



Nutrition management guideline for maple syrup urine disease: An evidence- and consensus-based approach



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ABSTRACT

In an effort to increase harmonization of care and enable outcome studies, the Genetic Metabolic Dietitians International (GMDI) and the Southeast Regional Newborn Screening and Genetics Collaborative (SERC) are partnering to develop nutrition management guidelines for inherited metabolic disorders (IMD) using a model combining both evidence- and consensus-based methodology. The first guideline to be completed is for maple syrup urine disease (MSUD). This report describes the methodology used in its development: formulation of five research questions; review, critical appraisal and abstraction of peer-reviewed studies and unpublished practice literature; and expert input through Delphi surveys and a nominal group process. This report includes the summary statements for each research question and the nutrition management recommendations they generated. Each recommendation is followed by a standardized rating based on the strength of the evidence and consensus used. The application of technology to build the infrastructure for this project allowed transparency during development of this guideline and will be a foundation for future guidelines. Online open access of the full, published guideline allows utilization by health care providers, researchers, and collaborators who advise, advocate and care for individuals with MSUD and their families. There will be future updates as warranted by developments in research and clinical practice.

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1. Introduction

The Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Newborn Screening and Genetics Collaborative (SERC) have undertaken a multi-year project to develop nutrition

management guidelines for rare inherited metabolic disorders (IMD) for which there are limited peer-reviewed studies to provide evidence for various aspects of treatment. The goals of this project are to foster optimum nutrition management of affected individuals, reduce the uncertainty and variability in management, and direct future research. The first of these guidelines to be completed is for nutrition management of maple syrup urine disease (MSUD). While developing this first guideline, the previously published methodology [1] for the process was refined, included in the web-based portal and will be utilized for future guidelines.

MSUD (OMIM #24860) is an IMD caused by branched-chain α -ketoacid dehydrogenase (BCKD) deficiency resulting in the accumulation of the branched chain amino acids (BCAA), leucine (LEU), isoleucine (ILE), and valine (VAL) and their corresponding α -ketoacids (BCKA).

Exogenous (dietary) BCAA are major precursors for protein synthesis. Normally, they are also used as an alternative energy source when consumed in excess of anabolic needs or during endogenous muscle

Abbreviations: Allo-ILE, alloisoleucine; BCAA, branched-chain amino acids; BCKA, branched-chain α -ketoacids; BCKD, branched-chain α -ketoacid dehydrogenase; CoA, co-enzyme A; DRI, dietary reference intake; GMDI, Genetic Metabolic Dietitians International; HRSA, health resources and health administration; ILE, isoleucine; IMD, inherited metabolic disorders; Kcal, kilocalories; LEU, leucine; MeSH, medical subject heading; MS/MS, tandem mass spectrometry; MSUD, maple syrup urine disease; MySQL, a structured query language; NAD, nicotinamide adenine dinucleotide; NCBI, National Center for Biotechnology Information; PICO, population, intervention, comparison, and outcomes; PRO, protein; SERC, Southeast Regional Newborn Screening and Genetics Collaborative-Health Resources and Service Administration (HRSA) Region 3; TPP, thiamine pyrophosphate; VAL, valine.

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protein catabolism. The initial step in LEU, VAL, and ILE catabolism is a reversible transamination step to form the BCKAs: α -ketoisocaproic acid, α -keto-3-methylvaleric acid and α -ketoisovaleric acid. The second step is an irreversible oxidative decarboxylation step, within the inner mitochondrial membrane, catalyzed by the BCKD complex. It is a multi-enzyme macromolecule with three catalytic components (E1, E2, E3). The E1 component is made up of two E1 α and two E1 β subunits forming a heterotetramer. The catalytic components require the cofactors thiamin pyrophosphate (TPP) and flavin adenine dinucleotide (FAD) as well as the prosthetic group lipamide and two regulatory enzymes (a kinase and a phosphatase) [2].

MSUD is an autosomal recessive disorder. The genes encoding the various catalytic subunits/components (E1 α , E1 β , E2, E3, kinase, and phosphatase) have been mapped to chromosome loci: 19q13.1–13.2; 6q14; 1p31; 7q31–32, 16p11.2 and 4q22.1, respectively. MSUD-causing human mutations in five of the six BCKD genes (with the exception of the kinase) have been documented [2,3]. In a total of 78 cell lines from MSUD subjects, the large majority had mutations in the E1 subunits [4,5]. A common mutation among the Old Order Mennonites is Y393N, a point mutation in the E1 α subunit [3]. Individuals with MSUD are always homozygous or compound heterozygous for mutations in the same BCKD gene [6].

In the classical form of MSUD, with less than 3% residual enzyme activity, symptoms occur soon after birth. In the untreated neonate, the odor of maple syrup may be detected in the cerumen as early as 12–24 h, and in the urine by 48–72 h after birth. Elevated plasma concentrations of the BCAA including the unique BCAA alloisoleucine (allo-ILE), as well as a generalized disturbance of plasma amino acid concentration ratios are present by 12–24 h of age; elevated BCKA and generalized ketonuria, irritability, and poor feeding by 24–72 h; deepening encephalopathy manifesting as lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as “fencing” and “bicycling” by 4–5 days; and coma and central respiratory failure may occur by 7–10 days. Other phenotypes with various degrees of partial enzyme activity include the intermediate, thiamin-responsive, and intermittent forms of MSUD that can lead to severe metabolic intoxication and encephalopathy with catabolic stress [6].

Newborn screening using tandem mass spectrometry (MS/MS) [7] has the potential for early detection allowing early initiation of treatment for MSUD. Although there is the possibility of false positives due to generalized aminoacidemia, or hydroxyprolinemia [8] and false negatives for milder variants of MSUD [9] rapid follow up of positive newborn screening reports should result in fewer infants demonstrating the severe clinical symptoms in the newborn period [10]. Mutation analysis and enzymatic testing, although not necessary for diagnosis, may help predict severity of the disorder or thiamin responsiveness [5].

The goals of medical nutrition therapy in MSUD are to rapidly reduce toxic metabolites by restricting dietary BCAA to amounts allowing individuals to achieve and maintain plasma BCAA amino acid concentrations within the targeted treatment ranges; reduce catabolism; promote anabolism; monitor nutritional status and alter intake to promote normal growth, development and health maintenance; evaluate thiamin responsiveness if the individual has residual BCKD activity; and supplement with thiamin if the individual is responsive. Heretofore, the treatment practices utilized to achieve these goals have varied. The process and resulting guideline described in this report are based on evaluation and summary of published and practice literature, consensus and expert opinion regarding nutrition management of MSUD.

2. Methods

The Nutrition Management Guideline for MSUD is an evidence- and consensus-based guideline created through a rigorous, transparent and systematic development process [1]. The process, created for this

project, was adapted from the Academy of Nutrition and Dietetics [11] with the addition of specific techniques to draw on the expertise from clinical practice to provide information where published research is lacking [1].

2.1. Question formulation

The MSUD workgroup consisted of eight experienced metabolic dietitians who began the process by independently identifying over 40 practice areas where uncertainty and/or variation in practice existed. These were categorized and prioritized. Five topics were identified for evidence analysis and guideline development. Research questions for each topic were formulated in the PICO (population, intervention, comparison, and outcomes) format [12].

2.2. Search process

Because of the known scarcity of peer-reviewed scientific literature in nutrition management of IMDs, the search process included both published scientific studies and gray, or practice, literature.

For the peer-reviewed literature, medical subject heading (MeSH) terms were specific to each question, but inclusion and exclusion criteria were the same for all questions. Eligibility for research questions was limited to human studies and published in English from 1985 to summer 2011 (except for the research question related to thiamin that used earlier references from 1971), with nutrition data included. There were no study-design, age or setting restrictions. PubMed was the primary database used. Searches were conducted by a research librarian. The titles and abstracts of identified articles were scanned for relevance and matched with inclusion/exclusion criteria by the workgroup. Excluded articles were noted and qualifying articles were gathered for review and abstracting. Reference lists within the identified articles were examined for additional resources. These were added if they contributed pertinent information.

Practice (or gray) literature sources, which are not accessible through standard search systems, include abstracts and presentations from scientific and practice-based meetings, clinical protocols and guidelines, unpublished research, communication among experts (including list-serves), professional newsletters, and book chapters. The search for gray literature involved requests to individuals (e.g., practitioners and researchers) and organizations through their professional list serves, as well as online searches for materials related to nutrition and MSUD. Identified resources were screened and prioritized for inclusion based on relevance and substantive information not available in scientific literature, and currency.

2.3. Critical appraisal and abstraction

Each scientific article was critically reviewed by a trained analyst using a Quality Criteria Checklist, and the study design and methodology, findings, and author's conclusions were abstracted to Evidence Abstract Worksheets [11]. Quality criteria addressed subjects' and control groups' selection and retention, intervention clearly described and followed, other intervening variables tracked, outcomes defined, measures validated, and appropriate statistical analysis. Based on the number of criteria met, each article was assigned a quality rating of positive, neutral or negative.

Practice resources were reviewed by workgroup members using a specially developed quality criteria checklist for gray literature that included the following: clear purpose, relevance to intended users, systematic development process, and clear clinical recommendations, applicable to practice, and free of conflict of interest.

2.4. Consensus input and evidence summary

Key information from all eligible evidence sources (scientific and gray literature) for each question was summarized on an evidence table. Many issues of concern to nutrition management were not addressed or were inconclusive from the combined sources. For these issues, expert input from nutrition and medical clinicians and researchers was sought using a Delphi survey, nominal group process meeting and a second-round Delphi survey [1]. By systematically employing these techniques, the level of agreement with a specific practice statement was quantified. Also, input from the target population (patient and family) was included in the nominal group process. The final conclusion statement for each question represented a synthesis of evidence from scientific publications, gray literature, and Delphi and nominal group consensus techniques.

2.5. Guideline development

Specific recommendations for nutrition management in each of the five topic areas were derived from the summaries, and each recommendation was rated with respect to strength (A = strong, B = fair, C = weak, D = consensus, E = insufficient evidence) and need for clinical action (I = imperative or II = conditional). See Table 1.

These practice recommendations along with background and other information to support their implementation are contained in the MSUD Nutrition Management Guideline document. The final document was reviewed, using the Appraisal of Guidelines for Research and Evaluation (AGREE II) criteria [13] by an external panel of metabolic dietitians, physicians and an expert in guideline development methodology who were not involved in the evidence analysis nor in the development phases of the MSUD guideline.

2.6. Web application

Guideline development is made possible with a secure application hosted on the SERC website. The application utilizes a structured query language (MySQL) database. An unlimited number of IMD can be supported with the application. Sections exist for literature management, Delphi survey and nominal group session management, and final guideline development. User-entered data is archived as changes are made, and the content is eventually locked through internal publishing prior to the final guideline development. Literature references and tables are managed natively, and additional published literature data obtained

Table 2

Research questions in PICO format.

<i>Nutrition treatment:</i> For the individual with MSUD or suspected MSUD, what nutrition interventions must be initiated at first presentation, during illness, trauma or surgery to achieve optimal outcomes?
<i>BCAA concentrations:</i> For the individual with MSUD treated through dietary modification, what are BCAA blood concentrations that lead to optimal nutritional, medical and quality of life outcomes?
<i>Thiamin:</i> For the individual with MSUD, what is the most effective method for initiating, dosing and evaluating response to thiamin supplementation?
<i>Pregnancy:</i> For the woman with MSUD, what specific nutritional interventions must be initiated during pregnancy, at delivery and during the postpartum period to achieve optimal outcomes for her and her newborn infant?
<i>Transplantation:</i> For the individual with MSUD undergoing liver transplantation, what specific nutritional interventions result in optimal nutritional, medical and quality of life outcomes?

through the National Center for Biotechnology Information (NCBI) E-Utilities. The complete MSUD Nutrition Management Guideline can be accessed through the SERC website [12].

3. Results

The research questions developed from the five main topic areas are listed in Table 2. In this report, the research questions' conclusion statements, recommendations and the strength of the supporting evidence are provided. Based on the methodology described above, the complete online guideline also provides detailed evidence information with links to the sources, specific nutrient intake recommendations, biochemical and clinical monitoring recommendations and links to resources for both professionals and families.

3.1. Acute dietary treatment

Nutrition therapy plays an essential role in restoring and maintaining metabolic homeostasis in MSUD. At diagnosis or any time there is a risk of metabolic decompensation during trauma, surgery, illness or inappropriate dietary intake, the goals are to: closely monitor biochemical and clinical status [14–17]; prevent catabolism and the accumulation of endogenous BCAA and BCKA; and provide adequate BCAA-free exogenous protein [10,14–21], energy [10,14,16–23], fluid [14,17,20,22], and VAL and ILE to promote anabolism [10,14–17,20–24]. When the patient is metabolically stable, LEU requirements can be met from intact protein

Table 1
Recommendation ratings and application.^a

Recommendation rating		
A	Strong	The benefits clearly exceed the harms (or the harms clearly exceed the benefits in the case of a strong negative recommendation); and the quality of the supporting evidence is excellent/good. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.
B	Fair	The benefits exceed the harms (or the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong as "A". In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.
C	Weak	The quality of evidence that exists is suspect or well-done studies show little clear advantage for one recommendation over another.
D	Consensus	Expert opinion supports the recommendation even though the available scientific evidence did not present consistent results, or controlled trials were lacking.
E	Insufficient evidence	There is a lack of pertinent evidence and this may be due to an unclear balance between benefits and harms.
Clinical action/application		
I	Imperative	The recommendation is broadly applicable to the target population without conditions. An imperative recommendation can be stated in "require," or "must," or "should achieve certain goals," terminology.
II	Conditional	The recommendation clearly defines a specific situation that limits its applicability. A conditional recommendation can be stated in "if/then" terminology.

^a Adapted for this guideline from: American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics* 2004; 114(3):874–7.

sources [10,14,15,17,19–21,24–26]. Seriously ill individuals need aggressive treatment that may include dialysis, hemofiltration, parenteral nutrition and/or tube feedings [5,10,14,16–21,23,24,27]. Non-acutely ill individuals can often be managed with a “sick day” guideline that provides detailed instruction for preventing catabolism and monitoring clinical status [18,20,24].

Recommendations

Acute dietary treatment

1. Provide aggressive nutrition management during illness or at first presentation to prevent or reverse catabolism and promote anabolism by supplying: adequate energy (up to 150% of usual energy intake); BCAA-free protein (increased to replace BCAA-containing intact protein); fluid (up to 150 mL/kg with careful monitoring of electrolytes and possible cerebral edema); and electrolytes and insulin (if needed). (B.I)¹
2. Use parenteral nutrition alone (providing BCAA-free amino acids, lipids and/or glucose) or in conjunction with enteral feedings, when necessary to meet energy needs in severe illness. (B.II)
3. Include nutritional intervention when dialysis, hemoperfusion or similar treatment is necessary to lower plasma BCAA and remove toxic metabolites. (C.II)
4. Monitor BCAA, acid–base balance, urine α -ketoacids, blood glucose and clinical symptoms closely during illness. If hemofiltration or dialysis is necessary, blood gas, hematocrit, total protein, sodium, calcium, phosphorus, urea, and creatinine should also be monitored. (B.I)
5. Add ILE and VAL, even if they are already in the 200–400 μ mol/L range, to help lower elevated plasma LEU into the treatment range. (B.II)
6. Reintroduce intact protein (or complete amino acid mixtures) when elevated plasma LEU approaches the upper limit of the treatment range: 200 μ mol/L for infants and children \leq 5 years of age; and 300 μ mol/L for individuals $>$ 5 years of age. (B.I)
7. Consider use of breast milk (mean LEU concentration of 1 mg/mL) as a source of intact protein (and BCAA) in the dietary management of infants with MSUD if there is frequent anthropometric, clinical, and laboratory monitoring of the infant and mother has adequate milk production. (D.I)
8. Manage mild illnesses with patient-specific sick-day instructions to include reduction of intact protein by 50–100% for 24–48 h by replacement with additional BCAA-free medical food, adequate hydration, addition of non-protein energy sources, and close monitoring. (D.II)

¹Definitions of the rating of recommendations are given in Table 1.

3.2. Achieving recommended BCAA blood concentrations

The goal of dietary BCAA restriction for the individual with MSUD is to achieve and maintain plasma BCAA concentrations as close to normal as possible while preventing and correcting BCAA deficiencies [20,28]. Studies reporting the analyses of BCAA concentrations in MSUD have focused primarily on identifying plasma concentrations that result in adverse outcomes. Elevated LEU concentrations are most often associated with abnormal brain morphology [29,30] and cognitive impairment [31–33]; and impact on social and psychomotor function varies [31–33]. Low plasma BCAA, particularly ILE and to a lesser extent VAL,

results in severe but reversible epithelial damage to the skin, eye and gastrointestinal tract [20,34,35]. Poor growth is reported as a result of BCAA deficiency [28]. Reports differ in the plasma BCAA ranges that are considered acceptable, but agree that frequent biochemical monitoring is necessary to assess the effectiveness of dietary intervention and detect deficiencies or excesses. Although relaxing dietary BCAA restriction in adolescents and adults has been reported in case studies and postulated to improve quality of life [29,30,36], this practice poses a risk of adverse outcomes [30] and has not been rigorously or objectively evaluated.

Recommendations

Achieving appropriate BCAA blood concentrations

1. Maintain plasma LEU concentrations, with frequent monitoring, between 75 and 200 μ mol/L for infants and children \leq 5 years old and between 75 and 300 μ mol/L for individuals $>$ 5 years of age to achieve favorable cognitive outcomes. (B.I)
2. Maintain plasma ILE and VAL concentrations, with frequent monitoring, between 200 and 400 μ mol/L (or slightly above the normal ranges) in all individuals to avoid metabolic instability and BCAA deficiencies. (B.I)
3. Employ MSUD-specific dietary management strategies to achieve recommended BCAA concentrations. (A.I). See Tables 3 and 4.
4. Maintain plasma BCAA within the recommended ranges throughout life. (C.II)

3.3. Thiamin

Thiamin pyrophosphate (TPP) is a co-factor for the multi-subunit enzyme, BCKD, and thiamin is an adjunct to be considered in the treatment regime for MSUD. Because it is a water-soluble vitamin [37], reported thiamin dosages have varied from 10 to 1000 mg/day, [38, 39] and have been given for extended periods of time in both the newborn period and later without any reported toxic side-effects [37]. Patients with MSUD for whom supplemental thiamin has increased dietary BCAA tolerance (or decreased plasma BCAA on a constant dietary intake) appear to be individuals with some residual BCKD activity [6,40–45], especially those with E2 mutations [2,46, 47]. This response is apparent within one month with a dosage of 50–200 mg/day [44]. Patients should be continued on a BCAA-restricted diet during the assessment of the thiamin response, as well as during long-term supplementation [6,21,42,48].

Recommendations

Thiamin supplementation

1. Perform a thiamin challenge for all individuals with MSUD except those known to be homozygous for the 1312T>A mutation or other mutations resulting in less than 3% BCKD enzyme activity. (B.II)
2. Initiate a thiamin challenge with a dosage of 50–200 mg/day. (C.I)
3. Evaluate response to thiamin challenge over a one month period by assessing plasma BCAA and/or tolerance for dietary BCAA. (D.II)
4. Maintain thiamin supplementation and appropriate dietary BCAA restriction in thiamin-responsive individuals. (D.II)

Table 3
Nutrient recommended intake and sources in the dietary treatment of well individuals with MSUD.

Nutrient	Recommendation	Source
LEU	Sufficient intake to allow adequate protein synthesis for growth, repair and health maintenance and to achieve LEU concentrations in recommended treatment range. LEU allowance is also dependent on residual BCKD activity, age, weight, sex, life stage and health of the individual with MSUD.	<ul style="list-style-type: none"> • Intact protein (PRO) <i>In infants:</i> breast milk or infant formula with known LEU content <i>In children and adults:</i> foods such as fruits/vegetables and some grains/cereals that are typically low in protein and for which there is a known LEU content
PRO	DRI ^a Plus additional 20–40% if an amino acid–based medical food is used ^b	<ul style="list-style-type: none"> • Intact PRO (as above) • BCAA-free medical food^c
VAL, ILE	VAL and ILE are essential amino acids and may need to be supplemented when BCAA are restricted to achieve appropriate LEU blood concentrations. To promote anabolism of LEU, when LEU blood concentrations are high, additional supplementation of VAL and ILE is often required	<ul style="list-style-type: none"> • Intact PRO • Supplemental VAL, ILE^d
Energy	DRI ^a	<ul style="list-style-type: none"> • Intact PRO • BCAA-free medical food • Free foods^e • Modified low-PRO food^f
Other nutrients, minerals and vitamins ^f	DRI ^a	<ul style="list-style-type: none"> • Intact PRO • BCAA-free medical food • Supplemental nutrients, vitamins and minerals^g

Requirements for individuals with MSUD change with catabolic illness/conditions.

^a Dietary reference intakes: recommended intakes for individuals by age, size, sex, and life stage. <http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables>.

^b See ref. [71] pp 126–129.

^c Medical food is a food that is formulated to be consumed or administered enterally under the supervision of a physician and that is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation [section 5(b), Orphan Drug Act (21 U.S.C. 360ee) (b)(3)] [72].

^d 1% solutions are convenient for adding to the medical food when supplementation is necessary.

^e Free foods contain little or no detectable PRO/BCAA and consist mostly of sugars, pure starches and/or fats.

^f Modified low-protein foods include pastas and baked goods where higher protein grains/flours are replaced by protein-free starches.

^g Included are essential fatty acids and DHA, vitamin D, vitamin A, calcium, iron, zinc, selenium. Most BCAA-free medical foods are supplemented sufficiently with the nutrients and micronutrients that may be deficient in a diet low in BCAA. Compliance with taking the full medical food prescription is important in meeting these nutrient requirements. In addition, there are some medical foods that have been modified to improve taste, decrease calories or volume in order to increase compliance that may have insufficient supplementation of some micronutrients, vitamins and minerals.

3.4. Pregnancy and postnatal period

The woman with MSUD who is pregnant requires increased protein intake to support the proliferation of maternal tissues and growth of the fetus, while keeping the plasma BCAA within the treatment range to maintain metabolic homeostasis [12,21,49–51]. Energy intake must also support increased needs associated with pregnancy [12,49,50]. Supplemental vitamins and minerals may be needed for those nutrients not adequate in the medical food consumed [12,50]. Assessment of plasma carnitine concentrations has been recommended with provision of supplemental carnitine if the free carnitine falls below normal concentrations; however there is no strong evidence for this [50]. Catabolism should be prevented or minimized in all stages of pregnancy and the postpartum period. Tube or parenteral feeding may be needed, if oral

intake is not adequate [52]. Nutritional counseling will be needed for assisting the pregnant woman to achieve adequate intake during periods of nausea or decreased appetite [21]. Breastfeeding by a woman with MSUD is encouraged if there is close monitoring of intake and nutritional and clinical status [12].

Table 4
Recommended daily nutrient intakes of BCAA, PRO, energy and fluids for individuals with MSUD when well.^a

Age	Nutrient					
	LEU mg/kg	ILE mg/kg	VAL mg/kg	Protein g/kg	Energy kcal/kg	Fluid mL/kg
0 to 6 months	40–100	30–90	40–95	2.5–3.5	95–145	125–160
7 to 12 months	40–75	30–70	30–80	2.5–3.0	80–135	125–145
1–3 years	40–70	20–70	30–70	1.5–2.5	80–130	115–135
4–8 years	35–65	20–30	30–50	1.3–2.0	50–120	90–115
9–13 years	30–60	20–30	25–40	1.2–1.8	40–90	70–90
14–18 years	15–50	10–30	15–30	1.2–1.8	35–70	40–60
19 years + ^b	15–50	10–30	15–30	1.1–1.7	35–45	40–50

^a Adapted from Marriage, B [21].

^b Males and non-pregnant, non-lactating females.

Recommendations

Pregnancy and postnatal period in women with MSUD

1. Monitor closely and provide individualized dietary guidance to assure that intake is adequate to meet the increased protein, BCAA and energy requirements of pregnancy. (B.I)
2. Maintain plasma BCAA concentrations in the normal (MSUD) treatment range (LEU: 75–300 μ mol/L; ILE and VAL: 200–400 μ mol/L) throughout pregnancy. (B.I)
3. Treat pregnancy-related poor appetite, nausea and vomiting aggressively to prevent or minimize endogenous protein catabolism. See treatment strategies to prevent endogenous catabolism in Research Question 1. (A.I)
4. Evaluate the need for vitamin and/or mineral supplementation based on the pregnant woman's prescribed medical food, dietary adherence and laboratory assessment. (D.II)
5. Pay special attention to the prevention of catabolism during particularly vulnerable periods of labor/delivery and the first two weeks postpartum, as well as up to six weeks postpartum. (C.I)
6. Provide increased nutrient intake and close clinical and biochemical monitoring for the woman with MSUD who is breastfeeding. (D.I)

3.5. Liver transplantation

Liver transplantation is a viable option for individuals with MSUD [12,53–56] and the risks and benefits should be evaluated on a case-by-case basis [57–59]. To be candidates for liver transplantation, individuals should be in good metabolic control through dietary management of their BCAA [54]. In the perioperative period, continuous glucose infusion is necessary to prevent catabolism, sodium/water homeostasis maintained to avoid brain edema, plasma amino acid analyses available to monitor the BCAA concentrations, and parenteral BCAA-free amino acids available should transplantation fail [12,54]. Studies report that after successful transplantation, patients can consume a diet with no BCAA restrictions, and are no longer at risk for metabolic decompensation or future central nervous system insult [53,60,61]. There are no published studies reporting nutrition counseling during the transition to an unrestricted diet, nor the monitoring of growth and nutritional status to ensure that their dietary intake is appropriate. Consensus supports diet transition counseling and post-transplant nutrition and anthropometric monitoring [12].

Recommendations

Liver transplantation in individuals with MSUD

1. Consider liver transplantation as a viable treatment option for individuals with MSUD. (B.II)
2. Attempt to bring candidates for liver transplant into good metabolic control (prior to surgery) through dietary management of BCAA. (C.II)
3. Prevent metabolic decompensation in the perioperative period. (B.I)
4. Allow relaxation of the BCAA-restricted diet and lift precautions for severe metabolic decompensation for individuals with MSUD who have had successful liver transplantation. (C.I)
5. Provide nutrition counseling to assist in dietary transition, and monitor the anthropometric and nutritional status of individuals with MSUD who have had successful liver transplantation. (E.II)

4. Discussion and conclusion

The worldwide incidence of MSUD is approximately 1:185,000. Although there are areas of much higher incidence, such as among the old-order Mennonite community where the incidence may be as high as 1:200 births, most clinics see very few individuals with MSUD. With such small patient populations, it is difficult to accumulate outcome data except through multicenter collaboration. The majority of publications are case studies and case series, often retrospective and lack data from age-matched controls. The MSUD Nutrition Management Guideline attempts to address these deficiencies in the peer-reviewed literature with the addition of a systematic review of gray literature and consensus data from two Delphi surveys and one nominal group session. Treatment recommendations and guidelines are currently published for a number of disorders but often they rely on either consensus and expert opinion [62] or literature review [63]. The approach used for this guideline project is to combine information from all sources and add systematic rating scores for the resulting recommendations.

The backbone of this guideline comes from the five research questions. These were chosen based on the workgroup's assessment of nutritional management topics that were inadequately

addressed in the literature or for which there appeared to be divergent opinions. The recommendations that are derived from the assessment of all sources vary widely in the strength of their ratings (from A to E). Those recommendations with the weakest ratings had no or few published studies on the topic, had studies that failed to demonstrate statistical significance, and/or were addressed mainly through a consensus process. This does not signify that a recommendation with a weak rating should be ignored, or is invalid. But, it does highlight the fact that there are no adequate peer-reviewed publications describing well-designed studies on the topic [64].

There are new and novel therapies being examined for the treatment of MSUD. These include, but not limited to, the use of norleucine [65], antioxidants [66,67], hepatocyte transplantation [68], sodium phenylbutyrate [69] and carnitine [70]. There are limited data to indicate how these adjuvant therapies will impact or change dietary recommendations. Future versions of the guidelines can be expected to address these treatments.

In addition to the recommendations based on the research questions, the guideline provides background information about MSUD, nutrient intake recommendations by age, nutrition monitoring recommendations and links to appropriate resources and tools to help implement the recommendations. http://gmdi.org/index.php?option=com_content&view=article&id=22&Itemid=17.

Use of a dedicated, secure, online portal to access pre-publication guideline materials allowed the workgroup to communicate remotely during the evidence gathering, assessment and writing phases; and will allow timely revisions and updates of the published version by the workgroup. Online open access allows users of the published guideline to submit comments, focus on single topics or delve more deeply into the conclusions and recommendations through the linked evidence, surveys and other resources.

Using this dynamic process, the guideline provides an evaluation of the current knowledge of nutrition management of individuals with MSUD while pointing to the need for more collaboration in the study of outcomes using various treatment modalities.

Conflicts of interest

Dianne Frazier – received honoraria from Nutricia North America and Abbott Nutrition for consulting and lectures.

Courtney Allgeier – employee of Abbott Nutrition.

Caroline Homer – received honorarium for lecturing from Abbott Nutrition.

Barbara Marriage – employee of Abbott Nutrition.

Beth Ogata – none declared.

Frances Rohr – none declared.

Patricia Splett – none declared.

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