State of California—Health and Human Services Agency
Department of Health Care Services

TOBY DOUGLAS
DIRECTOR

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TO: ALL COUNTY CALIFORNIA CHILDREN SERVICES (CCS) PROGRAM ADMINISTRATORS, MEDICAL CONSULTANTS, STATEWIDE CONSULTANTS, AND STATE SYSTEMS OF CARE DIVISION STAFF

SUBJECT: AUTHORIZATION OF THE SERVICES AND PRODUCTS FOR THE KETOGENIC DIET AS A TREATMENT FOR EPILEPSY

I. PURPOSE

The purpose of this Numbered Letter (N.L.) is to disseminate policy regarding the CCS Program's process for reviewing and authorizing requests for the ketogenic diet as a treatment for epilepsy.

II. BACKGROUND

Anti-epileptic drugs (AEDs) are the preferred treatment to control seizures in most children with refractory epilepsy. The AEDs are effective at controlling seizures in approximately two-thirds of all children with seizure disorders.[1] However, the remaining one-third of children who do not respond or do not respond adequately to AEDs typically relies on non-pharmacologic treatments when surgical options are not recommended or utilized. One of the oldest and most common non-pharmacologic treatments is the ketogenic diet. The ketogenic diet is a high fat, low carbohydrate diet with adequate protein that results in ketosis. Since the 1920's, the ketogenic diet has been associated with a reduction in intractable seizures. However, as new AEDs were developed and became readily available from the 1950's onward, the popularity of the ketogenic diet waned as a treatment for refractory epilepsy. A renewed interest in the ketogenic diet occurred in the mid-1990's when it became apparent that the newer generation of AEDs did not adequately inhibit seizures in approximately one-third of all children. This renewed interest led to a resurgence in the use of the ketogenic diet and resulted in increased research to evaluate its efficacy.

[1] Kwan, P. & Broodie, M.J. Effectiveness of first antiepileptic drug. Epilepsia. 2001; 42(10):1255-60.

Evidence-based studies over the last two decades have given credence to the effectiveness of this diet when AEDs do not provide the desired effects in infants, children, and adults. Studies have shown that for individuals who do not respond to AEDs, the ketogenic diet or one of its variations is effective at reducing seizures in 60 percent of this population by 50 percent and 30 percent of this population by 90 percent.[2] In 2008, results from a meta-analysis led an Expert Consensus Panel to conclude that the ketogenic diet should be considered as a treatment method in children with intractable epilepsy following two unsuccessful trials with AEDs and the treatment of choice for seizures that result from glucose transporter protein-1 (GLUT-1) deficiency or pyruvate dehydrogenase deficiency (PDHD).[3] The Expert Consensus Panel also identified a number of conditions that are responsive to the diet and warrant initiation before the failure of two AEDs. These conditions include infantile spasms, Doose syndrome, Rett syndrome, tuberous sclerosis complex, Dravet syndrome, and children with epilepsy who are exclusively tube fed or formula fed.[3] However, a 2012 United States (U.S.) Consensus Report regarding infantile spasms recommends the ketogenic diet as a "second-line therapy when adrenocorticotropic hormone (ACTH) or vigabatrin fail or are deemed inappropriate for a given patient." [4]

The recommendations supporting the use of the ketogenic diet continue to be forthcoming both nationally and internationally. In 2012, the Cochrane Collaboration noted that their most recent review of the literature based on four randomized, controlled trials led to a stronger position in support of the ketogenic diet for treating refractory epilepsy.[5] Also, in 2012, The National Institute for Health and Clinical Excellence (NICE) endorsed the use of the ketogenic diet for "children and young people who have had seizures not responsive to appropriate anti-epileptic drugs."[6] At this point, the ketogenic diet is well recognized as a safe and effective non-pharmacological treatment for refractory epilepsy in the U.S. and throughout most of the world.

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[2] Henderson, C.B., Filloux, F.M., Alder, S.C., et al. Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. Journal of Child Neurology. 2006; 21(3):193 – 198.
[3] Kossoff, E.H., Zupec-Kania, B.A., Amark, P.E., et.al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia. 2009; 50(2):304-317.
[4] Pellock, J.M., Hrachovy, R., Shinner, S., Baram, T.Z., et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010; 51(10): 2175-2189.

[5] Levy, R.G., Cooper, P.N., Giri, P. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database of Systemic Reviews. 2012; March 14, Issue 3.
[6] National Institutes for Health Care and Excellence. NICE Clinical Guidance CG137 - The epilepsies: the diagnosis and management of epilepsies in adults and children in primary and secondary care. Jan. 2012. Website: http://guidance.nice.org.uk/CG137. Website accessed 10/25/13.

III. **POLICY**

A. Effective the date of this N.L., the requests for the use of the ketogenic diet as a non-pharmacological treatment for refractory seizures will be authorized as an Early and Periodic Screening, Diagnosis, and Treatment Supplemental Services (EPSDT-SS) benefit to full-scope, no share of cost Medi-Cal beneficiaries, or as a CCS Program benefit for the CCS-only recipients when the following criteria are met:

1. The ketogenic diet is requested by a CCS-paneled neurologist or a CCS-paneled primary care physician (PCP) when a client currently on the ketogenic diet relocates and is awaiting establishment of neurology services.

2. The ketogenic diet will be implemented and monitored by a CCS-paneled registered dietitian (RD).

3. The CCS Program hospital or CCS Program facility has approved written guidelines and/or protocols for pre-evaluation, initiation, monitoring, and discontinuation of the diet. These guidelines and/or protocols will be updated biennially.

B. Documentation from the CCS-paneled neurologist and/or the CCS-paneled RD must support the following:

1. Client and/or family/guardian demonstrate knowledge and skills necessary for compliance with recommended diet.

2. Client and/or family/guardian demonstrate a high level of motivation to achieve and maintain the recommended level of ketosis and understand the rationale and benefits of strictly adhering to the diet.

3. No contraindications are present. Contraindications include but are not limited to:[3]

    a. Primary carnitine deficiency.

    b. Carnitine palmitoyltransferase I or II deficiency.

    c. Carnitine translocase deficiency.

    d. Porphyria.

    e. Pyruvate carboxylase deficiency.

    f. Fatty acid oxidation defects.

        (1) Medium-chain acyl dehydrogenase deficiency.

        (2) Long-chain acyl dehydrogenase deficiency.

        (3) Short-chain acyl dehydrogenase deficiency.

        (4) Long-chain 3-hydroxyacyl-CoA deficiency.

        (5) Medium-chain 3-hydroxyacyl-CoA deficiency.

    g. Inability to maintain adequate nutrition.

    h. Parent or caregiver noncompliance.

C. The CCS Program's authorized benefits for implementation and follow-up include the following:

1. The CCS-Paneled Neurologist supervision.

2. Inpatient and outpatient RD services for Medical Nutrition Therapy (MNT). Outpatient RD services require an authorization to the outpatient provider number. The CCS-paneled RD time is recorded using 15 minute increments, or units with 1 unit equal to 15 minutes.

3. The maximum authorized MNT time allowed is as follows:

    a. Pre-evaluation – 3 hours (12 units) per patient.

    b. Pre-diet Preparation/Initiation (applicable for outpatient services) – 5 hours (20 units) per patient.

    c. Monitoring/Follow-up

        (1) Within 1 – 2 weeks of diet initiation – 3 hours (12 units) per patient.

        (2) Monthly (for first 3 months) – 3 hours (12 units) per patient.

        (3) Every 3 months for the remainder of the first year – 2 hours (8 Units) per patient.

        (4) After the first year, 2.5 hours (10 units) every 6 months for children older than 5 years of age; younger children and adolescents may require additional time.

        (5) Additional times to adjust diet as medically indicated and address caregiver and/or provider concerns will be allowed. Medical indication, such as abnormal laboratory values, increased seizure activity, illness, or patient and/or caregiver concern must be documented and available for the CCS Nurse Case Manager if requested.

    d. Discontinuation – 6 hours (24 units) per patient over the weaning period.

4. Hospitalization to initiate the ketogenic diet.

5. Nutritional products ordered by the CCS-paneled neurologist for oral and enteral feedings.

6. Gram scales.

7. Laboratory tests ordered by the CCS-paneled neurologist.

8. Urine test strips for monitoring ketone levels.

D. The following items related to the ketogenic diet are not the CCS Program benefits and will not be authorized by the CCS Program:

   1. Books, including audio versions.

   2. CDs.

   3. Videos.

   4. Materials not previously listed as allowable.

E. When the ketogenic diet is effective at controlling seizures, the child will remain CCS Program eligible:

   1. Following the neurologist discontinuing AEDs or decreasing AEDs to less than 2 different medications per day.

   2. If the frequency and duration of seizures no longer requires monthly medical office visits.

   3. If the frequency and duration of seizures does not require 4 or more changes in dosage or type of medication in the previous 12 months.

   4. For the initial 12 months following discontinuation of the ketogenic diet due to efficacy or as long as the CCS-paneled Neurologist deems medically necessary.

F. Authorization for use of the ketogenic diet for conditions other than epilepsy:

   1. The ketogenic diet may be authorized for other CCS-eligible conditions including, but not limited to, glioblastomas, metabolic disorders and other neurological conditions when medically appropriate.

   2. Authorization for medical conditions other than seizure disorders requires state level approval from a Systems of Care Division Medical Consultant or designee.

IV. **POLICY IMPLEMENTATION**

A. The CCS Program Nurse Case Manager or designee shall ensure that the following are verified:

1. The request for a ketogenic diet is from a CCS-paneled neurologist and is accompanied by the necessary documentation indicating medical need. Documentation from the neurologist requesting implementation or continuation of the ketogenic diet must be submitted within 6 months of the last patient visit or follow-up contact.

2. The request is accompanied by the necessary documentation from the CCS-paneled RD that the client and family/guardian have been pre-evaluated and demonstrate knowledge and skills necessary for compliance with the recommended diet.

3. Hospital or neurology clinic/outpatient clinic guidelines/protocols for pre-evaluation, initiation, monitoring, and discontinuation of the ketogenic diet have been submitted and are current and approved by the administering CCS Program's facility.

B. If the request is determined to be medically appropriate, the authorizations should be processed as follows:

1. For full-scope Medi-Cal, no share of cost beneficiaries, the request should be processed as an EPSDT-SS (91) Service Authorization Request (SAR). Instructions for completing the EPSDT-SS (91) SAR can be found in Section 12.3 of the CMS Net SAR/Web Manual. These instructions can be accessed at http://www.dhcs.ca.gov/services/ccs/cmsnet/Pages/WebManual.aspx or by using the following link: EPSDT-SS SARs Requiring County Approval.

2. For the CCS-only beneficiaries and Medi-Cal Share of Cost beneficiaries, the request should be processed using the 97 SAR prefix as follows:

a. The MNT provided by the CCS-paneled RD for the ketogenic diet should be authorized using HCPCS Z5802. Updates to this code may be communicated through "This Computes" or an updated N.L.

b. The inpatient hospital initiation of the ketogenic diet should be authorized using inpatient stay. No separate RD authorization is required.

c. Gram scales should be authorized using the EPSDT-SS Z5999 code or the department's current workaround procedure for obtaining items not covered by Medi-Cal but obtainable for the CCS Program beneficiaries. Updates to the workaround will be communicated through "This Computes."

d. Laboratory tests should be authorized using the Physician's Service Code Grouping 01 (SCG 01).

e. Urine test strips for ketone monitoring should be ordered using the 11-digit Medi-Cal code for the product.

The Systems of Care Division will continue to monitor developments in the treatment of epilepsy and the efficacy of the ketogenic diet, and will update authorization for services as appropriate. For more information regarding the ketogenic diet, see attachment 1.

If you have any questions regarding the authorization of the ketogenic diet, please contact Donna Vaughan MS, RD, IBCLC at (916) 323-8064 or via e-mail at donna.vaughan@dhcs.ca.gov .

Sincerely,

ORIGINAL SIGNED BY ROBERT J. DIMAND

Robert J. Dimand, M.D.
Chief Medical Officer
Systems of Care Division

Attachments

Attachment 1

Addendum: Ketogenic Diet Policy

Introduction

Since the 1920's, the ketogenic diet, a high fat, low carbohydrate diet that results in ketosis, has been associated with a reduction in intractable seizures. As new anti-epileptic drugs (AEDs) were developed and became readily available from the 1950s onward, the use of the ketogenic diet as a treatment for epilepsy waned. A renewed interest in the ketogenic diet occurred in the mid-1990s when it became apparent that the newer generation of AEDs did not adequately inhibit seizures in approximately thirty percent of children. This renewed interest led to a resurgence in the use of the ketogenic diet and resulted in increased research establishing the efficacy of the diet.

Evidence based studies have given credence to the effectiveness of this diet when AEDs do not provide the desired effects in infants, children, and adults. Studies have shown that for individuals who do not respond to AEDs, the ketogenic diet or one of its variations is effective at reducing seizures in 60 percent of this population by 50 percent and 30 percent of this population by 90 percent.[1] In 2008, results from a meta-analysis led an Expert Consensus Panel to conclude that the ketogenic diet should be considered as a treatment method in children with intractable epilepsy following two unsuccessful trials with AEDs and the treatment of choice for seizures that result from glucose transporter protein-1 (GLUT-1) deficiency or pyruvate dehydrogenase deficiency (PDHD).[2] The Expert Consensus Panel also identified a number of conditions that are responsive to the diet and warrant initiation before the failure of two AEDs. These conditions include infantile spasms, Doose syndrome, Rett syndrome, tuberous sclerosis complex, Dravet syndrome, and children with epilepsy who are exclusively tube fed or formula fed.[2] However, a 2012 United States (U.S.) Consensus Report regarding infantile spasms recommends the ketogenic diet as a "second-line therapy when ACTH or vigabatrin fail or are deemed inappropriate for a given patient." [3]

At this point, the ketogenic diet is recognized as a safe and effective non-pharmacological treatment for refractory epilepsy in the U.S. and throughout most of the world. This addendum will focus on numerous aspects of the ketogenic diet that should be considered when implementing the ketogenic diet as Medical Nutrition Therapy (MNT) for refractory epilepsy.

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[11] Henderson, C.B., Filloux, F.M., Alder, S.C., et al. Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. Journal of Child Neurology. 2006; 21(3):193 – 198.

[2] Kossoff, E.H., Zupec-Kania, B.A., Amark, P.E., et.al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia. 2009; 50(2):304-317.

[3] Pellock, J.M., Hrachovy, R., Shinner, S., Baram, T.Z., et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010; 51(10): 2175-2189.

The Ketogenic Diet and Recent Variations

The classic ketogenic diet is a 4:1 ratio of fat to carbohydrate and protein, limits calories to 80 percent- 90 percent of recommended intake and restricted fluids. Current protocols provide adequate calories and proteins for growth and do not restrict fluid intake. A number of variations to the classic ketogenic diet have emerged over the last decade as many patients found the diet unpalatable and difficult to follow for extended lengths of time.

Recent studies demonstrate that variations on the classic ketogenic diet such as the Modified Atkins Diet (MAD), Medium Chained Triglyceride (MCT) Diet, or Low Glycemic Index Diet also result in a significant reduction in the frequency of seizures in some individuals.[2] In fact, one recent study indicates that the Modified Atkins Diet is as effective as the classic ketogenic diet in reducing seizures in children.[4] Since variations on the classic ketogenic diet are less restrictive, more palatable, and the body of evidence is increasing regarding their efficacy, they are being implemented in children and adults in greater frequency.[5]

Besides the macronutrient variations of the different ketogenic diets, the form the diet is consumed in may increase the effectiveness of the treatment. A study published in 2013 indicates that children using "a liquid (classic) ketogenic formula showed better growth patterns and significantly more seizure control" than patients who followed the Modified Atkins Diet and patients on anti-epileptic medications alone.[6] The benefit of the liquid formula is that all macronutrients and micronutrients are tightly controlled. However, long-term compliance with using a liquid ketogenic formula was not evaluated. Given a lack of compliance with the classic ketogenic diet, a liquid formula may only be appropriate for individuals requiring enteral nutrition.

Variations on the classic ketogenic diet may not be appropriate for some forms of epilepsy. A recent study determined that the Modified Atkins Diet and Low Glycemic Index Diet were not as effective as the classic ketogenic diet for controlling seizures in children with GLUT-1 deficiency.[7]

At this time, the classic ketogenic diet with adequate calories, proteins, and without fluid restrictions continues to be the primary non-pharmacological dietary treatment for refractory epilepsy in children. The Expert Consensus Panel recommends that the type of ketogenic diet chosen "should be based on the dietary needs and habits of the individual child." [2] The ketogenic diet will continue to evolve as research

[4]Chen, W., & Kossoff, E.H. Long-term follow-up of children treated with the modified Atkins diet. Journal of Child Neurology. 2010; 27(6): 754-758.
[5] Carvenka, M.C., Kossoff, H.E. Dietary treatment of intractable epilepsy. Continuum: Lifelong learning in Neurology. 2013; 19(3, Epilepsy): 756-766.
[6] El-Rashidy, O.F., Nassar, M.F., Abdel-Hamid, I.A., Shalta, R.H., et.al. Modified Atkins diet vs classic ketogenic formula in intractable epilepsy. Acto Neurol Scand. 2013; 128(6): 402-408.
[7] Klepper, J., Leiendecker, B.L. Glut1 deficiency syndrome and novel ketogenic diets. Journal of Child Neurology. 2013; 28(8): 1041-1044.

continues and evidence supports the expanded use of the ketogenic diet beyond refractory epilepsy.[7]

Comparisons of the Different Types of Dietary Treatments[8]

	Usual Starting Macronutrient Prescription		
	Fat	**Protein**	**Carbohydrate**
Classical Ketogenic	90% of energy, long chain; 4:1 ratio	10% of energy combined from protein and carbohydrate	
MCT	30 – 60% of energy from MCT, 11 – 45% from long chained	10% of energy	15 – 19% of energy
Modified Atkins	Not Measured – high fat foods encouraged	Not limited	10 g/d children 15 g/d daily for adults
Low Glycemic Index	60% of energy	20 – 30 % of energy	40 – 60 g/d, low glycemic index only

Initiation

As the diet has evolved so has the method of initiation. Until the last ten years, fasting and hospitalization were standard protocols for initiation. A study done in 2005 determined that initiating the diet without a fasting period resulted in the same efficacy as fasting and resulted in less side effects.[9] Fasting may be appropriate when a quicker state of ketosis is determined to be beneficial.[2] Likewise, studies have shown that the diet can be initiated on an outpatient basis with lower ratios of fat to carbohydrate and protein and less restriction of calories, fluids, and proteins in many cases.[10] Inpatient initiation is still desirable for many patients, especially infants and those requiring enteral feeds.[2] Method of initiation should be determined based on diet prescription, type of epilepsy, concurrent conditions, age of patient, and patient's and caregiver's needs.

It is generally recommended that individuals strictly follow the diet for a minimum of three to four months to determine the efficacy of the diet. While some individuals note a reduction in seizures within the first few days of initiation, others do not see a decrease in seizure activity until three months or longer after adhering to the diet. Due to the wide variation in obtaining a reduction in seizure activity, the Expert Consensus Panel recommends that "the ketogenic diet should be used for at least 3.5 months before considering discontinuation".[2]

[8] Neal, E.G., Gross, J.H. Efficacy of dietary treatments for epilepsy. Journal of Human Nutrition and Dietetics. 2010; 23: 113 -119.
[9] Bergqvist, A.G., Schall, J.I., Gallagher, P.R., et al. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. Epilepsia. 2005; 46(11): 1810-1819.
[10] Vaisleib, I.I., Buchhalter, J.R., & Zupanc, M.L. Ketogenic diet: outpatient initiation, without fluid or calorie restrictions. Pediatric Neurology. 2004; 31(3): 198-210.

Monitoring the Individual on the Ketogenic Diet

Children prescribed the ketogenic diet require close monitoring by the registered dietitian (RD) and the neurologist. All children should be seen by the RD within two weeks of initiation and monthly for the first three months. For the remainder of the first year, follow-ups should occur at least every three months. Infants under the age of one may need to be monitored more frequently. After the first year, follow-ups may be extended to every six months as long as the patient and/or caregiver demonstrates compliance, seizure activity remains stable, healthcare provider recommends less frequent appointments and communication between patient or caregiver, and health care provider is accessible in the interim.

The Expert Consensus Panel recommends the following be monitored every three months for the first year of treatment:

RD Nutrition Assessment

- Obtain height, weight, ideal weight for stature, growth velocity, BMI when appropriate
- Review diet prescription (calories, protein, and fluid)
- Review vitamin and mineral supplementation based on dietary reference intake (DRI) guidelines
- Assess compliance to therapy
- Adjust therapy if necessary to improve compliance and optimize seizure control

Neurology Assessment

- Efficacy of the diet
- Anti-convulsant reduction (if applicable)
- Should diet be continued?

Laboratory Assessment

- Complete blood count with platelets
- Electrolytes to include serum bicarbonate, total protein, calcium, magnesium, and phosphate
- Serum liver and kidney profile (including albumin, AST, ALT, blood urea nitrogen, creatinine)
- Fasting lipid profile
- Serum acylcarnitine profile
- Urinalysis
- Urine calcium and creatinine
- Anticonvulsant drug levels (if applicable)

Optional (if applicable)

- Serum Beta-Hydroxybutyrate (BOH) level
- Zinc and selenium levels
- Renal ultrasound
- DEXA scan
- EEG

The above are general guidelines set forth by the Expert Consensus Panel.[2] They are not standards of care. The physician and RD should assess each patient individually based on clinical judgment and established protocols.

In addition to medical monitoring, the individual or parent/caregiver of the child is frequently instructed to monitor urinary ketone levels at home several times per week. Recommended range for urinary ketones is usually "moderate to large" as indicated by the color chart on the outside of the test strip container or found in the directions. A health care provider who is part of the ketogenic team will instruct the patient or parent/caregiver on the recommended level of ketosis and use of the ketone test strips when they are prescribed.

Duration and Cessation

The length of time an individual should remain on the diet to obtain optimal benefits is not clearly delineated. Typically, if a child has greater than a 50 percent reduction in seizure activity, the diet can be discontinued after two years. However, when greater than a 90 percent reduction of seizures has occurred, the diet has been reported useful for six to twelve years.[11] An extended length of dietary treatment may be beneficial for patients with seizures that result from GLUT-1 deficiency or PDHD.[2] Giving credibility to discontinuing the ketogenic diet after two years of efficacy was a study published in 2007 which reported that children who have become seizure free after following the diet for two years, remained seizure free.[12] While no definite length of time to remain on the diet has been clearly defined, it is recommended that weaning from the ketogenic diet be gradual, over two to three months, unless a faster wean is medically indicated.[2]

Ketogenic Diet and Medication

[11] Groesbeck, D.K., Bluml, R.M. & Kossoff, E.H. Long-term use of the ketogenic diet in the treatment of epilepsy. Dev. Med. Child Neurology. 2006; 48(12): 978-981.
[12] Martinez, C.C. & Pyzik, P.L., Discontinuing the ketogenic diet in seizure-free children. Epilepsia. 2007; 48(1): 187-190.

While the ketogenic diet is typically implemented in children that have not responded to AEDs, it is frequently used as an adjunct treatment with medication. Many children taking AEDs will find a greater reduction in seizure activity using both treatments concurrently. For children that respond positively to the diet, the dose of medication is often reduced and in some instances completely discontinued "after several months of success".[2] Children that respond positively to the diet will remain California Children's Services (CCS)-eligible for one year following discontinuation of the ketogenic diet due to efficacy even if they no longer meet the medical criteria for eligibility.

Most AEDs are safe to use concurrently with the ketogenic diet. However, there are a few AEDs that may interact adversely with this form of MNT. Children taking phenobarbital may have increased seizure activity when the ketogenic diet is added as a treatment.[13] In addition, patients taking carbonic anhydrase inhibitors, such as acetazolamide or methazolamide, are at an increased risk for metabolic acidosis especially after initiation of the diet due to a reduction in bicarbonate levels and to increased acid levels caused by ketones.[14] Therefore, it is recommended that bicarbonate levels be monitored when carbonic anhydrase inhibitors are prescribed. Even with the possibility of adverse effects, the Expert Consensus Panel states, "There are no known drug-nutrient interactions that would prohibit the use of the ketogenic diet while taking anti-seizure medications".[2] Nonetheless, children prescribed AEDs and placed on a ketogenic diet should be monitored for possible adverse effects.

Many medications contain sufficient amounts of carbohydrates that prevent or reduce the desired level of ketosis resulting in less than adequate seizure control. Medications in the forms of elixirs, syrups, and liquid suspensions tend to have higher levels of carbohydrates than most other forms of medication. Some medications in solid forms may also contain levels of carbohydrates that prevent ketosis. Therefore, whenever possible, it is important to choose medications with the lowest carbohydrate content available.

Nutrient Supplementation

Since the ketogenic diet severely limits many nutrient dense foods, it is low in numerous vitamins and minerals thus requiring supplementation. A carbohydrate-free multivitamin and mineral supplement plus added calcium and vitamin D are the standards for supplementation. Supplementation of other nutrients including, but not limited to fiber, zinc, iron, and carnitine may be warranted and advised based on individual need. Additional recommendations for vitamin supplementation are identified in the 2008 Consensus Statement.[2]

[13] Morrison, P.F., Pyzik, P.L., Hamdy, A., Hartman, A.L., Kossoff, E.H. The influence of concurrent anticonvulsants on the efficacy of the ketogenic diet. Epilepsia. 2009; 50(8): 1999-2001.
[14] Takeoka, M., Riviello, J.J., Pfeifer, H., Thirle, E.A. Concomitant treatment with topiramate and the ketogenic diet in pediatric epilepsy. Epilepsia. 2002; (43)9: 1072-1075.

Adverse Effects

The ketogenic diet can result in adverse effects even though it is composed of readily available food items. Fortunately, only in rare instances are the side effects severe enough to warrant discontinuation of the diet.[2] Potential side effects need to be addressed with the patient or primary caregiver before diet initiation. Adverse effects are frequently divided into two categories - early on-set and late on-set adverse effects.

Early on-set side effects include acidosis, hypoglycemia, gastrointestinal distress (including diarrhea, vomiting, abdominal pain, and constipation), dehydration, and lethargy. The most common adverse effects are gastrointestinal disturbances. Most early on-set problems are temporary and less severe when the diet is initiated without fasting. Guidelines for treating hypoglycemia and acidosis should be followed based on established protocols.

Late on-set side effects may include dyslipidemia, kidney stones, carnitine deficiency and delayed growth. A number of studies have also identified cardiac abnormalities,[15] pancreatitis,[15] and higher risk for bone fractures[15] as possible side effects. Interestingly, one study found that children who remained on the diet for greater than six years had lipid levels near baseline and normal liver function.[11]

A study published in 2010, that investigated health outcomes after discontinuation of the diet found "most subjects over 18 years had normal heights, were eating a carbohydrate rich diet, and apparently maintained seizure control. Overall, there did not appear to be any particularly serious long-term adverse effects."[16] However, further investigation is warranted as this study was based on self-reported data.

Contraindications

The ketogenic diet is recommended as a treatment for children and adults with many different forms of epilepsy. The following conditions preclude its use as a treatment method to control intractable seizures. Contraindications include but are not limited to:[2]

- Primary carnitine deficiency
- Carnitine palmitoyltransferase I or II deficiency
- Carnitine translocase deficiency
- Porphyria
- Pyruvate carboxylase deficiency
- Fatty acid oxidation defects
    - Medium-chain acyl dehydrogenase deficiency

[15] Kang, H.C., Chung, D.E., Kim, D.W., Kim, H.D. Early and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004; 45:1116.

[16] Patel, A., Pyzik, P.L., Turner, Z., Rubenstein, J.E., Kossof, E.H., Long-term outcomes of children treated with the ketogenic diet in the past. Epilepsia. 2010; 51(7): 1277-1282.

- Long-chain acyl dehydrogenase deficiency
- Short-chain acyl dehydrogenase deficiency
- Long-chain 3-hydroxyacyl-CoA deficiency
- Medium-chain 3-hydroxyacyl-CoA deficiency

- Inability to maintain adequate nutrition
- Parent or caregiver noncompliance

The ketogenic diet may be contraindicated in individuals who are suitable candidates for epilepsy surgery; individuals with medical conditions that may worsen while using the diet such as liver disease, reflux disease, chronic metabolic acidosis, dyslipidemia, cardiomyopathy or renal calculi; or individuals that have special dietary requirements.[2]

Mechanisms of Action

The mechanisms underlying the anticonvulsant and antiepileptic effects of the ketogenic diet are not well understood. Initially, it was believed that the formation of ketone bodies or the resulting acidosis were the mechanisms of action. Numerous investigations over the last two decades have challenged the role of acidosis and ketones, except for the possibility of acetones as anticonvulsive agents. Most researchers believe other metabolic changes that occur contribute to the reduction of seizures. Metabolic changes induced by the ketogenic diet hypothesized as mechanisms of action include, but are not limited to: increased mitochondrial biogenesis (increased metabolic enzymes and mitochondrial number), increased glutathione peroxidase levels, enhanced gamma aminobutyric acid (GABA) levels, increased activation of ATP sensitive potassium channels, elevated free fatty acids in the brain, and inhibition of the glutamatergic excitatory synaptic transmission.[17,18,19]

Which of these metabolic changes is responsible for the reduction in seizure activity remains unknown. It is plausible that numerous factors work independently or that a number of factors have a synergistic effect in reducing seizure activity. What has become evident is that the ketogenic diet leads to reduced neuronal excitability and stabilization of the synapsis in some individuals.[20] The exact mechanism of action remains obscure and requires further investigation to draw empirical conclusions.

[17] Hartman, A.L., Gasior, M., Vining, E.P.G. & Rogawski, M.A. The neuro pharmacology of the ketogenic diet. Pediatric Neurology. 2007; May; 36(5):281-292.
[18] Bough, K.J., Wethering, J., Hassel, B., et al. Mitochondrial biogenesis in the anti-convulsant mechanism of the ketogenic diet. Ann Neurol. 2006; 60(2): 223-235.
[19] Danial, N.N., Hartman, A.L., Stafstrom, C.E. & Thio, L.L. How does the ketogenic diet work? Four potential mechanisms. 2013. 28(8): 1027-1033.
[20] Bough, K.J. & Rho, J.M. Anticonvulsant mechanisms of the ketogenic diet. Epilepsia. 2007; Jan 48(1): 43-58.

Uses Other than Epilepsy

There is growing evidence that the ketogenic diet may be an effective treatment or provide some benefit for individuals with conditions other than epilepsy. While the research is limited, it appears that the ketogenic diet may have a role in treating disorders of cellular proliferation, such as astrocytomas, gliomas, gastric cancer and prostate cancer.[21] Also, preliminary evidence suggests that the ketogenic diet may provide potential benefits for Alzheimer Disease, Parkinson's Disease, amyotopic lateral sclerosis, autism disorders, depression, and migraine headaches.[22] Lastly, one recent study supports the use of the ketogenic diet in palliative care. A pilot trial of the ketogenic diet in 16 patients with advanced metastatic tumors, reported improved emotional functioning and less insomnia in six patients thus possibly leading to improved quality of life.[22] Research is ongoing for additional uses of the ketogenic diet beyond epilepsy and other neurological disorders as metabolic research has once again come into the limelight.

Conclusion

The classic ketogenic diet and the newer variations are now well accepted as effective dietary treatments for children and adults with refractory epilepsy. Research undertaken within the last fifteen years demonstrates a clear picture of the efficacy and safety of the ketogenic diet for use with children and adults. Research also demonstrates that the response to the various ketogenic diets is determined by the etiology and type of epilepsy. With more palatable variations of the diet available and proof of the diet's effectiveness, neurologists are prescribing the ketogenic diet in greater frequency for their patients. As a result, more individuals are now living seizure free or experiencing decreased seizure activity, which is the goal of all epilepsy treatments.

At this time there is more than adequate evidence-based research for the CCS Program to authorize the ketogenic diet as a non-pharmacological treatment for intractable seizures for children who are CCS-eligible due to epilepsy. As the research continues, the dietary treatment for epilepsy and other neurological disorders will continue to evolve. The Systems of Care Division will continue to monitor dietary treatments for epilepsy and adjust the ketogenic diet policy as warranted.

[21] Baranano, K.W. & Hartman, A.L. The ketogenic diet: uses in epilepsy and other neuologic illnesses. Curr Treat Options Neurol, 2008, November 10(6): 410-419

[22] Schmidt M.[1], Pfetzer N., Schwab M., Strauss I., Kammerer U., Nutr Metab (Lond). 2011 July 27; 8(1): 54. Doi: 10.1186/1743-7045-8-54.

Attachment 2

Ketogenic Diet Checklist
for Providers and Nurse Case Managers

Patient: _____ CCS Case Number: _____
Facility: _____ Date of Request: _____

Directions for Nurse Case Managers: When items 1 – 7 and either 8 or 9 are checked **yes**, request for authorization may be approved. For items checked **no**, needed documentation must be obtained before authorization.

		Yes	No	N/A*
1	Medical Nutrition Therapy (MNT) is requested by a CCS paneled neurologist within six months of child's last neurology appointment or by a CCS paneled PCP for a child on the ketogenic diet who has relocated and is awaiting establishment of neurology services.			
2	Documentation from a CCS paneled neurologist justifying medical need for use of the ketogenic diet.			
3	Documentation from a CCS paneled registered dietitian or CCS paneled neurologist that the child's primary caretaker demonstrates knowledge, skills and motivation for compliance with the diet.			
4	Documentation from a CCS paneled neurologist that no medical contraindications are present.			
5	Hospital and/or special care center where MNT is originating has a CCS paneled registered dietitian available for initiating and monitoring the client per Section III C-3 of N.L. xxx.			
6	Approved and current hospital or neurology clinic guidelines/protocols for implementing and monitoring patient following the ketogenic diet have been submitted.			
7	All requested benefits are CCS allowable as indicated in Section III C of N. L. xxx.			
8	Authorization for a full-scope, no share of cost Medi-Cal beneficiary is processed as an EPSDT-SS (91) SAR using prefixes as indicated in Section IV B of N. L. xxx.			
9	Authorization for CCS only beneficiary or Medi-Cal share of cost beneficiary is processed as a 97 SAR using prefixes as indicated in Section IV B of N.L. xxx.			

Authorized: Yes _____ No _____ If no, reason for denial: _____
Date: _____ Case Manager: _____
* N/A – Not applicable