Anthem

Clinical UM Guideline

Subject: Ketogenic Diet for Treatment of Intractable Seizures
Guideline #: CG-MED-05
Status: Reviewed
Publish Date: 09/27/2023
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Description

This document addresses the use of a ketogenic diet to assist in the treatment of seizures.

Clinical Indications

Medically Necessary:

The use of a ketogenic diet for children and teenagers with seizures refractory to antiepileptic drugs is considered **medically necessary.**

Not Medically Necessary:

The use of a ketogenic diet for all other indications is considered **not medically necessary.**

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
99499	Unlisted evaluation and management service [when specified as services related to ketogenic diet]
ICD-10 Diagnosis	
G40.011-G40.019	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable
G40.111-G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable
G40.211-G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptics syndromes with complex partial seizures, intractable
G40.311-G40.319	Generalized idiopathic epilepsy and epileptic syndromes, intractable
G40.A11-G40.A19	Absence epileptic syndrome, intractable
G40.B11-G40.B19	Juvenile myoclonic epilepsy, intractable
G40.C11-G40.C19	Lafora progressive myoclonus epilepsy, intractable
G40.411-G40.419	Other generalized epilepsy and epileptic syndromes, intractable
G40.803-G40.804	Other epilepsy, intractable
G40.813-G40.814	Lennox-Gastaut syndrome, intractable
G40.823-G40.824	Epileptic spasms, intractable
G40.833-G40.834	Dravet syndrome
G40.89	Other seizures
G40.911-G40.919	Epilepsy, unspecified, intractable

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

Discussion/General Information

The ketogenic diet is a high-fat, low-protein, low-carbohydrate diet which has been used for the treatment of uncontrolled seizures. The diet has a 4:1 ratio of fats to carbohydrates. The composition of the diet induces ketosis, a physiologic state in which circulating ketone bodies are used as the primary fuel source in the absence of simple sugars. Ketosis is thought to inhibit seizures, although the mechanism is unknown. The ketogenic diet is quite restrictive, requiring the cooperation of the individual, family and an appropriately trained dietician. The diet may be initiated in the inpatient or outpatient setting. In the inpatient setting, children are admitted to the hospital and fasted for 1 to 2 days. The diet is then instituted gradually over a number of days. The main reason for hospitalization is to monitor the period of initial fasting, which exposes children to metabolic derangements and dehydration. In a study by Kossoff (2008), it was reported that individuals who responded to the diet, did so quickly (often within 1 to 2 weeks), but universally within the first 2 months. In children in whom the seizures are not improved after 2 months, the study suggests a regular diet could be reintroduced and other treatment options considered.

Published data shows that some children benefit from the ketogenic diet, as demonstrated by a significant reduction in seizure frequency. A meta-analysis by Henderson and colleagues (2006) supports the current uncontrolled case series reporting on the therapeutic effect of the ketogenic diet in the treatment of seizures in pediatric epileptic individuals. The analysis of 1084 pooled individuals demonstrated a greater than 50% seizure reduction in individuals who stayed on the ketogenic diet versus those who discontinued the diet.

Neal (2008) studied the effectiveness of a ketogenic diet on intractable seizures in a randomized controlled trial. Of 145 children initially enrolled, 103 completed the study and were included in the final analysis. Dropout reasons varied from changing their mind to diet intolerance. After 3 months of ketogenic diet, the mean percentage of seizures in the 54 children on the diet fell to 62% of

baseline. For the 49 children in the control group, seizures increased to 137% of baseline. The authors were surprised by the increase in seizures of the control group. Their most probable explanation is an unusual increase in seizure frequency of 3 of the children in the control group. When that data was excluded, the seizure frequency increase in the control group over 3 months was only 12%.

In 2014, Taub and colleagues looked at the records of 276 children who had been initiated on the ketogenic diet. A total of 65 children achieved freedom from seizures for a minimum of 1 month. The median time to seizure freedom after initiation of ketogenic diet was 1.5 months. Seizures recurred in 53 children with a median time to seizure recurrence of 3 months. The recurrence of seizures was reported as an occasional breakthrough and not a return to baseline seizure frequency.

A 2015 study by Lambrechts and colleagues assessed the long-term efficacy and tolerability of a ketogenic diet as an add-on treatment for children with refractory epilepsy. A total of 48 children were included initially in the study. Evaluation was done at baseline, 6 weeks, and every 3 months after initiation of diet. At each visit, the children were evaluated for seizure severity, side effects and blood and urine samples. At the 1-year follow-up, 16 children remained on the diet, and 11 remained on the diet at 2 years. In terms of seizure frequency, seizure outcome for 35 children was analyzed and the highest response was seen at 6 and 9 months of treatment. A total of 15 children had seizure clusters during baseline. After 3 months, 9 children were responders for cluster reduction. After 3 months of treatment, most of the children on the ketogenic diet had a decrease in seizure severity. Side effects included abdominal pain, vomiting, and fatigue. There were no reported abnormalities on electrocardiograms and no kidney stones. While there are limitations to this study including non-randomization, uncontrolled selection of children, and limited sample size, the results concluded that ketogenic diet was effective for children with drug-resistant epilepsy with response to diet noted after 6 months of treatment.

In a 2017 randomized controlled trial by Lambrechts and colleagues, the authors reported on the tolerability and efficacy of ketogenic diet in 48 participants (age 1 to 18 years of age) with refractory epilepsy. Primary outcome was reduction of seizure frequency by greater than or equal to 50% when compared with seizure frequency at baseline. Participants were randomized to either the ketogenic diet or to care as usual. At a 4-month follow-up, of the participants who received ketogenic diet treatment, 13 responded to the treatment (3 were seizure free while another 3 had greater than 90% reduction in seizure frequency). In the care as usual group, 2 participants were seizure free, and 1 participant had a greater than 90% reduction in seizure frequency. The most commonly reported side effect occurring in the ketogenic diet group was gastrointestinal symptoms.

A 2016 study by Ozdemir and colleagues reported on the effect of ketogenic diet on cardiac functions. A total of 61 participants with intractable epilepsy on the ketogenic diet for at least 12 months were followed. All participants received baseline serum carnitine, selenium levels, electrocardiographic and echocardiographic exams. During the 12-month follow-up, the participants received Doppler imaging to look at the ventricular systolic and diastolic functions. During the year of ketogenic diet, 33 participants were seizure free, 25 participants had seizures decreased by greater than or equal to 90%, and 3 participants had seizures decreased by greater than or equal to 50%. After 1 year of ketogenic diet, the only significant difference when compared to baseline values was decreased A-wave velocity. Ketogenic diet does not appear to have a disturbing effect on ventricular functions in the midterm, however additional longer term studies are necessary to assess the long-term effect of ketogenic diet on cardiac functions.

In a 2017 study by Winjen and colleagues, the authors reported on long-term clinical outcomes of children and adolescents with intractable epilepsy. Participants between 1 and 18 years old with diagnosed intractable seizures failing at least two anti-epileptic drugs who were not eligible for epilepsy surgery were included in the study. The participants were randomized to either the ketogenic diet (n=26) or to care as usual (n=22). Care as usual was defined as those continuing to take their anti-epileptic drugs, weekly telephone meetings with an epilepsy nurse, with follow-up visits to a neurologist and pediatrician after 4 months. Those assigned to the ketogenic diet were admitted to a tertiary epilepsy center for a 5-day introduction to the diet. Those in the ketogenic diet group were followed for 16 months. A total of 15 of 26 participants completed the follow-up of 16 months. A seizure reduction of ≥ 50% compared to baseline was 50% in the ketogenic diet group at 4 months, 34.6% at 16 months and 18.2% in the care as usual group at 4 months. The participants in the ketogenic diet group reported more gastro-intestinal problems at 4 months when compared to the care as usual group. At 16 months, those in the ketogenic diet group had fewer side effects with regard to behavior/irritability, motor problems/coordination, and cosmetic/dermatological problems. The study does show a reduction in seizures while on the ketogenic diet, however there are limitations to the study including the care as usual group was only followed for 4 months and there was a large number of participants in the ketogenic diet group who dropped out leaving a retention rate of 58% at 16 months.

Armeno (2019) reported the results of a prospective cohort study involving 45 children with a median age of 6 years and refractory epilepsy treated with ketogenic diets for a minimum of 2 years. The authors reported that 3 subjects developed acidosis, 5 constipation and 22 dyslipidemia. Nutrient deficiency occurred in 24 subjects, including vitamin D, copper, zinc, magnesium and calcium. All were treated successfully with supplements or caloric adjustments. Normal growth was observed in most subjects at 2 years, with a median SDS weight of -0.86 and -0.4 for males and females, respectively. Normal growth was observed in most subjects as well, with a median SDS height at 2 years of -0.67 and -0.42 for males and females, respectively. Growth retardation for height and weight was reported in 3 and 1 subject, respectively at the end of 2 years. Regarding seizure frequency, 4% of subjects were reported to be seizure-free. Another 26% had a >90% seizure reduction, 43% had a 50-90% seizure reduction, and 27% had a <50% seizure reduction. The authors concluded that nutritional follow-up is helpful in improving body weight, but could not avoid growth deceleration. They state that their findings confirm that children with refractory epilepsy on KD treatment require careful growth monitoring. Several limitations of this study are that confounding variables related to growth, such as antiepileptic drug use, type of epileptic syndrome, and severity of neurologic dysfunction, were not considered in the evaluation. Additionally, the association between height velocity and hormonal growth status (IGF-1) before starting and while on the diet was not addressed.

A smaller retrospective study of 29 children with refractory epilepsy treated with ketogenic diets for a minimum of 2 years was reported by (Romão Luz, 2019). The mean age of initiation was 7.9 years. At the time of the study, 18 of the subjects (62.1%) had ceased the diet. The remaining 11 subjects were still being treated with a ketogenic diet. For the 18 that ceased the diet, the mean duration was 18.2 months. The retention rate was 77.8% (n=14) at 12 months and 55.6% (n=10) at 18 months. The authors reported that of those subjects who stopped between 3 to 18 months, the reasons were family choice (n=5) or inefficacy (n=3). Regarding efficacy, at the end of the study period, 4 subjects (13.8%) became seizure free, 4 subjects (13.8%) had a ≥ 90% reduction in seizure activity and 9 subjects (31%) achieved a 50%-90% decrease in seizure activity. Of the 215 subjects who completed at least 18 months of the ketogenic diet, for 4 (26.7%) had a reduction of the number of antiepileptic drugs. Another 10 (66.7%) maintained the same number of antiepileptic drugs, and in one case there was the need to add one more antiepileptic drug. Acute complications were documented in 26 subjects, with the most frequent being hypoglycemia and nausea/vomiting. Hypercholesterolemia was present in 23 subjects (79.3%) and hypertriglyceridemia in 21 subjects. These results are promising, but the small population, lack of comparison group and other methodological limitations prevent generalization beyond the experimental setting.

Ruiz Herrero (2020) reported the results of a small retrospective-prospective cohort study involving 26 children with refractory epilepsy treated with ketogenic diets for a minimum of 2 years. The median length on the diet was 3.91 years. The most frequent reason cited for discontinuation was long duration. The authors reported a 100% reduction in seizure events in 12 out of 25 children (48%) at 3 months, 11/25 (44%) at 6 months, 15/25 (60%) at 12 months, 17/25 (68%) at 24 months, 10/17 (58.8%) at 3 years, 7/12

(58.3%) at 4 years, 4/6 (66.6%) at 5 years, and 3/5 (60%) at 6 years. A reduction in seizure incidence higher than 90% was reported in 68% of subjects at 3 months of initiation the diet, 72% after 6 months, 76% after 12 and 24 months and 3 years, 66.6% after 4 and 5 years, and 60% after 6 years. The number of subjects able to reduce their anti-epilepsy medications vs. baseline were 6/25 at 3 months, 5/25 at 6 months, 6/25 at 12 months, 9/25 at 2 years, 2/17 at 3 years, 2/1 at 4 years, 1/7 at 5 years, and 0/6 at 6 years. After 2, 3, and 4 years, one subject did not take any anti-epilepsy medications and after 5 years, two children did not take any AEDs. Out of 26 subjects, 11 had early onset side effects, including nausea and vomiting (n=4), constipation (n=3), hypoglycemia (n=3), hypercalciuria (n=3), fatigue (n=2), acidosis (n=1), diarrhea (n=1), hypocalcemia (n=1), and hypertriglyceridemia (n=1). In most cases symptoms were reported to be mild. In 4 subjects, symptoms were more severe ad a change in tier was prescribed. Most subjects were found to be adequately nourished in every check-up. Amongst the group younger than 5 years old, there was one case of mild malnutrition after 4 years on the diet, two cases of overweight at 3 and at 12 months, and one with obesity at 24 months. Amongst the children older than 5, there was one subject who was mildly malnourished at 3, 12, and 24 months, and one case of severe malnutrition at 12 months. There was one overweight subject at 3 months and at 3 years, and 2 cases at 6 and at 24 months. Obesity criteria was achieved by two subjects at 3 years, and one child at 4 years on the diet. Deficiencies in prealbumin, retinol binding protein, ferritin, were noted in a limited number of subjects throughout the study period. The height z-score was significantly lower after 2 years on the diet vs. baseline. However, there were no significant differences in the weight and BMI z-score. No significant differences were reported in the weight, height, and BMI z-score after 2 years among those children who started before 2 years of age and those who started after 2 years of age. This longitudinal study provides some interesting data regarding the long-term effects of ketogenic diets for children with epilepsy. However, the small population and heterogeneity of etiologies may limit the utility of these results.

The ketogenic diet has been initiated in an inpatient setting, primarily to monitor the individual during the initial fasting period, but also to provide the intense education required to maintain a ketogenic diet once discharged. However, studies have suggested that the diet can be safely initiated in the outpatient setting. In 2004, Vaisleib and colleagues reported on a case series of 37 individuals who underwent outpatient induction of the ketogenic diet, whose outcomes were compared retrospectively to those who underwent inpatient dietary induction. The mean age of the individuals was 6.6 years, with a range of 1.8 to 14 years. The authors reported that there was no evidence that inpatient initiation of the ketogenic diet was superior to outpatient initiation.

The use of a ketogenic diet is being studied for population groups other than children and teenagers. The peer-reviewed published literature is limited to small group sizes and observational studies or retrospective reviews (Cervenka, 2017; Thakur, 2014).

References

Peer Reviewed Publications:

1. Armeno M, Verini A, Del Pino M, et al. A prospective study on changes in nutritional status and growth following two years of ketogenic diet (KD) therapy in children with refractory epilepsy. Nutrients. 2019; 11(7):1596. pii: E1596.
2. Cervenka MC, Hocker S, Koenig M, et al. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. Neurology. 2017; 88(10):938-943.
3. Henderson CB, Filloux FM, Alder SC, et al. Efficacy of the ketogenic diet as a treatment option for epilepsy: Meta-analysis. J Child Neurol. 2006; 21(3):193-198.
4. Klein P, Janousek J, Barber A, Weissberger R. Ketogenic diet treatment in adults with refractory epilepsy. Epilepsy Behav. 2010; 19(4):575-579.
5. Kossoff EH, Laux LC, Blackford R, et al. When do seizures usually improve with the ketogenic diet? Epilepsia. 2008; 49(2):329-333.
6. Lambrechts DA, de Kinderen RJ, Vles HS, et al. The MCT-ketogenic diet as a treatment option in refractory childhood epilepsy: A prospective study with 2-year follow-up. Epilepsy Behav. 2015; 51:261-266.
7. Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand. 2017; 135(2):231-239.
8. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008; 7(6):500-506.
9. Ozdemir R, Kucuk M, Guzel O, et al. Does ketogenic diet have any negative effect on cardiac systolic and diastolic functions in children with intractable epilepsy? One-year follow-up results. Brain Dev. 2016; 38(9):842-847.
10. Romão Luz I, Pereira C, Garcia P, et al. Ketogenic diet for refractory childhood epilepsy: beyond seizures control, the experience of a Portuguese pediatric centre. Acta Med Port. 2019; 32(12):760-766.
11. Ruiz Herrero J, Cañedo Villarroya E, García Peñas JJ, et al. Safety and effectiveness of the prolonged treatment of children with a ketogenic diet. Nutrients. 2020; 12(2):306. pii: E306.
12. Taub KS, Kessler SK, Bergqvist AG. Risk of seizure recurrence after achieving initial seizure freedom on the ketogenic diet. Epilepsia. 2014; 55(4):579-583.
13. Thakur KT, Probasco JC, Hocker SE, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology. 2014; 82(8):665-670.
14. Vaisleib II, Buchhalter JR, Zupanc ML. Ketogenic diet: outpatient initiation, without fluid, or caloric restrictions. Pediatr Neurol. 2004; 31(3):198-202.
15. Wijnen BFM, de Kinderen RJA, Lambrechts DAJE, et al. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. Epilepsy Res. 2017; 132:91-99.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Martin-McGill KJ, Jackson CF, Bresnahan R, et al. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020 Jun 24;6(6):CD001903.
2. Roehl K, Sewak SL. Practice paper of the Academy of Nutrition and Dietetics: classic and modified ketogenic diets for treatment of epilepsy. J Acad Nutr Diet. 2017; 117(8):1279-1292.

Websites for Additional Information

1. National Institute of Neurological Disorders and Stroke (NINDS). NINDS Epilepsy and Seizures Information Page. Available at https://www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures. Accessed on March 20, 2023.

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History

Status	Date	Action
	09/27/2023	Updated Coding section with 10/01/2023 ICD-10-CM changes; added G40.C11-G40.C19.
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References section.
Reviewed	05/12/2022	MPTAC) review. Updated References section.
Reviewed	05/13/2021	MPTAC review. Updated Reference section. Reformatted Coding section.
	10/01/2020	Updated Coding section with 10/01/2020 ICD-10-CM changes; added G40.833-G40.834.
Reviewed	05/14/2020	MPTAC review. Updated Discussion/General Information and References sections.
Reviewed	06/06/2019	MPTAC review. Updated References section.
Reviewed	07/26/2018	MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Updated Discussion/General Information and References sections.
Reviewed	08/03/2017	MPTAC review. Updated Discussion/General Information, References, and Index sections.
Reviewed	08/04/2016	MPTAC review. Updated Discussion/General Information and References sections. Removed ICD-9 codes from Coding section.
Reviewed	08/06/2015	MPTAC review. Updated Discussion/General Information and References.
Reviewed	08/14/2014	MPTAC review. Updated Discussion/General Information and References.
Reviewed	08/08/2013	MPTAC review. Updated Discussion/General Information.
Reviewed	08/09/2012	MPTAC review. Updated Discussion/General Information and References.
Reviewed	08/18/2011	MPTAC review. Updated Discussion/General Information and References.
Reviewed	08/19/2010	MPTAC review. No change in Clinical Indications.
Reviewed	08/27/2009	MPTAC review. Removed “Place of Service” section. Updated Discussion and References.
Revised	08/28/2008	MPTAC review. References, Coding and Web Sites updated. Added “not medically necessary” statement.
Revised	08/23/2007	MPTAC review. Deleted “highly motivated” from Clinical Indication statement. Rationale and References updated.
Reviewed	09/14/2006	MPTAC review. No change in position; References updated.
Revised	09/22/2005	MPTAC Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.			No document
Anthem SE Memo	07/10/2002	Memo 1113	Ketogenic Diet for Refractory Epilepsy
WellPoint Health Networks, Inc.	04/28/2005	2.10.01	Ketogenic Diet for Intractable Seizure Disorder

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