Nutrition Management of Maple Syrup Urine Disease

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Contents

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Core Messages

- Maple Syrup Urine Disease (MSUD) is caused by a deficiency in the branched-chain ketoacid dehydrogenase enzyme complex that metabolizes the ketoacids of leucine, isoleucine and valine.
- Infants with classical MSUD can present with intoxication syndrome and require aggressive nutrition support to prevent or reverse catabolism.
- Nutrition management includes use of medical foods devoid of branched-chain amino acids, dietary leucine restriction, supplemental valine and isoleucine, and provision of adequate energy, protein, vitamins and minerals.
- The goal of therapy is to maintain plasma leucine concentrations of 100–200 μmol/L for infants and children <5 years and 100–300 μmol/L for those over 5 years of age.

17.1 Background

Maple Syrup Urine Disease (MSUD) is an inborn error of the branched-chain α-ketoacid dehydrogenase (BCKADH) enzyme complex required for the catabolism of the branched-chain amino acids (BCAA) leucine, valine, and isoleucine [1] (Fig. 17.1). MSUD is rare in the general population with an incidence of 1 in 200,000 live births, but in the Old Order Mennonite population, the incidence is approximately 1 in 350 live births due to a founder variant (c. 1312T > A) in the BCKADHA gene [2]. MSUD is so-named because patients with this disorder have a characteristic sweet odor detectable in the urine and cerumen.

Of the BCAA, leucine and its corresponding ketoacid, alpha-ketoisocaproic acid are the primary toxic compounds in this disorder. The pathophysiology of MSUD is not completely understood; however, all three BCAA share common transporters at the blood-brain barrier that have a higher affinity for leucine compared to other amino acids [3, 4]. In cerebral tissue, increased leucine leads to an underlying depletion of glutamate and increased

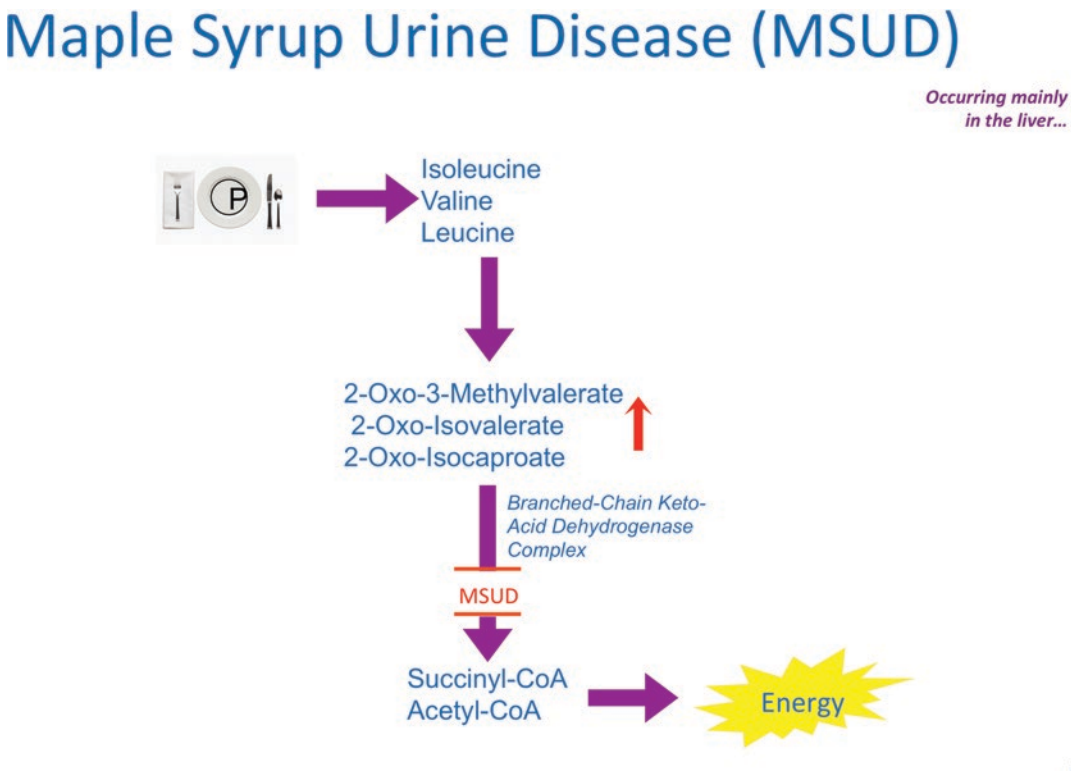

Fig. 17.1 Metabolic pathway in the metabolism of the branched-chain amino acids leucine, isoleucine, and valine

lactate concentrations. Glutamate is an excitatory neurotransmitter and depletion has been associated with learning and memory deficits, depression, and anxiety [5]. Additionally, elevated leucine in the brain alters water homeostasis, increases oxidative stress, and competes with entry of other amino acids into the central nervous system affecting protein signaling and production of other neurotransmitters [3, 6]. Elevated leucine increases renal sodium losses that can lead to hyponatremia and contribute to the development of cerebral edema [3]. Additionally, abnormal biomarkers of inflammation have been measured and may have a role in the pathophysiology [7].

Neonates with classical (severe) MSUD come to attention shortly after birth with poor feeding, weak suck, and weight loss, progressing to a metabolic intoxication crisis (Chap. 4). This is characterized by lethargy, irritability, vomiting, and fluctuating muscle tone. If the infant is not treated immediately, seizures, cerebral edema, and coma can be fatal [3, 4]. There are several classifications of disease severity, including classical (<2% enzyme activity) and intermediate, intermittent, and thiamin-responsive variants [1]. BCKADH is a thiamin-dependent enzyme and individuals with residual enzyme activity may benefit from thiamin supplementation, but those with classical MSUD do not. Nevertheless, a trial of thiamin is often completed (doses 50–200 mg/d for four weeks) to assess response [8]. Patients with variant forms of MSUD may present later in infancy or childhood with poor growth and developmental delay, or with nonspecific symptoms such as confusion, ataxia, or acute psychosis in older individuals [9]. Newborn screening identifies infants with high blood leucine, although those with classical MSUD can be symptomatic before newborn screening results are available, while those with variant forms may not be detected [9]. The diagnosis is based on clinical symptoms and a plasma amino acid profile with elevated concentrations of leucine, valine, and isoleucine and the presence of allo-isoleucine, a derivative of isoleucine that is a specific marker of MSUD [1]. Genetic testing can further confirm the diagnosis with predictive phenotype-genotype correlation [1, 10].

Nutrition management for MSUD has improved greatly (Box 17.1) and, with vigilant care, can result in good cognitive and developmental outcomes, especially if illnesses or other catabolic events are aggressively managed [11, 12]. Liver transplantation is an option for the treatment of this disorder [13].

Box 17.1: Principles of Nutrition Management for MSUD

Restrict:	Leucine
Supplement:	Valine and isoleucine, if plasma concentrations are low Thiamin[a]
Toxic metabolite:	Leucine and its keto-acid, alpha-ketoisocaproic acid

[a]A trial of 50–200 mg thiamin is given in some centers for patients with variant forms of MSUD

17.2 Nutrition Management

17.2.1 Chronic Nutrition Management

Patients who present with symptoms in the newborn period and have been medically stabilized, as well as those who are asymptomatic at diagnosis, are started on a leucine-restricted diet. Table 17.1 provides suggested goals for nutrient intakes for both symptomatic and asymptomatic infants with MSUD [4, 8, 14]. The source of intact protein to meet leucine needs can be provided by a standard infant formula; however,

Table 17.1 Suggested daily nutrient intakes for infants with classic MSUD during metabolic decompensation (initial presentation or when acutely ill) and when asymptomatic [8, 14]

	Acute [14]	Asymptomatic [8, 14]
Energy (kcal/kg)	120–140	100–120
Lipid (% of energy)	40–50%	DRI
Protein (g/kg)	3–4	2–3.5
Leucine (mg/kg)	0	40–100 mg/kg
Isoleucine (mg/kg)	80–120	30–95
Valine (mg/kg)	80–120	30–95

breast milk (mean leucine concentration of 1 mg/mL) can be considered if growth and monitoring parameters remain within goal and the mother's milk production remains adequate [8, 15].

The steps for initiating a diet in an infant with MSUD are outlined in Box 17.2.

Box 17.2: Initiating Nutrition Management of an Asymptomatic Infant with MSUD

Goal: Reduce or normalize plasma leucine.

Step-by-step:

1. Establish intake goals based on the infant's diagnostic plasma leucine level, clinical status and laboratory values.
2. Determine amount of standard infant formula or breast milk required to provide the infant's leucine needs. Determine the amount of protein and energy that will be provided by this amount of formula or breast milk.
3. Subtract the protein provided by the standard infant formula or breast milk from the infant's total protein needs.
4. Calculate the amount of BCAA-free medical food required to meet the remaining protein needs.
5. Calculate the amount of valine and isoleucine provided by the infant formula or breast milk. Determine the amount of supplemental valine and isoleucine to add to meet recommended intakes (Table 17.2). Provide valine and isoleucine in solutions of 10 mg/mL (1 g amino acid in 100 mL water).
6. Determine the number of calories provided by both the infant formula or breast milk and BCAA-free medical food. If more energy is required, provide the remaining calories from additional BCAA-free medical food. A protein-free energy module can be used if there is a concern about excessive protein intake.
7. Determine the amount of fluid required to provide a caloric density of 20–25 kcal/ounce.
8. Divide total volume into appropriate number of feedings over a 24-hour period.

Box 17.3: Recommendations for Adjusting the MSUD Diet Prescription

1. Estimate the increase or decrease in the intake of leucine, isoleucine and/or valine that will be needed to improve the plasma amino acid concentrations. Adjustments in 10% increments are typical but can be higher or lower based on BCAA concentrations.
2. Adjust the amount of infant formula or breast milk to increase or decrease leucine in the diet.
3. Recalculate the valine and isoleucine content provided by the revised amount of infant formula or breast milk.
4. Recalculate the amount of supplemental isoleucine and valine needed to meet your revised intake goals.
5. Recalculate the amount of MSUD medical food required to meet the energy goal.
6. Re-check plasma amino acid concentrations.

Once the diet has been established, adjustments in leucine, valine and isoleucine intakes should be based on blood BCAA concentrations rather than maintaining a specific mg/kg intake goal (Box 17.3). The amount of the BCAA required per kilogram of body weight decreases as the patient matures [8] (Table 17.2).

Complementary feedings can be introduced to infants with MSUD at the typical age recommended for all infants, unless motor delays are present. To allow for solid food introduction, the volume of standard infant formula or breast milk is decreased and leucine from these sources is replaced with leucine from solid foods. High protein foods contain too much leucine to be incorporated into the diet in all but the mildest forms of MSUD. Foods with a moderate protein content such as starchy vegetables and regular grain products will provide the majority of leucine in the diet. Modified low protein foods made from wheat or other starch can be introduced to allow for a greater volume of food with a very low leucine content.

Table 17.2 Recommended daily nutrient intakes of BCAA, protein, and energy for individuals with MSUD when well [8, 15]

	Nutrient				
Age	LEU mg/kg	ILE mg/kg	VAL mg/kg	Protein g/kg	Energy kcal/kg
0–6 months	40–100	30–90	40–95	2.5–3.5	95–145
7–12 months	40–75	30–70	30–80	2.5–3.0	80–135
1–3 years	40–70	20–70	30–70	1.5–2.5	80–130
4–8 years	35–65	20–30	30–50	1.3–2.0	50–120
9–13 years	30–60	20–30	25–40	1.2–1.8	40–90
14–18 years	15–50	10–30	15–30	1.2–1.8	35–70
19 years +[a]	15–50	10–30	15–30	1.1–1.7	35–45

[a]Males and non-pregnant, non-lactating females

Box 17.4: Counting Leucine Intake in the MSUD Diet

Only dietary leucine must be counted

- The valine and isoleucine content of food is about half that of the leucine content.
- Patients will not consume too much valine and isoleucine if they meet their prescribed leucine intake.
- Each gram of protein contains approximately 60 mg leucine (Box 17.5).
- References listing the leucine content of foods and beverages are available.

Box 17.5: Estimated Leucine from the Protein Content of Foods

- Use serving size and grams of protein listed on "How Much Phe" or other resource.
- To estimate the leucine content:
  - Breads and cereals: 70 mg leucine/g protein
  - Vegetables: 50 mg leucine/g protein
  - Fruit: 40 mg leucine/g protein
  - Mixed foods: 60 mg leucine/g protein

In MSUD, only the leucine content of foods and beverages need to be counted (Box 17.4). There is no need for caregivers to calculate the valine and isoleucine content of foods. Unless there is a concern about low energy intake, caregivers do not need to count calories from foods or beverages since the medical food provides the majority of energy, especially for infants.

Resources are available to provide the leucine content of foods and beverages [16, 17] or the leucine content can be estimated from resources listing the protein content of foods, such as "How Much Phe" (howmuchphe.org). Low protein recipes from cookbooks/websites are available for MSUD; or resources for PKU can be adapted for MSUD by estimating the leucine content from the provided protein content (Box 17.5). For older individuals with MSUD, counting protein rather than leucine may be appropriate and easier for the patient, if metabolic control can be maintained with this less accurate method. Some clinics have adapted the "simplified diet" for PKU and successfully managed patients with MSUD using similar guidance (Chap. 10).

Medical Food For the great majority of individuals with MSUD, a medical food is required for life (Table 17.3). In patients with classical MSUD, medical foods provide up to 80–90% of protein needs and a majority of energy needs, especially in infancy.

Infants with MSUD are prescribed a complete medical food containing all amino acids except BCAA with a fat, carbohydrate, and micronutrient content similar to standard infant formulas. Toddlers and young children are transitioned to

Table 17.3 Selected medical foods for the treatment of MSUD

Infant/Toddler (complete[a])	Older Child/Adult (complete[a])	Older Child/Adult (incomplete[b])
Complex Essential MSD Mix[c]	Complex Junior MSD Drink Mix[c]	Complex MSD Amino Acid Blend[c]
MSUD Anamix Early Years[c]	Ketonex-2[d]	Camino Pro MSUD Drink[f]
Ketonex-1[d]	MSUD Lophlex LQ[c]	MSUD Maxamum[c]
Ketonex-2[d]	BCAD-2[e]	MSUD Gel[g]
BCAD-1[e]	Vilactin AA Plus[f]	MSUD Cooler 15[g]
BCAD-2[e]		MSUD Express[g]

Examples of medical foods available in the US (as of March 2021)
[a]Contains L-amino acids (without BCAA), as well as fat, carbohydrate, vitamins, and minerals
[b]Contains L-amino acids (without BCAA), but low in or devoid of fat, carbohydrate, vitamins, and/or minerals. See company websites for specific nutrient composition
[c]Nutricia North America (Rockville MD; nutricia-na.com)
[d]Abbott Nutrition (Columbus, OH; abbottnutrition.com)
[e]Mead Johnson Nutrition (Evansville, IN; meadjohnson.com)
[f]Cambrooke Therapeutics (Ayer, MA; cambrookefoods.com)
[g]Vitaflo USA (Alexandria, VA; vitaflousa.com)

complete medical foods designed for those over age 2 years that contain all amino acids except BCAA with age-appropriate fat, carbohydrate, and micronutrient profiles [18]. There are several other medical foods on the market, as well, including those more concentrated in amino acids with little or no fat and some with reduced carbohydrate content. These can decrease the amount of medical food required to meet an individual's protein needs and, thus, can be helpful if excess energy intake is a concern. However, decreasing energy from medical food may lead to excessive intake of leucine-containing foods or may decrease energy intake to a point that the individual is losing weight. Both of these situations can cause elevations in blood leucine. The vitamin and mineral content of medical foods vary. Intake needs to be assessed and supplemental vitamins and minerals provided, if necessary [8].

Isoleucine and valine supplements When leucine intake is reduced sufficiently to maintain leucine concentrations in the goal range, the plasma concentrations of isoleucine and valine may be lower than recommended and supplementation with either or both of these amino acids is often necessary, especially for those with classical MSUD [4, 8, 14, 15]. Without supplementation, deficiency of isoleucine can lead to skin lesions similar to that seen in acrodermatitis enteropathica [19, 20]. A 10% oral solution (10 mg/mL) of these amino acids can be made by dissolving 1 g of valine or isoleucine in 100 mL water. Maintaining plasma concentrations of 200–400 μmol/L for valine and 100–400 isoleucine is suggested to prevent deficiency [4, 8, 14]. Alternatively, some clinics prescribe medical foods designed for treatment of isovaleric acidemia that are devoid of leucine but contain valine and isoleucine (i.e., I-Valex®, Abbott Nutrition) for their patients with MSUD to avoid the need for valine or isoleucine supplements [21] although this may make it more difficult to individualize intake of these two amino acids.

17.2.2 Acute Nutrition Management

Symptomatic MSUD in a neonate is a medical emergency and requires the immediate initiation of medical and nutrition support to reverse catabolism [3, 4, 6, 8, 14, 15]. Additionally, individuals of any age are at risk for metabolic decompensation with any intercurrent illness or other stress leading to catabolism. During these episodes, altered mental status, ataxia, acute dystonia, and seizures can develop; progression to cerebral edema can be fatal [3, 4]. Families and individuals with MSUD should know the signs of metabolic decompensation and be provided with an emergency protocol that includes directions for both the family and for emergency personnel who may become involved in their care. Information for contacting the on-call met-

abolic physician must be included in any protocol.

There are many factors to consider during an illness and the entire metabolic team must be aware of the potential of an impending emergency. Often, a "sick-day" diet prescription is provided for use at the first sign of an illness [4, 8]. For minor illnesses, use of the sick-day diet may allow for management of the disorder on an outpatient basis, but many factors go into this decision, including age of the child, severity of MSUD (i.e., classical vs. variant MSUD), severity and length of illness, and ability of the family to manage a complicated protocol at home. Home monitoring with dinitrophenylhydrazine (DNPH) solution can be used as an immediate marker to assess diet modifications. DNPH specifically reacts with the α-ketoacids produced in MSUD and can be detected in urine [4]. If DNPH is not available, measuring urine ketones with Ketostix® can be a substitute. Although measuring urine ketones is not as specific as utilizing DNPH, ketones can be used as a marker of impending crisis [3]. Many clinics use ketone measurements to adjust at-home diet composition since the availability of DNPH is limited. Sick-day diets must be individualized for each patient and general guidelines for designing these diets are outlined (Box 17.6).

Box 17.6: Guidelines for Designing a "Sick-Day" Diet for Patients with MSUD

- The "sick-day" diet must provide enough energy to meet the individual's estimated requirement, which may be higher than their usual caloric intake.
- Increase protein equivalents by increasing medical food to approximately 120% of usual intake. This also supplies more energy from carbohydrate and/or fat.
- Decrease the leucine prescription. Remove 50–100% of usual leucine intake, depending on the degree of illness, for 24 hours and reassess with the medical team.
- Prevent low blood concentrations of isoleucine and valine. Provide the same amount of isoleucine and valine as in the patient's usual diet by supplementing with isoleucine and/or valine. Additional isoleucine and valine may be required to prevent low concentrations.
- Provide small, frequent feedings throughout a 24-hour period.
- Monitor plasma concentrations of the BCAA to guide appropriate diet adjustments.

There should be a low threshold when deciding if a patient's clinical condition warrants an emergency department visit or admission. Admissions require a medical team specialized in treating inborn errors of metabolism, access to frequent and rapid turnaround time for plasma amino acids, electrolytes, and other critical laboratory values [4, 8], as well as all components for providing the diet, including medical foods and specialized parenteral solutions, if necessary. General guidelines for nutrition management during hospital admissions are provided (Box 17.7). Promoting protein anabolism is key to reducing BCAA concentrations and requires an energy intake above maintenance requirements, removal or significant reduction in leucine intake, and prevention of valine and isoleucine deficiency. Non-protein calories are often provided by peripheral or central line access. An energy intake of 1.25–1.5 times the patient's estimated energy requirement (EER) is necessary from both dextrose (50–70% of calories) and lipids (30–50% of calories); however, energy needs may be as high as three times the EER, especially in older children and adults [4]. A continuous insulin infusion is often required to prevent hyperglycemia. Administration of excess fluid and use of hypotonic solutions needs to be avoided given the high risk of cerebral edema [3, 4].

To reduce the leucine concentration, a sufficient supply of all other amino acids, including valine and isoleucine, must be provided. A source of BCAA-free amino acids is needed as soon as possible to provide total protein equivalents of 2–3.5 g/kg in infants and greater than DRI needs for all ages [3, 4, 8]. Protein equivalent needs can be met with continuous nasogastric feedings of an MSUD medical food (0.7–1.2 kcal/mL at a rate of 30–60 mL/hour) with peripheral administration of dextrose and lipid solutions for addi-

Box 17.7: Management During Admission for Illness in MSUD

The initial treatment of intoxication syndrome is a medical emergency and is managed by the metabolic physician[a].

- Provide appropriate energy and leucine-free amino acid sources for acute illness from parenteral and/or enteral sources (Table 17.1).
- Maintain blood isoleucine and valine concentrations >200 μmol/L as leucine decreases. When anabolic, leucine can decrease very rapidly, and isoleucine and valine needs exceed the patient's usual isoleucine and valine tolerance.
- Reassess plasma amino acids every 12–24 hours, or as clinically indicated.
- Monitor electrolytes and fluid volume.
- Restart a source of leucine when plasma concentrations are <200 μmol/L in infants and children <5 years, and <300 μmol/L in those >5 years of age.
- Do not discharge patient until plasma leucine has decreased sufficiently, and patient is tolerating enteral feedings.

[a]Chapter 4 provides additional information for managing metabolic decompensation

tional energy [4]. However, if sufficient gastrointestinal administration of medical food is not possible, BCAA-free parenteral solutions can be obtained from specialty compounding pharmacies. During metabolic decompensation, blood concentrations of isoleucine and valine are typically lower than leucine. If the patient is only provided a BCAA-free medical food, concentrations of these two amino acids can become deficient before the leucine concentration normalizes. Supplementation of enteral or parenteral isoleucine and valine at 20–120 mg/kg/d is needed to maintain sufficiently elevated blood concentrations of 400–800 μmol/L for both amino acids to promote a rapid reduction in blood leucine [4, 8]. Sources of leucine are not added back into the diet until the leucine concentration decreases to at least the upper limit of the target range (200 μmol/L for infants and young children and 300 μmol/L for older individuals) [8, 22].

With aggressive management during a metabolic crisis, the leucine concentration can be expected to decrease by 50% after 24 hours [6, 8, 22], or at a rate of 500–1000 μmol/L per day [4]. A slower rate of decrease in leucine concentration is noted during admissions with infection or illness compared to the decrease in leucine when the patient is admitted because of inadequate dietary adherence [22].

Finally, caregivers and individuals with MSUD need to be aware that metabolic decompensation can be precipitated by events other than illness – significant injury and surgery are also catabolic events that need attention from the metabolic team. For surgical procedures, reducing the fasting time by providing an energy source (i.e., IV dextrose) during and after the procedure until oral intake can be restarted is often necessary [3, 6].

17.3 Monitoring

In addition to frequent monitoring of BCAA concentrations, a complete amino acid profile should be periodically evaluated. It is best to collect blood samples at a consistent time during the day, either after an overnight fast or approximately 2–3 hours after a meal [4, 8]. Table 17.4 provides recommended blood BCAA concentrations for healthy individuals with MSUD [4, 8]. Home collection of dried blood spots for monitoring BCAA and other amino acids allows for an increased frequency of monitoring that positively correlates with improved metabolic control [23].

Table 17.4 Recommended blood BCAA concentrations in MSUD [4, 8]

	μmol/L	mg/dL	Normal (μmol/L)
Leucine: < 5 years Leucine: > 5 years	100–200[a] 100–300	1.3-2.6 1.3–3.9	50–215
Valine	200–400	2.3–4.6	85–200
Isoleucine	100–300	1.3–3.9	25–90

[a]Recommended maximum blood concentration is 200 μmol/L for infants and children <5 years of age and 300 μmol/L for those >5 years of age

If leucine concentrations are elevated with routine monitoring, but the patient is not exhibiting signs of illness or other stress, there are several parameters to consider:

Evaluate energy intake Significant weight loss may increase BCAA concentrations due to catabolism. Increasing energy intake from medical food promotes weight gain (or maintenance in older patients) and also helps to reduce hunger so the individual may be less tempted to consume more leucine than prescribed. If a low fat or protein-concentrated medical food is prescribed, consider addition of a product with a greater calorie to protein ratio.

Evaluate the distribution of medical food throughout the day As in PKU, medical food distributed in 3 or 4 servings per day and given with a source of leucine at the same time will result in better utilization of BCAA and, thus, lower and more consistent leucine concentrations (Chap. 6).

Consider recommending additional protein equivalents from medical food Given the rapid oxidation of amino acids compared to intact protein sources, protein requirements for patients with metabolic disorders are often higher than recommended for the general population (Chap. 6). If excess energy intake is a concern, adding a low/no fat medical food concentrated in protein equivalents can increase total protein without significantly increasing energy intake from the medical food.

With your metabolic team, consider the possibility of a hidden illness, infection, or other catabolic stressors Urinary tract infections, sinus infections, or dental problems often increase leucine concentrations but may not be clinically obvious to the patient. Because of hormonal effects on protein metabolism, some women with MSUD have higher leucine concentrations just before menstruation [11]. Reduction in the leucine prescription and additional energy sources may be needed during these times.

Evaluate the amount of isoleucine and valine supplements added to the diet In the plasma amino acid profile, aim to maintain a 1 to 1 ratio of isoleucine to leucine concentrations, and at least a 2 to 1 ratio of valine to leucine concentrations [4]. If low concentrations of valine and/or isoleucine are found, increase the amount of supplements (10 mg/mL) to improve blood concentrations and normalize the ratios between the BCAA.

Box 17.8: Considerations if Plasma Leucine Concentrations Are Elevated (Without Signs of Illness or Stress)

1. Is the patient consuming sufficient energy?
2. Is all the medical food being consumed and distributed throughout the day?
3. Is protein intake from the medical food too low?
4. Are there hidden illnesses or infections?
5. Are blood concentrations of valine and/or isoleucine too low?
6. Is the patient taking the prescribed amount of leucine?
7. Is a decrease in the leucine prescription required?

Consider decreasing the patient's leucine prescription First, determine if the patient is taking the prescribed amount of leucine. Inadequate adherence to the diet regimen, especially "guessing" portion sizes, can lead to chronically elevated leucine concentrations. Typically, decreasing the leucine prescription is the last diet component to adjust since leucine tolerance is relatively constant throughout the lifespan. However, during periods of slowed growth, such as late infancy or late adolescence, a decrease in the prescribed amount of leucine may be needed. Assuring adequate energy intake is crucial when decreasing leucine in the diet prescription (Box 17.8).

Other laboratory parameters also need to be considered for diet monitoring (Box 17.9).

17.4 Transplantation

Liver transplantation is a treatment option for patients with MSUD to significantly decrease their risk of developing cerebral edema and other complications associated with high leucine con-

Box 17.9: Nutrition Monitoring of a Patient with MSUD[a]

- Routine assessments including anthropometrics, dietary intake, physical findings
- Laboratory Monitoring
  - Diagnosis-specific
    - Plasma amino acids
      - Leucine
      - Valine
      - Isoleucine
  - Nutrition-related laboratory monitoring of patients on BCAA-restricted diets may include markers of:
    - Protein sufficiency (plasma amino acids, prealbumin)
    - Nutritional anemia (hemoglobin, hematocrit, MCV, serum vitamin B12 and/or methylmalonic acid, total homocysteine, ferritin, iron, folate, total iron binding capacity)
    - Vitamin and mineral status (total 25-hydroxyvitamin D, zinc, trace minerals)
    - Others, as clinically indicated

[a]Suggested frequency of monitoring can be found in the GMDI/SERN MSUD Guidelines [15] (southeastgenetics.org/ngp)

centrations during illness or other catabolic stress [13, 24]. Liver transplantation restores 9–13% of whole-body BCKADH activity in the patient with MSUD, which is sufficient to allow for a diet without protein restriction or medical food. After transplantation, episodes of metabolic decompensation rarely occur, although there are two reports of decompensation in transplanted patients [25, 26]. Plasma BCAA concentrations range from 1.5 to 2 times normal during intercurrent catabolic stress. Long-term cognitive and adaptive functioning remains steady, or improves in some, following transplant [27, 28]. Since BCKADH activity is not found solely in the liver but is also active in muscle, heart, kidney, brain, and other tissues, a liver that is removed from a patient with MSUD can be donated to a recipient without MSUD in a domino liver transplant [25].

The goal of nutrition management for liver transplantation is to maintain good metabolic control prior to the surgery and prevent decompensation with administration of IV dextrose during pre-surgical fasting and the surgical procedure. The diet can be advanced to an unrestricted diet following the transplant [8]. Outcomes in liver transplantation for MSUD have been good. In 54 patients with MSUD who received a liver transplant, the overall survival rate was 98–100% [24]. After transplantation, patients tolerate unrestricted diets and have stable plasma BCAA concentrations [13]. However, studies have found that patients do not gain significant improvement in cognitive scores after transplant compared to their pre-transplant intelligence scores (mean IQ 78+/-24), although many of these patients had cognitive impairment prior to transplantation. Thus, for young patients with severe MSUD, undergoing a transplant early in life before brain damage is sustained is a viable treatment option [13, 24].

17.5 Summary

Early identification, aggressive treatment during catabolic events, and diligent nutrition management with frequent monitoring can result in positive outcomes for patients with MSUD. Treatment includes restricting BCAA with the use of medical foods, intact protein restriction, and isoleucine and valine supplementation, as needed, to maintain plasma BCAA concentrations in the target ranges. Regardless of the patient's age, acute metabolic decompensation in MSUD remains life-threatening and should be treated as a medical emergency with rapid, aggressive management to reverse catabolism. Liver transplantation is a viable option to prevent episodes of decomposition and allows for a diet without medical food and protein restriction.

17.6 Diet Calculation Example

17.6.1 MSUD Diet Calculation Example Using Standard Infant Formula as the Source of Leucine and Intact Protein

Patient Information	Nutrient intake goals (per day) (Table 17.5)
Weight: 4 kg Age: 8 days This patient presents asymptomatically. Plasma leucine concentration is 600 μmol/L, isoleucine is 80 μmol/L and valine is 180 μmol/L. Since this patient is asymptomatic with a relatively low leucine concentration, recommend leucine at the higher end of range	Leucine (LEU): 90 mg/kg (Range 40–100 mg/kg) Isoleucine (ILE): 50 mg/kg (Range 30–95 mg/kg) Valine (VAL): 50 mg/kg (Range 30–95 mg/kg) Protein: 3.0 g/kg (Range 2–3.5 g/kg) Energy: 100–120 kcal/kg Fluid: 150 mL/kg

Table 17.5 Selected Nutrient Composition of Formulas for MSUD Diet Calculation Using a Standard Infant Formula as the Source of Intact Protein

Medical Food	Amount	LEU (mg)	VAL (mg)	ILE (mg)	Protein (g)	Energy (kcal)
Anamix MSUD Early Years[a]	100 g	0	0	0	13.5	473
Enfamil Premium Newborn powder[b]	100 g	1250	640	640	10.8	510

[a] Nutricia North America (Rockville, MD)
[b] Mead Johnson Nutrition (Evansville, IN)
Note: Check manufacturer's website for the most up-to-date nutrient composition

Step-by-Step Calculation

Step 1 Calculate the infant's nutrient needs

Nutrient goal/kg × Infant weight

LEU: 90 mg LEU/kg × 4 kg = 360 mg/day

ILE: 50 mg/kg × 4 kg = 200 mg

VAL: 50 mg/kg × 4 kg = 200 mg

Protein: 3.0 g/kg protein × 4 kg = 12 g total protein

Energy: 110–120 kcal/kg × 4 kg = 440–480 kcal

Fluid: 150 mL × 4 kg = 600 mL (20 fluid ounces)

Step 2 Calculate the amount of standard infant formula needed to meet daily LEU requirement.

Amount of LEU required per day ÷ amount of LEU in 100 g of standard formula

$$360\,\text{mg}\,LEU \div 1250\,\text{mg}\,LEU = 0.29$$

$$0.29 \times 100 = 29\,\text{g Enfamil Premium needed to meet daily}\,LEU\,\text{requirement.}$$

Step 3 Calculate protein provided from the standard infant formula.

Amount of standard formula × amount of protein provided in 100 g of standard formula

$$0.29 \times 10.8\,\text{g protein in}\,100\,\text{g Enfamil} = 3.1\,\text{g protein from Enfamil}$$

Step 4 Determine the remaining amount of protein to be provided from BCAA-free medical food to meet the total protein prescription.

$$\text{Total protein needs} - \text{protein from standard formula} = \text{protein needed from medical food}$$

$$12\,\text{g} - 3.1\,\text{g}\left(\text{from Enfamil}\right) = 8.9\,\text{g protein needed from medical food}$$

Step 5 Calculate the amount of BCAA-free medical food needed to provide 8.9 g protein.

Protein needed to fill diet prescription ÷ protein provided in 100 g of medical food

$$8.9\ \text{g protein needed} \div 13\ \text{g protein in}\,100\ \text{g Anamix MSUD Early Years} = 0.68$$

$$0.68 \times 100 = 68\ \text{g Anamix MSUD Early Years required in the diet prescription}$$

Step 6 Calculate the amount of isoleucine and valine provided from standard infant formula (note no ILE or VAL in BCAA-free medical food)

Amount of standard formula × ILE in 100 g of standard formula

$$0.29\left(\text{Enfamil}\right) \times 640\,\text{mg}\,ILE = 186\,\text{mg}\,ILE$$

Amount of standard formula × VAL in 100 g of standard formula

$$0.29\left(\text{Enfamil}\right) \times 640\,\text{mg}\,VAL = 186\,\text{mg}\,VAL$$

Step 7 Calculate the remaining amount of ILE and VAL to be provided by supplements to meet requirements determined in step 1 (Goal minus amount in Enfamil)

$$ILE: 200\,\text{mg} - 186\,\text{mg} = 14\,\text{mg}\,ILE\,\text{to be provided}\,by\,ILE\,\text{supplement}$$

$$VAL: 200\,\text{mg} - 186\,\text{mg} = 14\,\text{mg}\,VAL\,\text{to be provided}\,by\,VAL\,\text{supplement}$$

Step 8 Determine how much amino acid solution is needed to provide remaining ILE and VAL.

Use amino acid solutions containing 10 mg/mL. This is made by adding 1 gram of amino acid (ILE or VAL) powder and adding water to make total volume of 100 mL

(This is equivalent to 1000 mg VAL or 1000 mg ILE in 100 mL = 10 mg/mL)

14 mg ILE divided by 10 mg/mL = 1.4 mL ILE solution (containing 10 mg/mL)

14 mg VAL divided by 10 mg/mL = 1.4 mL VAL solution (containing 10 mg/mL)

Round up to 2 ml of each solution.

Step 9 Calculate total energy provided from standard infant formula and BCAA-free medical food.

Amount of standard infant formula × kcal in 100 g of standard formula.

$$0.29\left(\text{Enfamil}\right)\times 510\,\text{kcal} = 148\,\text{kcal}$$

Amount of BCAA-free medical food × kcal of 100 g of BCAA-free medical food.

$$0.68\left(\text{Anamix MSUD Early Years}\right)\times 473\ \text{kcal} = 322\ \text{kcal}$$

Add standard formula + BCAA-free medical food for total kcal provided in diet prescription.

$$148\ \text{kcal} + 322\ \text{kcal} = 470\ \text{kcal}$$

Step 10 Calculate the final volume of the formula to make a formula concentration of 20–25 kcal per ounce (Table 17.6).

470 kcal ÷ 20 kcal/ounce = 23.5 ounces of formula (round to 24 ounces)

470 kcal ÷ 25 kcal/ounce = 18.8 ounces of formula (round to 19 ounces)

19–24 ounces meets the initial fluid goal of 600 mL (20 ounces)

(The volume prescribed will depend on infant's usual intake and growth)

Table 17.6 Diet Prescription Summary for Sample Calculation of MSUD Diet Using Standard Infant Formula as the Source of Intact Protein[a]

Medical Food	Amount	LEU (mg)	VAL (mg)	ILE (mg)	Protein (g)	Energy (kcal)
Anamix MSUD Early Years[b]	68 g	0	0	0	9.0	322
Enfamil Premium powder[c]	29 g	362	186	186	3.1	148
ILE Supplement	2 mL[d]			20		
VAL Supplement	2 mL[d]		20		–	
Total per day		362	206	206	12.1	470
Total per kg		90 mg/kg	52 mg/kg	52 mg/kg	3.0 g/kg	118 kcal/kg

[a]Rounded to nearest whole number for amount of formula powders, leucine, isoleucine, valine, and energy and to the nearest 0.1 g for protein

[b] Nutricia North America (Rockville, MD)

[c] Mead Johnson Nutrition (Evansville IN)

[d]Amino acid solution containing 10 mg/mL

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