiency
ASL	arginosuccinicaciduria
ASS	citrullinaemia
BCAA	branched-chain amino acid
NBS	newborn screening
UCD	urea cycle disorder

Introduction

Screening and diagnosis

The Health Resources and Services Administration of the US Department of Health and Human Services and the American College of Medical Genetics both recommend newborn screening (NBS) for three of the six urea cycle disorders (UCDs): arginosuccinicaciduria (ASL), citrullinaemia (ASS), and arginase deficiency (ARG) (Anonymous 2006). Newborn screening for these disorders facilitates early diagnosis, is likely to improve outcomes, and makes the most efficient use of the health care team. Early detection of these three disorders may allow for the judicious use of nitrogen-scavenging drugs, together with adequate and rapid nutritional intervention, with the aim of improving the outcome.

Even with the use of NBS, not all UCDs are detected during the newborn period. In clinical practice, patients can be categorized into early-onset or late-onset. The early-onset or neonatal group tends to have more severe forms of the disorders than the late-onset group, who present after the neonatal period (Brusilow and Horwich 2001). Patients from the latter group have presented to clinic at ages ranging from infancy to 60 years with symptoms from minor behavioural changes to coma.

Disease severity

The clinical presentations of patients with UCDs may differ depending on genotype, residual enzyme activity, and protein intake (Acosta et al 2005; Brusilow and Horwich 2001). Clinical work with UCDs has revealed considerable variation in protein tolerance, with age, sex, and genotype all contributing to this variability. Patients with the mildest forms of a UCD may tolerate a normal diet, in contrast to patients with a severe form, who will require a very restricted diet. Thus, it is important to emphasize that diets for these

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patients must be individualized, in spite of the availability of drugs that enhance waste nitrogen loss.

Outcomes

UCDs are marked by an accumulation of glutamine in astrocytes, as well as astrocyte oedema and dysfunction with resulting encephalopathy (Norenberg et al 2005). The neurological outcome of patients with UCDs depends on many factors, including the age at diagnosis, the degree of enzyme impairment, the time when diet therapy is initiated, and the number, duration, and severity of hyperammonaemic episodes, although the predictive value of some of these factors is uncertain (Nicolaides et al 2002). The relationship between elevated plasma concentrations of ammonia and glutamine with poor neurological outcome is well known, as discussed by Gropman and colleagues elsewhere in this issue.

Hyperammonaemia

Approximately 16% of protein by weight is nitrogen (N) (Berry and Steiner 2001), and the main sources of waste N are the breakdown of food proteins and catabolism of body proteins. In a healthy person, amino acids that are not needed for protein synthesis are metabolized in various biochemical pathways, with the remainder of the N being converted to urea. Inadequate energy, inadequate protein or essential amino acid (EAA) intakes, infections, fever, surgery, extensive physical activity, and labour and delivery may all precipitate catabolism of body proteins in the patient with a UCD. Elevated concentrations of plasma ammonia occur when there is a defect in one of the enzymes of the urea cycle that normally convert waste N to urea.

Treatment

The aim of treatment for the patient with a UCD is to maintain normal plasma ammonia and amino acid concentrations with nutritional management and drug therapy. Nutritional therapy for a UCD consists of a protein-restricted diet supplemented with an EAA mixture high in branched-chain amino acids (BCAAs) to ensure adequate intakes of essential and conditionally essential amino acids. Enough protein-free energy must be administered both to permit the normal turnover of protein necessary at all ages and to prevent net catabolism of body proteins. Monitoring of nutritional status becomes even more critical when both dialysis and medications are used to lower plasma ammonia concentrations, as dialysis may also decrease the concentrations of nutrients in the body and increase catabolism (Pupim et al 2004). The purpose of this paper is to describe current nutritional management practices for UCDs, including acute treatment, treatment during surgical procedures, and management of the chronic phase of these disorders.

Acute treatment

Introduction to acute treatment

An acute hyperammonaemic episode can occur at any age, even after diagnosis. The goal of treatment for all patients during an episode is to reduce concentrations of plasma ammonia. This is best achieved by quickly providing the patient with adequate energy to reduce catabolism and promote anabolism, by temporarily restricting protein intake, and through the use of N-scavenging drugs (Summar 2001).

The following five patients exemplify common presentations of a hyperammonaemic episode: a 4-day-old healthy boy who becomes acutely lethargic and develops seizures and coma; a 5-year-old boy who presents with sleepiness; a 10-year-old girl who arrives at the emergency department with ataxia and disorientation; a 23-year-old woman who becomes comatose during the delivery of her first child; and a 30-year-old woman who becomes comatose after eating a high-protein diet following gastric bypass surgery. Given the broad range of these episodes, it is essential to target nutritional management individually. This section will focus on the treatment of infants suffering an acute episode, because these cases are the ones most frequently encountered during initial diagnosis. The principles for both children and adults are similar, however.

Overall acute nutritional management of the newborn

Example: A newborn infant presenting with an episode appears normal for the first two days after birth, but suddenly experiences poor feeding on the third day. He is irritable and vomiting by the time he is admitted to hospital.

The acute nutritional management of such a newborn infant requires the immediate withdrawal of all protein for 24–48 h. Longer withdrawal of protein may induce catabolism that will worsen the hyperammonaemia. The nutritionist must also attempt to enhance anabolism via an intravenous hypercaloric protein-free solution given with insulin. This should ensure that the energy is used and that the patient becomes anabolic

(Fryburg et al 1995; Wolfe 2005). Plasma ammonia concentrations are controlled by dialysis and/or the use of the intravenous N-scavenging drug Ammonul (sodium phenylacetate and sodium benzoate, 10%/10%) in the USA. In Europe, intravenous preparations are not licensed, but they are available.

In the next phase, oral nutrition is restarted with the addition of a module of high-quality protein. Plasma ammonia concentrations are controlled using the oral N-scavenging medication. Depending on the plasma concentrations of ammonia and amino acids and the activity of the gastrointestinal tract, the feeds may be started at a 25–50% concentration of full protein requirements (e.g. if the full protein requirement for an infant is 1.4 g protein/kg body weight/day, then the starting feeds could range between 0.35 and 0.70 g protein/kg body weight/day), since it is important not to wait more than 48–72 h before reintroducing the feeds. Supplementation with the conditionally EAAs, as well as with L-arginine and/or L-citrulline, becomes essential at this time. Oral L-arginine and L-citrulline are both available, whereas only L-arginine is available in intravenous form. If an older patient becomes nauseated, the use of ondansetron (Zofran) and other antinausea medications may help improve the tolerance of enteral feeds. Adequate energy intake must be ensured throughout this phase.

Ammonia reduction

For the treatment of hyperammonaemia, ammonia may be reduced by dialysis methods. These methods are discussed elsewhere in this publication and include peritoneal dialysis, venovenous haemofiltration, and haemodialysis (Jouvet et al 2001). Each of these methods must be accompanied by nutritional support with the goal of promoting anabolism.

The impact of ammonia reduction methods on nutritional status

Studies in patients with renal failure have shown that 20–25% of the nutrients in plasma are removed from the body during haemodialysis, creating a catabolic state (Ikizler et al 2002). If an infant with a UCD is dialysed without aggressive nutritional management, plasma ammonia concentrations may rebound. If plasma ammonia concentrations are around 1000 μmol/L, we immediately insert a central line and administer large amounts of protein-free energy along with insulin to enhance glucose uptake and promote anabolism. Ensuring weight gain of 15–30 g/day reflects the achievement of an anabolic state in an infant (Fomon et al 1982).

The impact of sodium phenylbutyrate on branched-chain amino acids

Recently, Scaglia and colleagues (2004) showed that depletion of BCAAs may result from administration of sodium phenylbutyrate (Lee et al 2005). Continued low BCAAs may lead to decreased protein synthesis and catabolism, since they are instrumental in the regulation of protein synthesis (Buse and Reid 1975; Lynch et al 2003; Wagenmakers 1998). In an effort to maintain BCAAs within the therapeutic range during acute illness and during chronic management, essential amino acid mixtures with high levels of BCAAs may be given. When comparing the BCAA profiles of human milk, cow's milk, and an essential amino acid mixture, such as Cyclinex-1 (Abbott Nutrition), the concentration of BCAAs was found to be greatest in the essential amino acid mixture (Singh et al 2005) (Table 1a). There is also a wide selection of parenteral nutrition solutions containing BCAAs available for use. The solution with the highest percentage of BCAAs is TrophAmine (10% solution) (Table 1b). For adults, the parenteral nutrition of choice is either 10% HepatAmine or 20% ProSol. See Discharge Guidelines for further information on administering EAA mixtures high in BCAAs.

Decisions about nutritional intervention

If the gastrointestinal tract is functioning (for example, if there are bowel sounds), feeds should be given orally. If the infant is unable to swallow, an enteral feeding tube may be employed. Delays in feeding, regardless of method, must be avoided to prevent catabolism. If the patient is nauseous, a continuous feed works better than intermittent feeds. If long-term enteral feeding is required, surgical placement of a gastrostomy should be substituted for the nasogastric tube. For the comatose patient who has no bowel sounds, parenteral nutrition must be instituted, with feeding through a peripheral line if a central line is not available. Total parenteral nutrition will be required that provides adequate amounts of glucose, lipids, and amino acids. Most commonly, however, the patient is admitted with a partially functional gastrointestinal tract. In these cases, begin peripheral nutrition with lipids and dextrose to arrest catabolism, and then follow with the insertion of a nasogastric tube to deliver a slow, continuous drip of EAAs.

Table 1a Branched-chain amino acid composition of Cyclinex-1 (mg)

Amino acid	Amino acids (per 1 g protein equivalent)			
	Human milk (per 98 g)	Dialamine (Nutricia) (per 4 g)	Essential amino acid mix (Nutricia) (per 1.2 g)	Cyclinex-1 (Abbott Nutrition) (per 13 g)
Isoleucine	55	132	73	170
Leucine	93	205	125	289
Valine	62	185	79	190

Table 1b Branched-chain amino acid composition of some parenteral feeds

Amino acid	Branched-chain amino acids (mg/100 ml)						
	10% Travasol	15% Clinisol	10% TrophAmine	20% ProSol	HepatAmine	Vamin 18 EF	Vaminolact
Isoleucine	600	749	820	1080	900	560	310
Leucine	730	1040	1400	1080	1100	790	700
Valine	580	960	780	1440	840	730	360

Discharge guidelines

At discharge, the patient's family is given written details of the diet. This includes a sample diet guide and instructions for obtaining an EAA mixture high enough in BCAAs to ensure adequate high-quality protein, BCAAs, and energy. Based on our clinical experience with infants, typically about 50% of their dietary protein is provided in the form of an EAA mixture high in BCAAs, which results in maintenance of plasma amino acids within the reference range. As the infant ages, the proportion of dietary protein from this EAA mixture may be decreased to about 25% to allow for a greater variety of natural protein from regular foods, if plasma BCAAs are maintained within the reference range. Monitoring of plasma amino acids will determine the optimal proportion of EAA mixture supplemented. The metabolic dietitian and physician should also explain to parents the UCD symptoms, including a decrease in suck or decreased feeding, which are often seen in an infant who is developing hyperammonaemia, and work closely with them to titrate the N-scavenging drugs with the diet.

All patients must have an emergency plan to prevent decompensation (Leonard 2001). An emergency letter that includes the management protocol is prepared for patients to use in the event of illness. This letter is printed on a small card that is sealed in plastic, so that it may be carried in a purse or wallet. Parents are also instructed to keep a protein-free feed (composed of carbohydrates and frequently fat, vitamins, and minerals), in case of an emergency at home. Thus, if a parent calls to indicate that their child is lethargic, a well-trained and experienced dietitian or physician can direct the parent to use the protein-free feed to possibly avert an emergency. Parents are further instructed to follow up promptly with a local paediatrician or emergency room when warranted.

Some patients find that medications are easier to take with added flavouring. The N-scavenging drug is normally added to the EAA mixture, as the stability of the drug is unaltered after 24 h. If children refuse them, medicines and amino acid supplements should be given by tube (nasogastric or gastrostomy).

Urine ketone reagent strips can be used to assess patients with UCDs. Above-normal concentrations of urinary ketones indicate that a patient is catabolic. After an overnight fast the ketones may increase in the blood to a concentration of 2–6%, and after three days of fasting they provide 30–44% of the body's energy needs (Laffel 1999). If urinary ketones are increased, consumption of juices or other forms of carbohydrates is recommended to help reduce catabolism. Ketone concentrations in the urine of the newborn infant are less predictive of decompensation than they are in older infants, but they do give a useful indication of baseline levels. Urine is collected from the infant by placing a cotton ball in the diaper. The urine is then squeezed out of the cotton ball and tested using the ketone reagent strips, which we have used successfully as a home monitoring tool in our clinic along with other markers (including illness and energy and protein intakes) to assess catabolism for guiding treatment, especially as it relates to energy intake.

Surgical management

Careful attention to metabolic status and nutritional management is necessary before, during, and after surgical procedures. In addition to higher energy needs as a result of surgery (Long et al 1979), patients are at risk for inadequate energy intake because of the necessity for fasting prior to surgery. Patients may also be told to stop taking all medications while fasting. The metabolic dietitian and physician should work with the surgeons to ensure that there is no risk of decompensation prior to or during the surgery by admitting the patient to the hospital before planned surgery and providing them with intravenous glucose and lipid emulsion, as necessary. The surgical team must be reminded to give the patient a dose of N-scavenging drug before surgery, and to double the first dose after surgery, if necessary. If the surgical procedure is lengthy, total parenteral nutrition to provide energy and fluids should be continued during the operation and post surgery. Patients should be given enteral nutrition as soon as the gastrointestinal tract regains function. Unpublished work shows that the gastrointestinal tract has regained some function by 6 hours post surgery, and partial feeding may be started then. This careful attention and teamwork is essential in preventing a rebound in plasma ammonia concentration during or after surgery.

Clinical experience in patients with a UCD receiving a liver transplant confirms the need for close monitoring prior to, during, and following surgery. Before surgery, the patient may be transfused, and albumin replacement is given. Elevated plasma ammonia concentrations may develop quickly, requiring the removal of all dietary protein combined with administration of protein-free energy sources. Hyperalimentation, including dextrose and intravenous L-arginine along with intravenous sodium benzoate and sodium phenylacetate (Ammonul), is used during the transplantation procedure. Two days of sodium phenylbutyrate (Buphenyl) and a low protein intake may be required to normalize plasma ammonia concentrations post-transplantation.

Chronic management

Goals

The goals for long-term management of patients with a UCD are to achieve normal growth and development, to normalize plasma concentrations of ammonia, to prevent protein deficiency by administering essential and conditionally EAAs, and to prevent other nutrient deficiencies, including mineral and vitamin deficiencies. It is not uncommon to observe families failing to feed all the protein prescribed, because they are concerned about elevated ammonia concentrations. This is another reason why regular monitoring of the patient's nutritional status is important.

A detailed record of the diet of each patient is critical to ensure that nutrient intake recommendations, especially for protein, are achieved. If the recommended protein intake is not reached or if blood ammonia and amino acid concentrations are abnormal, the dose of N-scavenging drug may need to be titrated up to the maximum age-appropriate dose for the patient. Such titration will allow maximum protein tolerance for attaining the recommended intake of protein for proper growth and development while avoiding hyperammonaemia. Because of the complexity of the combined dietary and drug treatment, clear coordination between the physician prescribing the drug and the dietitian calculating the diet prescription is necessary. Titration of the drug requires tandem monitoring of plasma ammonia and amino acid concentrations with dietary protein and energy intake.

Nutrient intakes from three-day diet diaries can be calculated using appropriate software (e.g. Amino Acid Analyzer) prior to each blood test. A nutrition diary may reveal unbalanced protein intake during the day; for example, 15 g of protein may have been consumed at a single meal, while the remaining 10 g was given between the other two meals. Because N-scavenging drugs are typically prescribed in three to four equal doses throughout the day, we try to discourage large protein loads. It may be possible, however, to balance the doses of N-scavenging drug with the patient's eating pattern to avoid fluctuation in nitrogen loads and ultimately to prevent hyperammonaemia.

Nutritional adequacy

While few data are available on the growth of infants and children with a UCD, what is known is that historically not enough protein was prescribed to these children to support normal growth. With the proper incorporation of EAA mixtures, however, achievement of adequate dietary protein intake is possible. Acosta and colleagues (2005) recently described a 6-month, uncontrolled outpatient study of 17 infants and toddlers with a UCD who were fed Cyclinex-1. Length and weight *z*-scores rose significantly, and protein status improved; further, three patients were stunted and two were wasted at the beginning of the

Table 2 Recommended daily intakes for patients with UCDs

Age	Nutrient				
	Protein intake[a] (g/kg)	Protein recommendation (g/kg)	Patient energy intake* (kcal/kg)	Energy recommendation (kcal/kg)	Fluid recommendation (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 mo	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 y	18.6–12.5	8–12	800–1040	945–1890	945–1890
4 to <7 y	21.0–19.0	12–15	1196–1435	1365–2415	1365–2445
7 to <11 y	22.0–24.0	14–17	1199–1693	1730–3465	1730–3465
Women					
11 to <15 y		20–23		1575–3150	15757–150
15 to <19 y		20–23		1260–3150	1260–1350
≥19 y		22–25		1785–2625	1875–2625
Men					
11 to <15 y		20–23		2100–3885	2100–3185
15 to <19 y		21–24		2200–4095	2200–4095
≥19 y		23–32		2625–3465	2625–3465

Acosta and Yannicelli (2001).
[a] Protein and energy intake data were collected from a chart review of patients in our clinic.

study, whereas only one patient remained stunted and wasted by the completion of the study. In addition, clinical data from our patients reveal that it is possible to give the recommended amount of protein when titrated appropriately with N-scavenging drugs. Recommended daily intakes of protein, energy, and fluids for infants, children, and adults with a UCD, along with clinical data, are given in Table 2.

Over-restriction of protein and all other nutrients must be avoided to prevent malnutrition. Plasma EAAs, albumin, and transthyretin are monitored every 4 to 6 months, and sometimes more frequently during periods of growth and illness. Patients who consistently over-restrict protein from fear of precipitating hyperammonaemia not only exhibit biochemical markers of poor nutrition, such as plasma concentration of transthyretin, but may also have hair loss and poor growth due to the resulting inadequate intakes of other nutrients besides protein. For instance, arginine deficiency in argininosuccinic aciduria results in a pattern

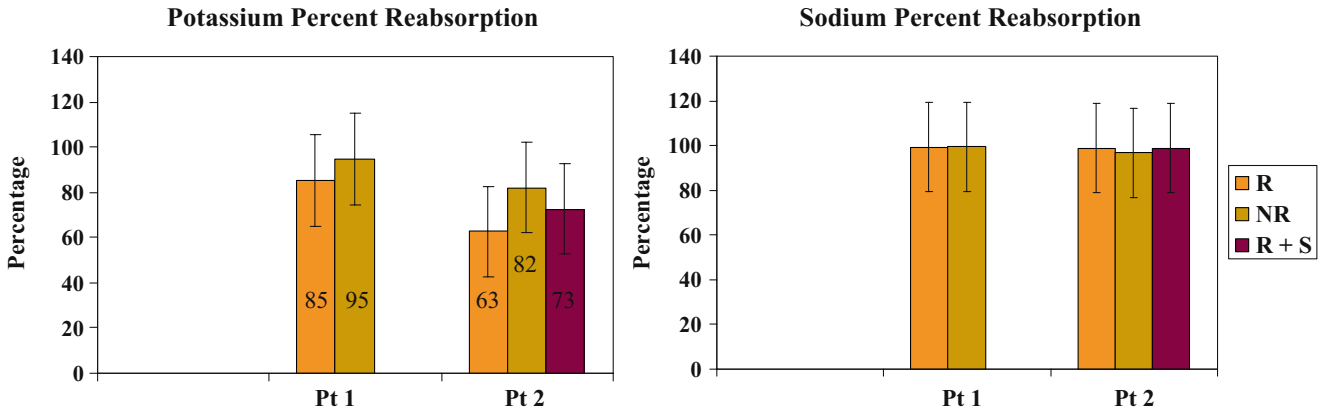

Fig. 1 Potassium and sodium renal tubular reabsorption in two patients with ASL receiving N-scavenging drugs. A balance study included phase 1 on-drug and phase 2 off-drug for both patients, and a phase 3 on-drug with potassium supplements in patient 2 was used to assess the impact of N-scavenging drug on potassium and sodium renal tubular reabsorption. Patient 1 received 478 mg/kg per day sodium phenylbutyrate during period 1, and patient 2 received 326 mg/kg per day sodium benzoate during periods 1 and 3 (Singh et al 2006).

of hair loss called trichorrhexis nodosa. With this condition, nodules form in the hair shafts, resulting in the splitting and breaking of the hair.

Protein-free energy

An adequate supply of protein-free energy is important to prevent catabolism, but it is also important that this energy not be consumed in excess to avoid overweight and obesity. In a survey of our clinic patients with UCDs, most had lower than normal muscle mass and were overweight for height. Because children and their parents know that consumption of carbohydrates will not lead to hyperammonaemia, the child often eats more carbohydrate and thus more energy than prescribed, thereby becoming overweight. This may result in potential inaccuracies in N-scavenging drug prescriptions based on body weight. Additionally, attempts to reduce body weight through reduced energy intake can be difficult, due to the risk of catabolism. Underweight children, by contrast, require the use of excess energy for catch-up growth, and this energy must be balanced by adequate amounts of EAAs from EAA mixture.

Vitamins and minerals that are required for normal nutritional status are not provided by a mere 0.5–1.0 g of natural protein per kg of body weight. For patients with a UCD, the use of an EAA mixture, which contains high BCAAs as well as vitamins and minerals, helps to ensure an adequate supply of most nutrients. If EAA mixtures containing vitamins and minerals are not given, then appropriate vitamin and mineral supplements should be considered.

Low plasma concentrations of potassium have been found in patients with ASL who suffered from vomiting and diarrhoea while on N-scavenging drugs. Inpatient studies conducted at a specialized centre for clinical investigations are shown in Figure 1. The results from two patients who were given their usual protein intake in period 1 and a lower protein intake in period 2 indicate that renal tubular reabsorption of potassium was much lower in the patient on sodium benzoate than in the patient on sodium phenylbutyrate. During period 3 for patient 2, potassium chloride was administered with sodium benzoate, and the renal tubular reabsorption of potassium improved. Renal tubular reabsorption of sodium was unaffected by N-scavenging drugs. We hypothesize that these drugs are large, anionic molecules that interfere with potassium exchange in the tubule and may be one of the factors contributing to low potassium levels in patients with ASL. Maintenance of nutritional therapy in patients with ASL and ASS disorders includes the administration of L-arginine (400–700 mg/kg body weight) in three or four divided doses. L-Citrulline (170 mg/kg body weight per day) is administered to patients with CPS I or OTC deficiency (Batshaw et al 2001). Citrate and carnitine are not routinely administered, except as part of Cyclinex-1. An assortment of EAA mixtures and low-protein foods are readily available to patients. These products can be purchased by patients directly from many companies online. The low-protein foods provide variety in taste, texture, and colour to the diet of the child with a UCD, while enhancing anabolism through provision of adequate protein-free energy (Table 3).

Table 3 Some low-protein food substitutes compared with regular foods

Regular food/Substitute	g protein
1 tbsp peanut butter	4
1 tbsp low-pro peanut butter (Dietary specialties)	0
1 slice cheese	3
1 slice low-pro cheese (Cambrooke foods)	<1
Milkshake (298g)	8
Low-protein smoothie (298g) (Frostline)	0
Hamburger 2.5oz (70g)	18
Camburger 2.5oz (Cambrooke foods)	1

Conclusions

The key to improving neurological outcomes in patients with UCDs is minimizing brain exposure to excess ammonia. To accomplish this, patients with a UCD need a metabolic team well versed in proper nutritional management in any circumstance, from acute treatment and treatment for surgery to chronic management. For infants detected and positively

diagnosed soon after birth through newborn screening, chronic nutritional management can be pursued immediately with a reasonable hope for an improved outcome. For infants, children, and adults who are diagnosed as a result of a hyperammonaemic episode, their first encounter with the metabolic team is likely to be for acute treatment. A metabolic team experienced in sound treatment protocols will permit the quickest possible treatment and ensure the best possible neurological outcomes in patients with UCDs.

Although a great deal of research and clinical experience has contributed to the formation of current treatment guidelines and practices, much more research is needed to develop evidence-based guidelines.

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