Molina Clinical Policy
Ketogenic Diet Induction for Treatment of Intractable Seizures in the Hospital Setting: Policy No. 344

Last Approval: 2/8/2023
Next Review Due By: February 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Ketogenic diet to control seizures in some patients with intractable childhood epilepsy is an established, effective non-pharmacologic treatment. A 2008 international expert panel consensus report stated that a ketogenic diet "should be offered to a child after two anticonvulsants are used unsuccessfully" and should begin and be monitored under close medical supervision of an experienced medical team that includes a dietitian. The ketogenic diet is very high in fat with approximately 90% of calories coming from fat; a ratio of 3-4 grams of fat for every 1 gram of carbohydrate and protein. A ketogenic diet depends on the child's age, weight, family diet (e.g., vegetarian, kosher, halal, organic), and the diet prescription (including the weight of a combination of fats, protein and carbohydrates). Side effects of a ketogenic diet may include constipation, reflux, weight changes, and kidney stones (due to uric acid build-up in the blood). Mood changes (e.g., hyperactivity, irritability) have also been reported. Issues can be decreased by staying hydrated and monitoring by the healthcare team. (AAP, 2020).

Protein is also included in amounts in order to help the child grow. Carbohydrates account for a very small percentage of calories. Common high-fat foods used in the diet are butter, heavy cream, oil, mayonnaise, cream cheese, bacon and cheese. While following a ketogenic diet, children must avoid high-carbohydrate foods such as: fruit and fruit juice; breads and cereals; starchy vegetables (e.g., corn, peas, and potatoes); beans; milk; soda; snack foods (e.g., chips, snack cakes, crackers); and sweets. (Stanford, 2021). A ketogenic diet can be effective for all seizure types and epilepsy syndromes including infantile spasms, myoclonic-astatic epilepsy, Dravet syndrome, Doose syndrome, myoclonic-astatic epilepsy, Rett syndrome, migrational disorders, GLUT-1 deficiency and tuberous sclerosis complex. Additional diets include the modified-Atkins diet, low glycemic index treatment, and MCT ketogenic diet. (AAP, 2020). Several studies show that a ketogenic diet can reduce or prevent seizures in many children with seizures that are not controlled by medication. Over 50% of children who follow a ketogenic diet report at least a 50% reduction in the number of seizures; approximately 10-15% become seizure-free. (Epilepsy Foundation, 2017).

To begin a ketogenic diet, the child is admitted to the hospital for 4 to 5 days to allow the body to start producing ketones. Patients may be unable to eat for 1 to 2 days until ketones are measured in the urine. Once ketones are present, the child is typically given high-fat, low-carbohydrate shakes. Following several meals consisting of these shakes, the child can begin eating solid foods. (Stanford, 2021). Children who are on the ketogenic diet will continue to take seizure medicines. In time, medication may be taken in smaller doses or fewer medications may be needed than before starting a ketogenic diet. The introduction of medication typically starts after one month on a ketogenic diet. It is important to note that the diet must be followed as prescribed – missing just one meal can cause the diet to lose its effect. Patients are monitored over time, usually every one-to-three months. Blood and urine tests are also performed to detect any issues. Height and weight are also documented to monitor growth. A ketogenic diet can be stopped when seizures are well controlled (typically for at least two years). The patient is weaned off the diet over several months or more – seizures may worsen if a patient is taken off the diet too quickly. Medication typically continues once a patient stops the diet. (Epilepsy Foundation, 2017).

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COVERAGE POLICY

1. Inpatient hospitalization for initiation of a ketogenic diet **is considered NOT medically necessary** in children and adolescents who are <18 years of age for the treatment of drug resistant epilepsy, intractable seizures and/or any other diagnosis due to insufficient peer reviewed medical literature. Generally, initiation may be safely performed in the outpatient, observation or home setting – hospital admission may not be medically necessary.

2. Inpatient hospitalization for initiation of a ketogenic diet **is considered experimental, investigational, and unproven** in adults who are >18 years of age for the treatment of drug resistant epilepsy, intractable seizures and/or any other diagnosis due to insufficient peer reviewed medical literature.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Peer reviewed medical literature indicates that ketogenic diets can significantly reduce seizure frequency in a sizable percentage of pediatric patients with epilepsy who have failed or cannot tolerate antiepileptic drugs. There is a paucity of evidence regarding the efficacy of ketogenic diets in adult patients. Therefore, the ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy but should not be recommended for adults with epilepsy.

Sourbron et al. (2022) reviewed the medical literature on the efficacy and tolerability of ketogenic diets and the Modified Atkins Diet (MAD) in children and adolescents with refractory epilepsy. Five randomized controlled trials were analyzed from seven publications; this included a total of 472 total children and adolescents ≤ age 18. Seizure reduction was reported in 35-56% of intervention group participants compared to 6-18% among the control group. The main reported side effects were gastrointestinal however, this was not severe. The authors concluded that dietary interventions are beneficial for children and adolescents with refractory epilepsy and who do not meet criteria for epilepsy surgery. The need for additional studies that are multi-center and long-term was also noted to evaluate potential biomarkers and side effects.

Yang et al. (2022) evaluated the efficacy, retention and safety of ketogenic diets for children with drug-resistant epilepsy. A comparison was made with children from a previous cohort at the author's institution. A retrospective study was conducted on 634 children who have drug-resistant epilepsy. Participants were categorized into two groups. The prior cohort was the control group and included 317 children who were evaluated between 2004 and 2011; the current group also included 317 children who were evaluated between 2015 and 2019. While the control group continued to receive care as they were while the current group received different care and worked on a long-term management strategy. Results were similar between both groups. In conclusion, the key to an effective ketogenic diet is correlated to goal and long-term management.

Wells et al. (2020) conducted a literature search of peer-reviewed articles of observational studies, as well as clinical trials or meta-analysis, that reported findings of ketogenic diet for children and adolescents with refractory epilepsy. Adverse effects of the diet were a large indicator of participants that dropped out of a trial. Over 40 categories of adverse effects including gastrointestinal, cardiovascular, renal/genitourinary and skeletal. Ketogenic diets that were stricter (e.g., 4:1 cKD) indicated higher incidences of adverse effects. Frequency and severity of these effects correlate with the restrictions of the diet. While future trials are needed, current literature indicates efficacy of ketogenic diets among children and adolescents.

A Cochrane review (Martin et al., 2018) assessed the efficacy of ketogenic diets for drug resistant epilepsy by reviewing the evidence from randomized controlled trials. Eleven randomized control trials that generated 15 publications were identified. All trials applied an intention-to-treat analysis with varied randomization methods. A total of 778 patients

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were included in the review (712 children and adolescents, ~~and~~ 66 adults). A meta-analysis was not conducted due to the heterogeneity of the studies and the quality of the evidence was low to very low. Reported rates of seizure freedom reached as high as 55% in a classical 4:1 ketogenic diet group after three months and reported rates of seizure reduction reached as high as 85% in a classical 4:1 ketogenic diet group after three months (grade rating low). One trial found no significant difference between the fasting-onset and gradual-onset ketogenic diet for rates of seizure freedom and reported a greater rate of seizure reduction in the gradual-onset ketogenic diet group. Studies assessing the efficacy of the modified Atkins Diet (MAD) reported seizure freedom rates of up to 25% and seizure reduction rates of up to 60% in children. One study used a simplified MAD (sMAD) and reported seizure freedom rates of 15% and seizure reduction rates of 56% in children. One study utilized a MAD in adults and reported seizure reduction rates of 35%, but no patients became seizure free. Adverse effects interventions were experienced in all studies; the most commonly reported being gastrointestinal syndromes which led participants dropping out of trials. (Other reasons for dropout included lack of efficacy and non-acceptance of the diet).

Although there was some evidence for greater antiepileptic efficacy for a classical 4:1 ketogenic diet over lower ratios, the classical 4:1 ketogenic diet was consistently associated with more adverse effects. One study assessed the effect of dietary interventions on quality of life, cognition and behavioral functioning, reporting participants in the ketogenic diet group to be more active, more productive and less anxious after four months, compared to the control group. However, no significant difference was found in quality-adjusted life years (QALYs) between the ketogenic diet group and control group at four or 16 months (grade rating very low). Randomized control trials discussed in the review show promising results for the use of ketogenic diets in epilepsy. However, the limited number of studies, small sample sizes and the limited studies in adults, resulted in a low to very low overall quality of evidence. There were adverse effects within all of the studies and for all ketogenic diet variations, such as short-term gastrointestinal-related disturbances and increased cholesterol. However, study periods were short, therefore the long-term risks associated with these adverse effects is unknown. Attrition rates remained a problem with all ketogenic diets and across all studies; reasons for this being lack of observed efficacy and dietary tolerance. Only one study reported the use of ketogenic diets in adults with epilepsy therefore further research would be of benefit. Other more palatable but related diets, such as the MAD, may have a similar effect on seizure control as the classical ketogenic diet, but this assumption requires more investigation. For people who have medically intractable epilepsy or people who are not suitable for surgical intervention, ketogenic diets remain a valid option; however, further research is required. (Martin et al., 2018).

Ketogenic Diets in Infants

Ruiz-Herrero et al. (2021) conducted a retrospective, descriptive and observational study on the use of ketogenic diets in infants (under age two). Fort-two infants who were treated between 2000-2018 were analyzed; 40 infants started a classic ketogenic diet. Four patients transferred to a Modified Atkins Diet. At follow-up, 79% of infants remained on a ketogenic diet at 3 months; at six months 57% remained on the diet, 38% at 12 months and 17% at 24 months. A reduction in seizures of ≥50% (when compared to baseline) was found in in 50%, 45%, 38% and 17% at 3, 6, 12 and 24 months, respectively. Seizure control was also excellent with a reduction of >90% in 33% (at 3 months), 31% (at 6 months), 26% (at 12 months) and 12% (at 24 months). The mean length of a ketogenic diet was 390 days (16 days to 4.9 years). Over 50% of patients withdrew due to lack of efficacy of the ketogenic diet. Early adverse effects occurred in 40% of infants during month one; the most common were asymptomatic hypoglycemia and gastrointestinal issues. Hypercalciuria and dyslipidaemia were reported late-onset side effects. The classic ketogenic diet is the most accepted diet in infants (ratio 3:1).

Inpatient Hospitalization Ketogenic Diet

There are no randomized, controlled trials in the peer reviewed medical literature or evidence based professional society guidelines that outline medically necessary eligibility for inpatient hospitalization, concurrent review and discharge in patients for the initiation of a ketogenic diet for any diagnosis. The literature consists of retrospective studies and case series that do not compare inpatient versus outpatient services. Additional research using double-blind, placebo-controlled designs is needed to further define patient selection criteria, efficacy, and safety of inpatient versus outpatient initiation of the ketogenic diet.

Lin et al. (2017) conducted a retrospective study of children with intractable epilepsy electively admitted for ketogenic diet initiation. Charts were reviewed for adverse effects during the admission period and then examined for seizure reduction and compliance at three months. A rating scale (1 to 4) was created for severity of any adverse events. A total of 158 children were included, with the mean age 4.6 years. Potentially attributable adverse effects occurred in

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126 (80%) children, most commonly emesis, food refusal, and hypoglycemia. Seventy-three (46%) children received some form of intervention by the medical team, most commonly the administration of juice (24%). Younger age was correlated with an increased likelihood of moderate to severe adverse effects during admission, often repeated hypoglycemia (3.6 versus 4.9 years, P = 0.04). Fasting was more likely to result in lethargy and a single blood glucose in the 30 to 40 mg/dL range, but it was not correlated with emesis, repeated hypoglycemia, or higher adverse effect scores. There was no statistically significant correlation between the severity of adverse effects and the three-month seizure reduction. The authors concluded that mild easily treated adverse effects occurred in most children admitted for the ketogenic diet. Younger children were at greater risk for significant difficulties and should be monitored closely. As fasting may lead to lethargy and hypoglycemia, it may be prudent to avoid this in younger children.

National and Specialty Organizations

The **International Ketogenic Diet Study Group (IKDSG)** published updated guidelines in 2018 which reevaluated best practices originally published in 2008. The IKDSG recommends ketogenic diets for children after two antiseizure drugs have failed; ketogenic diets may also be appropriate for other epilepsy syndromes. The family and child's situation should be taken into consideration when introducing a ketogenic diet, including flexibility with initiation (outpatient or inpatient setting) and whether to include fasting. In addition, the IKDSG guidelines include information on the management of children on a ketogenic diet with respect to frequency of follow up visits, nutrition, laboratory results, side effects, and discontinuation when appropriate. Updates made in 2018 focus on the decrease in use of fasting at initiation of a ketogenic diet, evidence to support alternative diets Modified Atkins Diet (MAD) and Low Glycemic Index Treatment (LGIT), utilizing a non-fasting classic ketogenic diet for children under age 2, implementing a one-month follow-up visit, and further explanations of ideal scenarios to implement a ketogenic diet. (Kossoff et al., 2018).

The **National Institute for Clinical Excellence (NICE)** (2022) published a clinical guideline titled *Epilepsies in Children, Young People, and Adults.* The guideline covers the diagnosis and management of epilepsy in the population in the primary and secondary care settings; guidance is also given on referral to tertiary services. A section is included on ketogenic diet which provides an overview of benefits; hospitalization is not referred to.

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT Code

CPT	Description
99499	Unlisted evaluation and management service [when specified as services related to ketogenic diet]

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

2/8/2023	Policy reviewed, no changes to criteria.
2/9/2022	Policy reviewed; no changes to coverage criteria; updated Overview, Summary of Medical Evidence and Reference sections.
2/8/2021	Policy reviewed, no changes to criteria, references updated.
6/17/2020	Policy reviewed, no changes to criteria, references updated.
6/19/2019	New policy.

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National and Specialty Organizations

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2. Epilepsy Foundation. Ketogenic diet. Available from Epilepsy.com. Accessed January 31, 2023.
3. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Bergqvist AGC, Practice Committee of the Child Neurology Society, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018 Jun; 3(2): 175–192. doi: 10.1002/epi4.12225. PMID: 29881797. PMCID: PMC5983110. Accessed January 31, 2023.
4. National Institute for Health and Care Excellence (NICE). Epilepsies in children, young people and adults [NG217]. Published April 27, 2022. Available from NICE. Accessed January 31, 2023.

Evidence Based Reviews and Publications

1. Advanced Medical Reviews (AMR) Peer Review. Policy reviewed on March 29, 2019 by an Advanced Medical Reviews (AMR) practicing, board-certified physician in the area of Neurology and Sleep Medicine.
2. Kossoff E. Ketogenic dietary therapies for the treatment of epilepsy. Available from UpToDate. Updated October 3, 2022. Accessed January 31, 2023. Registration and login required.
3. Stanford Children's Hospital. Ketogenic diet for seizures in children. Available from Stanford. Updated 2021. Accessed January 31, 2023.

Peer Reviewed Publications

1. Lin A, Turner Z, Doerrer SC, Stanfield A, Kossoff EH. Complications during ketogenic diet initiation: prevalence, treatment, and influence on seizure outcomes. Pediatr Neurol. 2017 Mar;68:35-39. doi: 10.1016/j.pediatrneurol.2017.01.007. PMID: 28188074.
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3. Ruiz-Herrero J, Cañedo-Villarroya E, Pérez-Sebastián I, Bernardino-Cuesta B, Pedrón-Giner C. Efficacy and safety of ketogenic dietary therapies in infancy: A single-center experience in 42 infants less than two years of age. Seizure. 2021 Nov;92:106-111. doi: 10.1016/j.seizure.2021.08.018. PMID: 34500220.
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6. Yang R, Wen J, Wei W, Chen H, Cao D, Chen L, et al. Improving the effects of ketogenic diet therapy in children with drug-resistant epilepsy. Seizure. 2022 Jan;94:183-188. doi: 10.1016/j.seizure.2021.10.021. PMID: 34802897.

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

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