Hospitalization for the Initiation of Ketogenic Diet for the Treatment of Intractable Seizures

Number: 0226

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers hospitalization for initiation of a ketogenic diet in the treatment of intractable seizures medically necessary when all of the following selection criteria are met:

A. Member has failed to respond to anti-convulsant medications (monotherapy and polytherapy) or is intolerant to anti-convulsant medications. There must have been an adequate trial of drug therapy (specifically, the correct anti-convulsant medications have been used in the correct dosage, the member has been carefully monitored for treatment effects and the member has been compliant with drug therapy for at least 1 year); and

B. Member must be younger than 18 years old; and

C. Since strict adherence to this dietary regimen is tantamount to its effectiveness, parents/family members
must be willing and dedicated to support compliance; and

D. There is reason to believe that the outpatient setting will not be effective in initiating the fasting and dehydration period required.

Aetna considers hospitalization for initiation of a ketogenic diet medically necessary in the treatment of members with glucose transporter protein type 1 deficiency or pyruvate dehydrogenase complex deficiency.

Aetna considers hospitalization for initiation of a ketogenic diet of unproven value for all other indications (e.g., adult super-refractory status epilepticus, Alzheimer's disease, autism spectrum disorder, individuals with cancers, mood disorders (e.g., bipolar disorder and depression), Parkinson's disease, schizophrenia, and spinal cord injury; not an all-inclusive list)

Note: Most Aetna plans exclude coverage of dietary supplements; please check benefit plan descriptions for details. These plans do not cover any food supplements for the ketogenic diet.

II. Aetna considers hospitalization for initiation of the Atkins diet in the treatment of intractable seizures or other indications experimental and investigational because its effectiveness has not been established.

III. Aetna considers determination of variants in BAD, KCNJ11, and SLC2A1 to predict response to ketogenic dietary therapies for epilepsy experimental and investigational because of insufficient evidence of the effectiveness of this approach.

Background
The ketogenic diet, a diet that is very high in fats and extremely low in carbohydrates and protein, has been used for the treatment of uncontrolled seizures.

The traditional ketogenic diet entails an initial fasting and dehydration period during which patients receive no food and fluid intake is limited until ketones are present in the urine. Thereafter, a diet high in fat and low in carbohydrate and protein is introduced.

Strict compliance with this unpalatable dietary regimen has been shown to have anti-convulsant effects, particularly in children. Hospitalization may be necessary during an initial starvation period to induce marked ketosis and weight loss. The length of hospital stay will depend on the proposed initial starvation period, and generally should not exceed 3 days.

According to an evidence-based guideline on diagnosis and management of epilepsy from the National Institute for Clinical Excellence (NICE, 2004), the ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy. The guidelines state, however, that the ketogenic diet should not be recommended for adults with epilepsy.

Than and colleagues (2005) stated that an early, dramatic response to the ketogenic diet is more likely in patients with predominant seizure types other than complex partial. It may also be more likely to occur in children who have infantile spasms. In all other patient demographics and diet parameters, an equal likelihood of similar success was found. In a randomized controlled study (n = 48), Bergquist et al (2005) compared the effectiveness of a gradual ketogenic diet initiation with the standard ketogenic diet initiation preceded by a 24- to 48-hour fast. These investigators found that in children with intractable epilepsy, a gradual initiation results in fewer adverse events and is tolerated better overall while maintaining the effectiveness of the ketogenic diet.
In a randomized controlled study, Neal et al (2008) examined the effectiveness of the ketogenic diet in the treatment of childhood epilepsy. A total of 145 children aged between 2 and 16 years who had at least daily seizures (or more than 7 seizures per week) and had failed to respond to at least 2 antiepileptic drugs, and who had not been treated previously with the ketogenic diet participated in this study. Children were seen at one of two hospital centers or a residential center for young people with epilepsy. Children were randomly assigned to receive a ketogenic diet, either immediately or after a 3-month delay, with no other changes to treatment (control group). Neither the family nor investigators was blinded to the group assignment. Early withdrawals were recorded, and seizure frequency on the diet was assessed after 3 months and compared with that of the controls. The primary endpoint was a reduction in seizures; analysis was intention-to-treat. Tolerability of the diet was assessed by questionnaire at 3 months. A total of 73 children were assigned to the ketogenic diet and 72 children to the control group. Data from 103 children were available for analysis: 54 on the ketogenic diet and 49 controls. Of those who did not complete the trial, 16 children did not receive their intervention, 16 did not provide adequate data, and 10 withdrew from the treatment before the 3-month review, 6 because of intolerance. After 3 months, the mean percentage of baseline seizures was significantly lower in the diet group than in the controls (62.0 % versus 136.9 %, 75 % decrease, 95 % confidence interval [CI]: 42.4 to 107.4 %; p < 0.0001). A total of 28 children (38 %) in the diet group had greater than 50 % seizure reduction compared with 4 (6 %) controls (p < 0.0001), and 5 children (7 %) in the diet group had greater than 90 % seizure reduction compared with no controls (p = 0.0582). There was no significant difference in the efficacy of the treatment between symptomatic generalized or symptomatic focal syndromes. The most frequent side effects reported at 3-month review were constipation, vomiting, lack of energy, and hunger. The authors concluded that these findings support the use of ketogenic diet in children with treatment-intractable epilepsy.
The Atkins diet, widely used for weight reduction, has recently been tried for the management of intractable seizures. The Atkins diet can induce a ketotic state, but has fewer protein and caloric restrictions than the traditional ketogenic diet. Kossoff et al (2003) reported the use on the Atkins diet in 6 patients (aged 7 to 52 years) for the treatment of intractable focal and multi-focal epilepsy. Five patients maintained moderate to large ketosis for periods of 6 weeks to 24 months; 3 patients had seizure reduction and were able to reduce anti-epileptic drug (AEDs). This preliminary finding needs to be validated by more research.

Weber and colleagues (2009) evaluated the tolerability and efficacy of the modified Atkins diet given to children and adolescents with AED treatment resistant epilepsy. A total of 15 children with medically intractable epilepsy were enrolled in the study. Inclusion criteria were at least 1 seizure a week and a trial of at least 2 AEDs without obtaining seizure freedom documented in a seizure calendar. At baseline subjects initiated a diet with carbohydrates restricted to make up 10 energy percent. If seizures were reduced by less than 50 % after 7 to 14 days, carbohydrates were further restricted to 10 g per day. No change in AED treatment was allowed. The diet was well-tolerated. After 3 months, 6 out of the 15 children (40 %) had a seizure reduction of more than 50 %, which was seen in different epileptic syndromes and different age groups. The responders reported an increase in quality of life and cognition. At 12 months follow-up, 3 (20 %) continued the diet with an unchanged marked seizure reduction. Results of this study confirmed the high tolerability and effect of the modified Atkins diet on seizure control in AED treatment resistant epilepsy. Moreover, the authors stated that further larger prospective studies are however needed to confirm these results.

Glucose is the brain's main source of energy. To pass the blood-brain barrier (BBB), glucose transporter protein type 1 (GLUT-1) is essential. Glucose transporter protein type 1
(GLUT-1) deficiency syndrome is caused by heterozygous mutations in the SLC2A1 gene, resulting in impaired glucose transport into the brain. It is characterized by a low glucose concentration in the cerebrospinal fluid (CSF; hypoglycorrhachia) in the absence of hypoglycemia, in combination with low-to-normal lactate in the CSF. The diagnosis is confirmed by genetic testing.

Rogovik and Goldman (2010) stated that the ketogenic diet can be considered an option for children with intractable epilepsy who use multiple anti-epileptic drugs. It is a treatment of choice for seizures associated with GLUT-1 deficiency syndrome (i.e., De Vivo disease) and pyruvate dehydrogenase (PDH) deficiency.

Ramm-Pettersen et al (2011) described the clinical consequences of mutations in the SLC2A1 gene, with special emphasis on GLUT-1 encephalopathy. This review was based on a non-systematic literature search in PubMed and the authors' experience within the field. Epileptic or epilepsy-like symptoms are usually the first sign in children with the GLUT-1 deficiency syndrome. Later on these children suffer delayed psychomotor development, microcephaly, ataxia, spasticity, or movement disorders; electroencephalographic abnormalities may develop. GLUT-1 deficiency syndrome should be suspected in children with epilepsy-like seizures and delayed development combined with a low content of glucose in spinal fluid. Treatment is a ketogenic diet, as ketone bodies pass the BBB using other transport proteins than GLUT-1. The authors concluded that GLUT-1 deficiency syndrome is a rare metabolic encephalopathy that is not well-known and probably under-diagnosed. An early diagnosis and early start of a ketogenic diet may give these children a normal or nearly normal life.

Graham (2012) stated that GLUT-1 deficiency syndrome often results in treatment-resistant infantile epilepsy with progressive developmental disabilities and a complex movement disorder.
Recognizing GLUT-1 deficiency syndrome is important, since initiation of a ketogenic diet can reduce the frequency of seizures and the severity of the movement disorder.

Pong et al (2012) noted that GLUT-1 deficiency syndrome is defined by hypoglycorrhachia with normoglycemia, acquired microcephaly, episodic movements, and epilepsy refractory to standard AEDs. Gold standard treatment is the ketogenic diet, which provides ketones to treat neuroglycopenia. These investigators: (i) described epilepsy phenotypes in a large GLUT-1 deficiency syndrome cohort to facilitate diagnosis; and (ii) described cases in which non-ketogenic diet agents achieved seizure freedom to highlight potential adjunctive treatments. A retrospective review of 87 patients with GLUT-1 deficiency syndrome (45% female, age range of 3 months to 35 years, average diagnosis 6.5 years) from 1989 to 2010 was carried out. Seventy-eight (90%) of 87 patients had epilepsy, with average onset at 8 months. Seizures were mixed in 68% (53/78): generalized tonic-clonic (53%), absence (49%), complex partial (37%), myoclonic (27%), drop (26%), tonic (12%), simple partial (3%), and spasms (3%). These researchers described the first 2 cases of spasms in GLUT-1 deficiency syndrome. Electrophysiologic abnormalities were highly variable over time; only 13 (17%) of 75 had exclusively normal findings. Ketogenic diet was used in 82% (64/78); 67% (41/61) were seizure-free and 68% of seizure-free patients (28/41) resolved in less than 1 week and 76% (31/41) in less than 1 month. Seven patients achieved seizure freedom with broad agents only. The authors conclude that GLUT-1 deficiency syndrome is a genetic metabolic encephalopathy with variable focal and multi-focal seizure types and electroencephalographic findings. Infants with seizures, spasms, or paroxysmal events should be tested for GLUT-1 deficiency syndrome. They stated that evidence is insufficient to recommend specific AEDs as alternatives to ketogenic diet. Early diagnosis and initiation of ketogenic diet and prevention
of unnecessary AED trials in GLUT-1 deficiency syndrome are important goals for the treatment of children with epilepsy.

An UpToDate review on “The ketogenic diet” (Kossoff, 2012) stated that “GLUT1 deficiency syndrome is a genetic disorder characterized by impaired glucose transport across the blood brain barrier resulting in generalized epilepsy, developmental delay, and an associated movement disorder. A low cerebrospinal fluid glucose level suggests this diagnosis. The diagnosis can be confirmed in most cases with genetic testing (SLC2A1 mutation). The ketogenic diet is a first-line treatment for this disorder and provides ketones as an alternative energy source for the brain”.

Tzadok et al (2014) described a cohort of isolated and familial cases of GLUT-1 deficiency syndrome, emphasizing seizure semiology, electroencephalographic features, therapeutic response, and mutation pathogenicity. SLC2A1 mutations were detected in 3 sporadic and 4 familial cases. In addition, mutations were identified in 9 clinically unaffected family members in 2 families. The phenotypic spectrum of GLUT-1 deficiency is wider than previously recognized, with considerable intra-familial variation. Diagnosis requires either hypoglycorrachia followed by SLC2A1 sequencing or direct gene sequencing. A ketogenic diet should be the first line of treatment; carbonic anhydrase inhibitors (e.g., acetazolamide or zonisamide) can be effective for seizure control.

Inborn errors of the pyruvate dehydrogenase complex (PDHc) are associated with developmental delay, lactic acidosis, neuroanatomic defects, and early death. Pyruvate dehydrogenase complex deficiency is a clinically heterogeneous disorder, with most mutations located in the coding region of the X-linked alpha subunit of the first catalytic component, pyruvate dehydrogenase (E1). Treatment of E1 deficiency has included cofactor replacement, activation of PDC with dichloroacetate, as well as ketogenic diets.
Wexler et al (1997) described the outcome of ketogenic diet treatment in 7 boys with E1 deficiency. These patients were divided into 2 groups based on their mutations (R349H, 3 patients; and R234G, 4 patients, 2 sibling pairs). All 7 patients received ketogenic diets with varying degrees of carbohydrate restriction. Clinical outcome was compared within each group and between siblings as related to the intensity and duration of dietary intervention. Subjects who either had the diet initiated earlier in life or who were placed on greater carbohydrate restriction had increased longevity and improved mental development. Based on the improved outcomes of patients with identical mutations, it appears that a nearly carbohydrate-free diet initiated shortly after birth may be useful in the treatment of E1 deficiency.

Klepper et al (2004) stated that the ketogenic diet has been used for decades to treat intractable childhood epilepsies. It is also the treatment of choice for GLUT-1 deficiency syndrome and PDHc deficiency. Recent studies have once again confirmed the effectiveness of the diet, but the diet is hardly known in Europe and has never been quite accepted as an effective treatment of childhood epilepsy. These investigators reported retrospective data on 146 children treated with the ketogenic diet in Austria, Switzerland, and Germany. In 2000 and 2002, standardized questionnaires were sent to 13 neuropediatric departments to evaluate indications, effects and side effects. In children with refractory epilepsy (n = 111), 8 % became seizure-free on the diet. Seizure reduction of greater than 90 % was achieved in additional 9 % of patients; a seizure reduction of 50 to 90 % was attained in additional 14 % of patients. There was a great variability between epilepsy departments. All patients with GLUT-1 deficiency syndrome (n = 18) and PDHc deficiency (n = 15) showed clinical improvement. In GLUT-1 deficiency syndrome, complete seizure control was achieved in 94 % of patients. Compliance was good in 82 % of all patients regardless of the indication for the diet. The authors concluded that in contrast to the general restraint towards the ketogenic diet in Europe, these findings
supported its effectiveness as the treatment of choice for GLUT-1 deficiency syndrome and PDHc deficiency. In children with refractory epilepsy, the ketogenic diet matched the effect of most anti-convulsants and was well-tolerated. These data and 2 workshops resulted in recommendations for the use of the ketogenic diet in children as a basis for a general diagnostic and therapeutic standard to compare and improve the use of the ketogenic diet in Europe.

Prasad et al (2011) noted that the PDHc is a mitochondrial matrix multi-enzyme complex that provides the link between glycolysis and the tri-carboxylic acid (TCA) cycle by catalyzing the conversion of pyruvate into acetyl-CoA. Pyruvate dehydrogenase complex deficiency is one of the commoner metabolic disorders of lactic acidosis presenting with neurological phenotypes that vary with age and gender. These researchers postulated mechanisms of epilepsy in the setting of PDHc deficiency using 2 illustrative cases (one with PDHc E1-alpha polypeptide (PDHA1) deficiency and the second one with PDHc E1-beta subunit (PDHB) deficiency (a rare subtype of PDHc deficiency)) and a selected review of published case series. Pyruvate dehydrogenase complex plays a critical role in the pathway of carbohydrate metabolism and energy production. In severe deficiency states, the resulting energy deficit impacts on brain development in-utero resulting in structural brain anomalies and epilepsy. Milder deficiency states present with variable manifestations that include cognitive delay, ataxia, and seizures. Epileptogenesis in PDHc deficiency is linked to energy failure, development of structural brain anomalies and abnormal neurotransmitter metabolism. The use of the ketogenic diet bypasses the metabolic block, by providing a direct source of acetyl-CoA, leading to amelioration of some symptoms. Genetic counseling is essential as PDHA1 deficiency (commonest defect) is X-linked although females can be affected due to unfavorable lyonization, while PDHB and PDH phosphatase (PDP) deficiencies (much rarer defects) are of autosomal recessive inheritance.
El-Gharbawy et al (2011) reported the case of a male child with X-linked PDH deficiency presented with severe neonatal lactic acidosis. Poor compliance following initiation of the ketogenic diet justified modification to a less restrictive form that improved compliance. One year after starting the modified diet, the subject remained clinically stable, showing developmental progress.

An UpToDate review on “The ketogenic diet” (Kossoff, 2012) stated that “The ketogenic diet may also serve to provide an alternative energy source for the brain in PDH deficiency, a mitochondrial disease characterized by lactic acidosis, severe neurologic impairments, and occasionally, intractable epilepsy”.

Determination of Variants in BAD and KCNJ11

Schoeler and colleagues (2015a) stated that in the absence of specific metabolic disorders, predictors of response to ketogenic dietary therapies (KDT) are unknown. These researchers examined if variants in established candidate genes KCNJ11 and BAD influence response to KDT. They sequenced KCNJ11 and BAD in individuals without previously-known glucose transporter type 1 deficiency syndrome or other metabolic disorders, who received KDT for epilepsy. Hospital records were used to obtain demographic and clinical data. Two response phenotypes were used: greater than or equal to 50% seizure reduction and seizure-freedom at 3-month follow-up. Case/control association tests were conducted with KCNJ11 and BAD variants with minor allele frequency (MAF) greater than 0.01, using PLINK. Response to KDT in individuals with variants with MAF less than 0.01 was evaluated. A total of 303 individuals had KCNJ11 and 246 individuals had BAD sequencing data and diet response data; 6 SNPs in KCNJ11 and 2 in BAD had MAF greater than 0.01. Eight variants in KCNJ11 and 7 in BAD (of which 3 were previously-unreported) had MAF less than 0.01. No significant results were obtained from association analyses, with either...
KDT response phenotype; p-values were similar when accounting for ethnicity using a stratified Cochran-Mantel-Haenszel test. There did not seem to be a consistent effect of rare variants on response to KDT, although the cohort size was too small to assess significance. The authors concluded that common variants in KCNJ11 and BAD did not predict response to KDT for epilepsy; they could exclude, with 80% power, association from variants with a MAF of greater than 0.05 and effect size greater than 3. They stated that a larger sample size is needed to detect associations from rare variants or those with smaller effect sizes.

**Determination of Variants in SLC2A1**

Schoeler and associates (2015b) examined if response to KDT was due to undiagnosed glucose transporter type 1 deficiency syndrome (GLUT1-DS). Targeted re-sequencing of the SLC2A1 gene was completed in individuals without previously known GLUT1-DS who received KDT for their epilepsy. Hospital records were used to obtain demographic and clinical data. Response to KDT at various follow-up points was defined as seizure reduction of at least 50%. Seizure freedom achieved at any follow-up point was also documented. Fisher's exact and gene-burden association tests were conducted using the PLINK/SEQ open-source genetics library. Of the 246 participants, 1 was shown to have a novel variant in SLC2A1 that was predicted to be deleterious. This individual was seizure-free on KDT. Rates of seizure freedom in cases without GLUT1-DS were below 8% at each follow-up point; 2 cases without SLC2A1 mutations were seizure-free at every follow-up point recorded. No significant results were obtained from Fisher's exact or gene-burden association tests. The authors concluded that a favorable response to KDT is not solely explained by mutations in SLC2A1; other genetic factors should be sought to identify those who are most likely to benefit from dietary treatment for epilepsy, particularly those who may achieve seizure freedom.
Ketogenic Diet for Adult Super-Refractory Status Epilepticus

In a prospective, phase I/II multi-center study, Cervenka and colleagues (2017) examined the feasibility, safety, and efficacy of a KD for super-refractory status epilepticus (SRSE) in adults. Patients 18 to 80 years of age with SRSE treated with a KD treatment algorithm were eligible for inclusion into this trial. The primary outcome measure was significant urine and serum ketone body production as a biomarker of feasibility. Secondary measures included resolution of SRSE, disposition at discharge, KD-related side effects, and long-term outcomes. A total of 24 adults were screened for participation at 5 medical centers, and 15 were enrolled and treated with a classic KD via gastrostomy tube for SRSE. Median age was 47 years (interquartile range [IQR] of 30 years), and 5 (33 %) were male. Median number of anti-seizure drugs used before KD was 8 (IQR 7), and median duration of SRSE before KD initiation was 10 days (IQR 7 days). Ketogenic diet treatment delays resulted from intravenous propofol use, ileus, and initial care received at a non-participating center. All patients achieved ketosis in a median of 2 days (IQR 1 day) on KD; 14 patients completed KD treatment, and SRSE resolved in 11 (79 %; 73 % of all patients enrolled). Side effects included metabolic acidosis, hyperlipidemia, constipation, hypoglycemia, hyponatremia, and weight loss; 5 patients (33 %) ultimately died. The authors concluded that KD is feasible in adults with SRSE and may be safe and effective; moreover, they stated that comparative safety and efficacy must be established with randomized placebo-controlled trials.

Ketogenic Diet for Individuals with Cancers

Erickson and colleagues (2017) noted that the efficacy and benefits of KD have recently been gaining worldwide and remain a controversial topic in oncology. In a systematic, these researchers evaluated the clinical evidence on isocaloric KD dietary regimes and revealed that evidence supporting the
effects of isocaloric KD on tumor development and progression as well as reduction in side effects of cancer therapy is missing. Furthermore, an array of potential side effects should be carefully considered before applying KD to cancer patients. The authors concluded that with regard to counseling cancer patients considering a KD, more robust and consistent clinical evidence is needed before the KD can be recommended for any single cancer diagnosis or as an adjunct therapy.

Maisch and associates (2018) stated that beside the classical anti-cancer treatment, patients often try to find proactive alternative therapies to fight their disease. Lifestyle changes such as introducing a KD is one of the most popular among them. The German Association of Urological Oncology presented a systematic review investigating the evidence of KD in cancer patients. These investigators performed a systematic literature research in the databases Medline, Livivo, and the Cochrane Library. Only clinical studies of tumor patients receiving chemotherapy while on a KD were included. The assessment of the results was performed according to the predefined primary end-points of overall survival (OS) and progression-free survival (PFS); and secondary end-points of quality of life (QOL) and reduction of adverse effects induced by cytostatics. A total of 9 studies met the inclusion criteria: 8 prospective and 1 retrospective study case series respectively cohort-studies, with a total of 107 patients. Currently there is no evidence of a therapeutic effect of a KD in patients with malignant tumors regarding the clinical outcome or QOL. The authors concluded that based on the current data, a KD cannot be recommended to cancer patients because prospective, randomized trials are missing.

Sremanakova and associates (2018) stated that a growing body of evidence indicates the importance of nutrition in cancer treatment. Ketogenic diets are one strategy that has been proposed to enhance traditional anti-cancer therapy. These investigators summarized the evidence concerning the
effect of oral ketogenic diets on anthropometry, metabolism, QOL and tumor effects, at the same time as documenting adverse events (AEs) and adherence in patients with cancer. These researchers searched electronic databases using medical subject headings (MeSH) and text words related to ketogenic diets and cancer. Adult patients following a ketogenic diet as a complementary therapy prior, alongside or after standard anti-cancer treatment for more than 7 days were included. Studies were assessed for quality using the Critical Appraisal Skills Program tools (https://www.casp-uk.net). A total of 11 studies were included with 102 participants (age range of 34 to 87 years) from early-phase trials, cohort studies and case reports. Studies included participants with brain, rectal or mixed cancer sites at an early or advanced disease stage. The duration of intervention ranged from 2.4 to 134.7 weeks (0.5 to 31 months). Evidence was inconclusive for nutritional status and AEs. Mixed results were observed for blood parameters, tumor effects and QOL; adherence to diet was low (50 out of 102; 49%; ranging from 23.5% to 100%). The authors concluded that high-quality evidence on the effect of ketogenic diets on anthropometry, metabolism, QOL and tumor effects is currently lacking in oncology patients. These researchers stated that heterogeneity between studies and low adherence to diet affected the current evidence; and there is an obvious gap in the evidence, high-lighting the need for controlled trials to fully evaluate the intervention.

Ok and co-workers (2018) noted that high-carbohydrate diets are generally provided to post-pancreatectomy cancer patients. Low energy density of this diet may obstruct proper energy intake and recovery. These investigators examined the effects of high-fat, high-energy ketogenic diet (KD) in these patients. After pancreatectomy, 9 patients were provided with general diet (GD) while 10 were served KD. Meal compliance, energy intake rate, meal satisfaction and presence of complications were monitored throughout hospital stay. Data on nutritional status, serum lipids and body composition were collected and compared between groups. Meal compliance,
energy intake rate and meal satisfaction score were higher in KD. There were no differences in complications, nutritional status and serum lipids. The decrease in body cell mass (BCM) was greater in GD. The authors concluded that post-pancreatectomy cancer patients who consumed KD had a higher energy intake and BCM. They stated that these findings suggested the potential use of KD as an adjuvant anti-cancer therapy.

Noorlag and colleagues (2018) stated that patients with malignant gliomas have a poor prognosis. Diets that lower blood glucose, such as ketogenic or caloric restricted diets (KCRDs), are hypothesized to reduce tumor growth and improve survival. In a systematic review, these researchers reviewed pre-clinical and clinical data on KCRDs in gliomas. They searched PubMed and Embase for pre-clinical and clinical studies on KCRDs in gliomas, and extracted data on surrogate and clinically relevant end-points, in accordance with PRISMA statement. Quality assessment of clinical studies was performed with use of Cochrane Collaboration’s tool. These investigators performed Fisher’s exact test to examine associations between surrogate and clinically relevant end-points. They included 24 pre-clinical studies, 7 clinical studies and 1 mixed study. Both pre-clinical and clinical studies were highly heterogeneous. Pre-clinically, KCRDs reduced tumor growth, but only a small majority of the in-vivo studies found improved survival. These effects were stronger in groups with decreased blood glucose than in those with increased ketones, and also when other therapies were used concomitantly. Finally, KCRDs influenced multiple molecular-biological pathways, including the PTEN/Akt/TSC2 and NF-κB pathway. In clinical studies, KCRDs appeared to be safe and feasible in glioma patients; however, available clinical data were insufficient to draw conclusions regarding efficacy. The authors concluded that KCRDs had positive effects on malignant gliomas in published pre-clinical studies; preliminary clinical data suggested that KCRDs were safe and feasible. However, these researchers stated that because of the paucity
of clinical data, the efficacy of KCRDs for improving survival and QOL of glioma patients remains to be proven in prospective studies.

van der Louw and co-workers (2018) noted that the mean OS rate of children with diffuse intrinsic pontine glioma (DIPG) is 9 to 11 months, with current standard treatment with fractionated radiotherapy and adjuvant chemotherapy. So far, novel therapeutic strategies have not yet resulted in significantly better survival. The main source of energy for glioblastoma cells is glucose. Thus, metabolic alterations induced by the use of the extremely carbohydrate-restricted ketogenic diet (KD) as adjuvant therapy are subject of interest in cancer research. These researchers examined the safety and feasibility of the KD in children with recurrent DIPG and no remaining therapeutic options. Safety was defined as the number of adverse effects; feasibility was defined as the number of patients who were able to use the KD for 3 months. Coping of patients and parents was measured with questionnaires; 3 of 14 children referred to the authors’ hospital between 2010 and 2015 were included; 2 patients completed the study, and 1 died before the end of the study. Hospitalizations were needed for placing a nasogastric tube (n = 1) and epileptic seizures (n = 1). Adverse effects related to the diet were mild and transient; parents were highly motivated during the study. The authors concluded that use of KD is safe and feasible, however the effect on survival has to be proven in a larger cohort of children who start the KD earlier after diagnosis, preferably as adjuvant therapy to fractionated radiotherapy.

Klement (2018) stated that altered glucose metabolism in cancer cells is an almost ubiquitous observation, yet hardly exploited therapeutically. However, ketogenic diets have gained growing attention in recent years as a non-toxic broad-spectrum approach to target this major metabolic difference between normal and cancer cells. Although most pre-clinical studies indicated a therapeutic potential for ketogenic diets in
cancer treatment, it is now becoming clear that not all tumors might respond positively. Early clinical trials have examined ketogenic diets as a monotherapy and -- while showing the safety of the approach even in advanced cancer patients -- largely failed to prove survival prolonging effects. However, it gradually became clear that the greatest potential for ketogenic diets is as adjuvant treatments combined with pro-oxidative or targeted therapies initiated in early stages of the disease. Beneficial effects on body composition and QOL have also been found. The authors concluded that ketogenic diets against cancer are worth further exploration, both in the laboratory and clinically. Patients wishing to undertake a ketogenic diet during therapy should receive dietary counselling to avoid common mistakes and optimize compliance. They stated that future research should focus more on important clinical end-points.

Ketogenic Diet for Alzheimer's Disease

Broom and colleagues (2018) noted that the prevalence of Alzheimer's disease (AD) is increasing as is the need for effective management. The pathophysiology of AD is still unclear, so existing research has focused on understanding the prominent features of the disease. These include amyloid plaques, which accumulate in the brains of those with AD; impaired glucose metabolism; and neuronal cell death. Emerging evidence suggests that a low-carbohydrate, high-fat ketogenic diet may help to mitigate the damage associated with these pathologies. The ketogenic diet could alleviate the effects of impaired glucose metabolism by providing ketones as a supplementary energy source. In addition, this diet may help to reduce the accumulation of amyloid plaques while reversing amyloid β toxicity. Research has begun to identify early underlying mechanisms in AD that could be targeted by new prevention strategies. Glycation of the ApoE protein leads to impaired transportation of important lipids, including cholesterol, to the brain, resulting in lipid deficiencies that could explain progression to the later pathologies of the
disease. The authors hypothesized that the ketogenic diet could be an effective treatment and prevention for AD, but both ketone production and carbohydrate restriction may be needed to achieve this. They stated that the ketogenic diet (including carbohydrate restriction) might be useful in the management of AD.

Ota and associates (2018) stated that clinical and animal studies suggested that a medium-chain triglyceride (MCT)-based ketogenic diet provides an alternative energy substrate to the brain and has neuroprotective effects, but the clinical evidence is still scarce. These researchers examined the effect of an MCT-based ketogenic formula on cognitive function in patients with AD. Participants were 20 Japanese patients with mild-to-moderate AD (11 men, 9 women, mean age of 73.4 ± 6.0 years) who, on separate days, underwent neurocognitive tests 120 mins after consuming 50 g of a ketogenic formula (Ketonformula) containing 20 g of MCTs or an iso-caloric placebo formula without MCTs. Subjects then took 50 g of the ketogenic formula daily for up to 12 weeks, and underwent neurocognitive tests monthly. In the 1st trial, although the patients' plasma levels of ketone bodies were successfully increased 120 mins after the single intake of the ketogenic formula, there was no significant difference in any cognitive test results between the administrations of the ketogenic and placebo formulae. In the subsequent chronic intake trial of the ketogenic formula, 16 of the 20 patients completed the 12-week regimen. At 8 weeks after the trial's start, subjects showed significant improvement in their immediate and delayed logical memory tests compared to their baseline scores, and at 12 weeks they showed significant improvements in the digit-symbol coding test and immediate logical memory test compared to the baseline. The authors concluded that the chronic consumption of the ketogenic formula was therefore suggested to have positive effects on verbal memory and processing speed in patients with AD. These preliminary findings need to be validated by well-designed studies.
The authors stated that this study had several drawbacks. First, the number of participants (n = 20) was small, which rendered the study vulnerable to type II error. Second, some of the patients had already been treated with anti-dementia drugs. However, because these researchers evaluated the improvement of cognition and clinical symptoms after the adjunctive administration of the ketogenic formula, previous medications would likely have affected these findings minimally, if at all. Third, the chronic study was an open-label one (single-arm design), and these investigators did not prepare a placebo group. Thus, the authors could not rule out the influence of placebo effects. A further study with a double-blind design is needed to clarify the effectiveness of ketogenic formula intake. Finally, these investigators did not obtain information on the patients' APOE genotype, which may have influenced the results.

Ketogenic Diet for Autism Spectrum Disorder

Gogou and Kolios (2018) noted that a nutritional background has been recognized in the pathophysiology of autism and a series of nutritional interventions have been considered as complementary therapeutic options. As available treatments and interventions are not effective in all individuals, new therapies could broaden management options for these patients. These researchers provided current literature data about the effect of therapeutic diets on autism spectrum disorder (ASD). A systematic review was carried out by 2 reviewers independently; prospective clinical and pre-clinical studies were considered. Therapeutic diets that have been used in children with autism include ketogenic and gluten/casein-free diet. These investigators were able to identify 8 studies conducted in animal models of autism demonstrating a beneficial effect on neurophysiological and clinical parameters. Only 1 clinical study was found showing improvement in childhood autism rating scale after implementation of ketogenic diet. With regard to gluten/casein-free diet, 4 clinical studies were found with 2 of
them showing a favorable outcome in children with autism. Furthermore, a combination of gluten-free and modified ketogenic diet in a study had a positive effect on social affect scores. No serious adverse events (AEs) have been reported. The authors concluded that despite encouraging laboratory data, there is controversy regarding the real clinical effect of therapeutic diets in patients with ASD. They stated that more research is needed to provide sounder scientific evidence.

Furthermore, an UpToDate review on “Autism spectrum disorder in children and adolescents: Overview of management” (Weissman and Bridgemohan, 2018) does not mention ketogenic diet as a therapeutic option.

Ketogenic Diet for Mood Disorders

Brietzke and colleagues (2018) stated that despite significant advances in pharmacological and non-pharmacological treatments, mood disorders remain a significant source of mental capital loss, with high rates of treatment resistance, requiring a coordinated effort in investigation and development of efficient, tolerable and accessible novel interventions. Ketogenic diet is a low-carb diet that substantially changes the energetic matrix of the body including the brain. It has been established as an effective anticonvulsant treatment, and more recently, the role of KD for mental disorders has been explored. Ketogenic diet has profound effects in multiple targets implicated in the pathophysiology of mood disorders, including but not limited to, glutamate/GABA transmission, monoamine levels, mitochondrial function and biogenesis, neurotrophism, oxidative stress, insulin dysfunction and inflammation. Pre-clinical studies, case-reports and case-series studies have demonstrated anti-depressant and mood stabilizing effects of ketogenic diet, however, to-date, no clinical trials for depression or bipolar disorder have been conducted. The authors concluded that because of its potential pleiotropic benefits, ketogenic diet should be
considered as a promising intervention in research in mood disorder therapeutics, especially in treatment resistant presentations.

Ketogenic Diet for Parkinson’s Disease

Phillips and colleagues (2018) noted that preliminary evidence suggested that diet manipulation may influence motor and non-motor symptoms in Parkinson’s disease (PD), but conflict exists regarding the ideal fat-to-carbohydrate ratio. In a pilot, randomized controlled trial (RCT), these researchers compared the plausibility, safety, and efficacy of a low-fat, high-carbohydrate diet versus a ketogenic diet in a hospital clinic of PD patients. They developed a protocol to support PD patients in a diet study and randomly assigned patients to a low-fat or ketogenic diet. Primary outcomes were within- and between-group changes in MDS-UPDRS Parts 1 to 4 over 8 weeks. These investigators randomized 47 patients, of which 44 commenced the diets and 38 completed the study (86% completion rate for patients commencing the diets). The ketogenic diet group maintained physiological ketosis. Both groups significantly decreased their MDS-UPDRS scores, but the ketogenic group decreased more in Part 1 (-4.58 ± 2.17 points, representing a 41% improvement in baseline Part 1 scores) compared to the low-fat group (-0.99 ± 3.63 points, representing an 11% improvement) (p < 0.001), with the largest between-group decreases observed for urinary problems, pain and other sensations, fatigue, daytime sleepiness, and cognitive impairment. There were no between-group differences in the magnitude of decrease for Parts 2 to 4. The most common adverse effects were excessive hunger in the low-fat group and intermittent exacerbation of the PD tremor and/or rigidity in the ketogenic group. The authors concluded that this pilot RCT showed that modified diets based on readily available ingredients, with normal protein levels, were plausible and safe treatment approaches in PD, with the ketogenic diet leading to greater improvements in many of the more disabling, less L-Dopa-
responsive non-motor symptoms. They stated that it was possible that a ketogenic diet could play a complementary role alongside L-Dopa in the treatment of PD, but due to the preliminary nature of these findings, larger and longer RCTs are needed before this can be stated with confidence.

Ketogenic Diet for Schizophrenia

Włodarczyk and colleagues (2018) noted that schizophrenia is a mental disorder that mostly appears in the 2nd or 3rd decade of life with no consistent appearance. The 1st-line pharmacological treatment are anti-psychotic drugs, which mainly act by suppressing the activity of dopamine. Unfortunately many of schizophrenic patients suffer from persistent positive or negative symptoms that cannot be fully treated with available medication. With exploration on the possible causes of the disease there is evidence on dopaminergic transmission defects, there is a need to find more holistic way in treating the disease and a diet regimen could be one of them. Ketogenic diet, which is a popular diet regimen that consists in low-carbohydrate (about 30 to 50 g/day), medium-protein (up to 1 g/kg daily) and high-fat intake (around 80% of daily calories) mainly known for its helpful role in weight-loss. The key mechanism is to generate ketosis. A state in which ketones bodies in the blood provides energy part of the body’s energy comes from ketone bodies in the blood. Possible hypothesis can be that ketogenic diet changes the ratio of GABA:glutamate in favor of GABA, by suppressing the catabolism and increasing the synthesis of GABA as well as glutamate metabolism, which could help to compensate the disrupted GABA levels in schizophrenic brain, leading to possible better outcome of the disease regarding symptomatology and preventing the weight-gain regarding some medications used and the correlating diseases responsible for weight gain. The clinical value of ketogenic diet in the management of patients with schizophrenia needs to be further investigated.
Ketogenic Diet for Spinal Cord Injury

In a longitudinal, randomized, pilot study, Yarar-Fisher and colleagues (2018) examined the safety and feasibility of a KD intervention in the acute stages of spinal cord injury (SCI); evaluated the effects of a KD on neurological recovery; and identified potential serum biomarkers associated with KD-induced changes in neurological recovery. The KD is a high-fat, low-carbohydrate diet that includes approximately 70 to 80% total energy as fat. A total of 7 subjects with acute complete and incomplete SCI (AIS A-D) were randomly assigned to KD (n = 4) or standard diet (SD, n = 3). Neurological examinations, resting energy expenditure analysis, and collection of blood for evaluation of circulating ketone levels were performed within 72 hours of injury and before discharge. Un-targeted metabolomics analysis was performed on serum samples to identify potential serum biomarkers that may explain differential responses between groups. The findings primarily demonstrated that KD was safe and feasible to be administered in acute SCI. Furthermore, upper extremity motor scores were higher (p < 0.05) in the KD versus SD group and an anti-inflammatory lysophospholipid, lysoPC 16:0, was present at higher levels, and an inflammatory blood protein, fibrinogen, was present at lower levels in the KD serum samples versus SD serum samples. The authors concluded that these preliminary results suggested that a KD may have anti-inflammatory effects that may promote neuroprotection, resulting in improved neurological recovery in SCI. Moreover, they stated that future studies with larger sample size are needed to demonstrate the efficacy of KD for improving neurological recovery.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Proprietary
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td></td>
<td>Hospitalization for initiation of a ketogenic diet - no specific code:</td>
</tr>
<tr>
<td></td>
<td>Other CPT codes related to the CPB:</td>
</tr>
<tr>
<td>81000</td>
<td>Urinalysis, by dip stick or tablet reagent for</td>
</tr>
<tr>
<td>81003</td>
<td>bilirubin, glucose, hemoglobin, ketones,</td>
</tr>
<tr>
<td></td>
<td>leukocytes, nitrite, pH, protein, specific gravity,</td>
</tr>
<tr>
<td></td>
<td>urobilinogen, any number of these constituents</td>
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<tr>
<td>97802</td>
<td>Medical nutrition therapy</td>
</tr>
<tr>
<td>97804</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other HCPCS codes related to the CPB:</td>
</tr>
<tr>
<td>A4250</td>
<td>Urine test or reagent strips or tablets (100 tablets or strips)</td>
</tr>
<tr>
<td>A9152</td>
<td>Single vitamin/mineral/trace element, oral, per dose, not otherwise specified</td>
</tr>
<tr>
<td>A9153</td>
<td>Multiple vitamins, with or without minerals and trace elements, oral, per dose,</td>
</tr>
<tr>
<td></td>
<td>not otherwise specified</td>
</tr>
<tr>
<td>S9470</td>
<td>Nutritional counseling, dietitian visit</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>E74.4</td>
<td>Disorders of pyruvate metabolism and gluconeogenesis</td>
</tr>
<tr>
<td>E88.09</td>
<td>Other disorders of plasma-protein metabolism, not elsewhere classified [glucose</td>
</tr>
<tr>
<td></td>
<td>transporter protein type 1 deficiency]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<td>-------------------------------------------------------</td>
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ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>C00.0 - C96.9</td>
<td>Malignant neoplasm</td>
</tr>
<tr>
<td>F20.0 - F20.9</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>F31.0 - F31.9</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>F32.0 - F39</td>
<td>Major depressive disorder</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>F84.0 - F84.9</td>
<td>Pervasive developmental disorders</td>
</tr>
<tr>
<td>G20</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>G21.0 - G21.9</td>
<td>Secondary parkinsonism</td>
</tr>
<tr>
<td>G30.0 - G30.9</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>G40.001, G40.011, G40.101, G40.111, G40.201, G40.211, G40.301, G40.311, G40.A01, G40.A11, G40.B01, G40.B11, G40.401, G40.411, G40.501, G40.801, G40.803, G40.811, G40.813, G40.821, G40.823, G40.901, G40.911</td>
<td>Epilepsy and recurrent seizures, with status epilepticus</td>
</tr>
<tr>
<td>S12.000A - S12.691S</td>
<td>Fracture of cervical vertebra and other parts of neck</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>S13.0xxA</td>
<td>Traumatic rupture of cervical intervertebral disc</td>
</tr>
<tr>
<td>S13.0xxS</td>
<td></td>
</tr>
<tr>
<td>S13.9xxS</td>
<td></td>
</tr>
<tr>
<td>S14.0xxA</td>
<td>Concussion and edema of cervical spinal cord</td>
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<tr>
<td>S14.0xxS</td>
<td></td>
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<tr>
<td>S14.101A</td>
<td>Injury of nerves and spinal cord at neck level</td>
</tr>
<tr>
<td>S14.9xxS</td>
<td></td>
</tr>
<tr>
<td>S22.000A</td>
<td>Fracture of thoracic vertebra</td>
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<tr>
<td>S22.0xxS</td>
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<tr>
<td>S23.9xxS</td>
<td></td>
</tr>
<tr>
<td>S24.0xxA</td>
<td>Unspecified injury of thoracic spinal cord</td>
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<tr>
<td>S24.159S</td>
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</tr>
<tr>
<td>S32.000A</td>
<td>Injury of nerves and spinal cord at thorax level</td>
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<tr>
<td>S32.2xxS</td>
<td></td>
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<tr>
<td>S33.0xxA</td>
<td>Dislocation and sprain of joints and ligaments of lumbar spine and pelvis</td>
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<tr>
<td>S33.0xxS</td>
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</tr>
<tr>
<td>S34.9xxS</td>
<td></td>
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</tbody>
</table>

The above policy is based on the following references:


46. Ramm-Pettersen A, Selmer KK, Nakken KO. Glucose transporter protein type 1 (GLUT-1) deficiency
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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0226 Hospitalization for the Initiation of Ketogenic Diet for the Treatment of Intractable Seizures

For the Pennsylvania Medical Assistance Plan, the use of Hospitalization for the Initiation of Ketogenic Diet may be considered for super refractory status epilepticus on a case by case basis.

www.aetnabetterhealth.com/pennsylvania annual 06/01/2020