AMERICAN EPILEPSY SOCIETY

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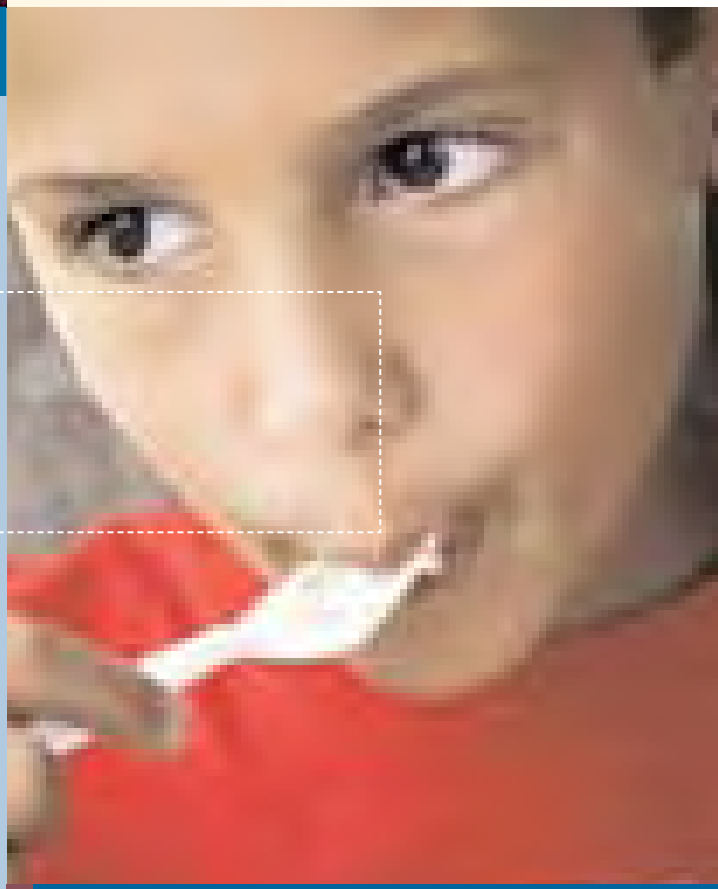
EPILEPSY UPDATE: A CASE SERIES

A CME Activity



When Medications Fail: The Ketogenic Diet

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When Medications Fail: The Ketogenic Diet

Children with medically refractory epilepsy should be evaluated for epilepsy surgery because this treatment offers the best chance of seizure freedom. However, when surgery is not an option and medications are either ineffective or problematic, the ketogenic diet (KGD) should be considered. The KGD is a carefully prescribed, high fat, low carbohydrate, adequate protein diet that has been employed in the treatment of medically refractory epilepsy since the early twentieth century.

CASE STUDIES

Case 1

Max is a 5-year-old boy with cryptogenic generalized epilepsy with seizures starting at 2 years of age. His seizure types included generalized tonic-clonic, atonic, myoclonic, and atypical absence. Despite almost daily seizures, his development was relatively age-appropriate: he was able to write his name, count to 20, and read short words. However, Max was becoming increasingly inattentive and was having more frequent behavioral outbursts.

As therapy with multiple anticonvulsants was either ineffective or produced intolerable side effects, the KGD was commenced. At the time the diet was started, Max was taking valproic acid and phenobarbital. After the KGD was initiated in the hospital, he was discharged on the diet, his regular antiepileptic medications, and dietary supplements, including carnitine and a multivitamin.

After 3 months on the KGD, a marked reduction in seizures was noted and a phenobarbital wean was commenced. On a combination of the KGD and valproic acid, Max remained free of his most disabling seizures and he only had occasional atypical absence seizures. With the improved seizure control, he was more focused and alert, with improved behavior.

Case 2

Gemma is an 11-year-old girl with Lennox-Gastaut syndrome and moderate mental retardation. When referred for dietary treatment at age 8 years, she had failed multiple anticonvulsant medications and atonic seizures were resulting in frequent falls. At the time of assessment, she was having up to 20 atonic seizures and countless atypical absence seizures per day, as well as 2 to 3 convulsive seizures per week.

Gemma found starting the diet difficult. She complained of hunger and did not like the taste of the cream. However, once ketotic, there was an almost immediate reduction in the frequency of her atonic and absence seizures.

Once discharged, Gemma began to enjoy her 'magic food.' The ketosis reduced her hunger and her parents found creative ways for her to enjoy her food, such as adding sugar-free chocolate flavoring to her cream and freezing it to make 'keto' ice cream.

During the first 2 years of diet therapy, Gemma did well. However, over the last year, she has become increasingly oppositional and frequently refused the KGD. During these periods, she fails to maintain ketosis and her seizure frequency markedly increases.

DISCUSSION

The classic KGD is based on a ratio of fats to carbohydrates and protein; typically a ratio of 4:1 (fats to carbohydrate and protein, respectively) is used, although lower ratios have been used in younger or medically fragile children. By limiting the dietary intake of carbohydrates, ketone bodies (e.g., β-hydroxybutyrate) produced via the breakdown of fatty acids become the body's primary fuel. Although the mechanism responsible for the diet's antiepileptic effects are not completely understood, the degree of ketosis often correlates with the diet's effectiveness.

Successful use of the KGD requires that it be prescribed and monitored by physicians and dieticians who are well-trained in its use. Although some centers may choose to initiate the diet in children <2 years of age, the KGD is usually reserved for children >2 years of age who have failed treatment with 2 to 3 appropriate anticonvulsant medications. Traditionally, the KGD has been initiated in hospital, allowing for close monitoring of any acute side effects (Table 1) and for the education

Table 1. Side effects and complications of the classic KGD

Acute	Chronic
Acidosis	Hyperlipidemia
Dehydration	Osteopenia
Hypoglycemia	Poor linear growth
Lethargy	Constipation
Vomiting	Kidney stones
	Bleeding abnormalities
	Increased infections/sepsis

of caregivers in the details of diet preparation and monitoring, trouble shooting, and managing side effects (Table 1). Although most side effects are transient or easily managed, serious side effects do occur (e.g. osteopenia, kidney stones), may be life-threatening (e.g. sepsis), and may require termination of the diet.

Initiating the diet after a period of fasting and fluid restriction has fallen out of favor because this initiation schedule can result in a higher rate of acute adverse events and there is little evidence that rapid induction of ketosis improves diet efficacy. More recently, some centers have begun successful outpatient initiation of the diet with a slower increase in the fats : carbohydrate-and-protein ratio.

Once successfully initiated, food and fluid intake is strictly prescribed and overseen by the caregivers and a specially trained dietician. Ketosis is monitored on a daily basis through the use of urinary strips.

Table 2. Typical vitamin and mineral supplementation*

Multivitamin with minerals including
B complex, vitamin C, folate, iron, magnesium, zinc
Calcium and vitamin D
Selenium
Carnitine

*Supplementation must be tailored individually for each child based on the daily recommended intake (RDI) by age.

Table 3. Laboratory serum monitoring*

Complete blood count
Ferritin and RBC folate
Electrolytes
Sodium, potassium, chloride, bicarbonate
Calcium, phosphorous, magnesium
Urea, creatinine, uric acid
Fasting lipid profile
Glucose
Total protein, albumin
Vitamin D, vitamin E, zinc
Total and free carnitine
Selenium

*Laboratory monitoring is typically performed every 3 months for the first year and then every 6 months during dietary treatment.

Vitamin and mineral supplementation is required to avoid deficiencies and should be adjusted to the daily recommended intake based on patient age (Table 2). Intermittent laboratory investigations should be performed (Table 3), as well as the maintenance of growth charts and bone scans.

Children who tolerate the KGD will experience some benefit in seizure control usually within weeks or at most a few months. Studies typically report a greater than 50% reduction in seizure frequency for more than 50% of children treated with the KGD. A randomized controlled study found that 38% of children had a greater than 50% reduction and 7% had a greater than 90% reduction in seizure frequency.

Table 4. Sample daily menu for classic 4:1, 1500-calorie ketogenic diet*

Breakfast	Lunch	After School Snack
Vegetable egg fritatta, including: • Cream (60 g) • Mushroom (26 g) • Egg (50 g) • Butter (25 g)	• Skinless chicken breast (22 g) • Melon (18 g) • Oil (5 g) • Mayonnaise (24 g)	Veggies and dip: • Carrots (14 g) • Mayonnaise with flavoring (6 g)
Dinner	**Bedtime Snack**	
• Lean beef (19 g) • American cheese (10 g) • Cabbage (22 g) • Butter (23 g) • Cream (60 g)	• Creamy gelatin dessert: – Sugar free gelatin (28 g) – Cream (15 g)	

*Approximate values listed. All diets should be individually prescribed for each patient.

Compliance may be difficult in older children because the KGD can be very restrictive, with small portions of the typical foods that children enjoy. Effort is required to enhance the palatability of a diet primarily based on heavy whipping creams, butters, and mayonnaise (Table 4). The carbohydrate content of medications, vitamins, and toothpaste must be considered in planning the diet.

Continued on page 3 (Reverse side)

Discussion continued from page 2

Up to 50% of the children who initiate the KGD will discontinue it within the first year because of noncompliance or lack of efficacy. In those for whom the diet is effective, weaning of medications can be attempted if a sustained improvement is seen after 3 months.

There are no studies to guide how long a child should be maintained on the KGD. For children who become seizure free after KGD initiation, the diet is typically maintained for at least 2 years of seizure freedom. However, attempts to wean may occur after only a year of seizure freedom and others may choose to continue the diet for much longer than 2 years. While there are concerns about the long-term adverse effects of the diet, it has been maintained in a small percentage of children for more than 10 years with good success.

ABOUT THE AUTHORS

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ACKNOWLEDGMENT

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For more information visit
www.AESNET.org

FAQs Frequently Asked Questions

Are some seizures more responsive to the KGD?

The KGD has been found to be effective for all seizure types. There is evidence that it may be particularly effective in certain epileptic encephalopathies such as Dravet syndrome, myoclonic-astatic epilepsy, and Lennox-Gastaut syndromes.

How can the palatability of the diet be improved?

Diet palatability is often improved through the use of carbohydrate-free flavorings. In a variation of the KGD, medium chain triglyceride (MCT) oil is used. Due to its "pro-ketotic" features, the addition of MCT allows more protein and carbohydrates to be offered. Although the use of MCT has been associated with diarrhea, this can be avoided with careful diet manipulation. Occasionally, MCT is added to a classic KGD to help with constipation. Lastly, many families share recipes and ideas through web-based KGD communities (e.g., www.matthewsfriends.org).

Are there less restrictive diets that also have the potential to reduce seizure frequency?

Yes, two popular weight loss programs are the basis for new dietary therapies for epilepsy. The modified Atkins diet for epilepsy is based on carbohydrate restriction to 10 grams per day. It differs from the Atkins diet in that fats such as cream and mayonnaise are encouraged in the epilepsy diet and hidden carbohydrates (e.g. sugar alcohols found in commercially prepared low carbohydrate products) must be avoided. The low glycemic index treatment (LGIT) is based on minimizing fluctuations in blood glucose. In this diet, food choice is significantly increased by permitting foods with a low glycemic index—foods that do not raise blood glucose. All diets for epilepsy should be monitored by a physician and dietician familiar with their use.

Are there any anticonvulsant medications that should not be used with the ketogenic diet?

Children treated with the KGD should be monitored for medication side effects that can be compounded by the diet, such as the metabolic acidosis and kidney stones associated with topiramate and zonisamide. A concern that concomitant treatment with valproic acid may increase the risk of idiosyncratic hepatic failure or carnitine deficiency has not been observed in a retrospective review.

Is the ketogenic diet ever used as a first-line therapy?

Yes, the KGD is the treatment of choice for glucose transport 1 (GLUT1) deficiency and pyruvate dehydrogenase deficiency. In these conditions, neurological sequelae occur secondary to impaired brain utilization of glucose. By promoting the use of ketones, the KGD provides an alternate fuel source for the brain.

Can diet therapies be used in adults?

Yes, the KGD and the alternative diet therapies have been successful in adults with epilepsy. Adults treated with the KGD must be monitored for hypercholesterolemia, hypertriglyceridemia, and menstrual irregularities.

Where should I direct families for additional resources?

The Charlie Foundation website is a good place to start (www.charliefoundation.org). Families may also want to consider purchasing The Ketogenic Diet: A Treatment for Children and Others With Epilepsy, written by John Freeman and colleagues, or The Ketogenic Cookbook, written by Dennis and Cynthia Brake.

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KNOWLEDGE GAP ADDRESSED

Current practice recommendations in the general neurology community are limited and need to be supported. This activity will make the general neurologist more aware of the complex issues involved in treating patients with epilepsy and be able to apply the appropriate resources.

LEARNING OBJECTIVES

- Evaluate efficacy and side effect profile of the ketogenic diet (KGD) versus AEDs to determine the most effective treatment in order to manage the patient with epilepsy more appropriately and to enhance his/her quality of life.
- Recognize that treatments may have consequences that impact a patient beyond seizure control, and how best to address these consequences.
- Given that patients with epilepsy can have a number of medical and psychological issues that require intervention, in addition to control of their seizures, determine the best ways to address these issues.
- Recognize the barriers that patients with epilepsy may encounter in an effort to sustain an optimal quality of life.

TARGET AUDIENCE

General neurologists, nurses, and other healthcare professionals involved in the care of patients with epilepsy.

ACCREDITATION STATEMENT

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION

The American Epilepsy Society designates this educational activity for a maximum of 0.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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It is the policy of the AES to make disclosures of financial relationships of faculty, planners, and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

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FACULTY DISCLOSURES

Drs. Austin, Bertram, Donner, Gilliam, and Goodkin – have indicated they have nothing to disclose.
Dr. Sperling – Speakers' Bureau: Pfizer, Inc., Ortho-McNeil, UCB Pharma; Intellectual Property/Patent Holder: Daeyang; Consulting/Advisory Board: Valeant, Dainippon Pharmaceuticals; Contracted Research: UCB Pharma, Schwarz Pharma, GlaxoSmithKline, Medtronics, Neuropace, Johnson & Johnson.

CME REVIEWER

Fred Lado, M.D., Ph.D. – has indicated he has nothing to disclose.

EDITORIAL REVIEWERS

Paul Shea and Kay Sloves – have indicated they have nothing to disclose.

SELF-ASSESSMENT QUIZ

To obtain credit you must read the newsletter and answer the Self-Assessment Quiz and CME Evaluation Survey. Mail them to:

American Epilepsy Society
Education Department
342 North Main Street
West Hartford, CT 06117-2507
or Fax to: (860) 586-7550

A CME certificate will be sent to you within three weeks should you obtain a grade of 75% (3 of 4 answers correct) or more.

1. Potential chronic side effects of the diet include:
a. infection
b. poor linear growth
c. constipation
d. kidney stones
e. all of the above

2. True or False: Children treated with the KGD should not be prescribed topiramate or valproic acid.

3. In the modified Atkins diet, carbohydrates are initially restricted to
a. 1 gram per day
b. 5 grams per day
c. 10 grams per day
d. 25 grams per day

4. True or False: The diet is not recommended for the treatment of focal seizures.

Please circle the correct answers:
1. a b c d e **2.** T F **3.** a b c d **4.** T F

CME EVALUATION SURVEY

Complete the Evaluation (please be sure to indicate how long it took to complete this activity).
The amount of time you attest to on this evaluation will be reflected on your certificate.

Name _____

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Degree(s): ☐ M.D. ☐ D.O. ☐ Pharm.D. ☐ RN ☐ PA ☐ B.S.
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Are you an AES member?
☐ YES ☐ NO

1. Effectiveness in Meeting Identified Learning Objectives
Was the activity effective in meeting the identified learning objectives?

SCALE: ☐ 5=Excellent ☐ 4=Very Good ☐ 3=Satisfactory ☐ 2=Fair ☐ 1=Poor

Evaluate efficacy and side effect profile of the ketogenic diet (KGD) versus AEDs to determine the most effective treatment in order to manage the patient with epilepsy more appropriately and to enhance his/her quality of life.
5☐ 4☐ 3☐ 2☐ 1☐

Recognize that treatments may have consequences that impact a patient beyond seizure control, and how best to address these consequences.
5☐ 4☐ 3☐ 2☐ 1☐

Given that patients with epilepsy can have a number of medical and psychological issues that require intervention, in addition to control of their seizures, determine the best ways to address these issues.
5☐ 4☐ 3☐ 2☐ 1☐

Recognize the barriers that patients with epilepsy may encounter in an effort to sustain an optimal quality of life.
5☐ 4☐ 3☐ 2☐ 1☐

2. Questions Relating to Your Intent to Make Practice Changes
Based upon your participation in this CME activity, please answer the following:

Did the information in this activity increase your ability to judge whether to use diet therapy for epilepsy?
☐ YES ☐ NO

Did the information in this activity increase your confidence in choosing a KGD for a specific clinical situation?
☐ YES ☐ NO

Will the information in this newsletter alter your prescribing patterns or influence the discussions that you have with patients when selecting an antiepileptic therapy?
☐ YES ☐ NO

Can we contact you in a follow-up survey to measure the impact of this educational intervention?
☐ YES ☐ NO

3. Based on your participation in this CME activity, which of the following strategies do you now plan to use in your practice that you haven't used before? (Check all that apply)

☐ I will consider the ketogenic diet (KGD) for my patients who cannot tolerate AEDs.

☐ I will consider the KGD for my patients who have Dravet syndrome, myoclonic astatic epilepsy, and Lennox-Gastaut syndrome

☐ I will consider the KGD for my patients who have glucose transport 1 (GLUT1) deficiency and pyruvate dehydrogenase deficiency.

☐ I will recommend ways to make the KGD more palatable for my pediatric epilepsy patients.

4. Are there any barriers to implementing these strategies? (Check all that apply)

☐ Time
☐ Cost
☐ Staffing
☐ Institutional treatment algorithm differences
☐ Formulary
☐ Patient adherence
☐ Other: _____

5. Effectiveness of the Individual Faculty Writer(s):

SCALE: 5=Excellent 4=Very Good 3=Satisfactory 2=Fair 1=Poor (Please Check)

Faculty	Knowledge of Subject Matter	Appropriateness of Teaching Strategies	Was Presentation Free of Commercial Bias?
Elizabeth J. Donner, M.D., and Howard Goodkin, M.D., Ph.D.	5☐ 4☐ 3☐ 2☐ 1☐	5☐ 4☐ 3☐ 2☐ 1☐	☐ Yes ☐ No If no, please describe below:

_____

_____

6. Please rate the educational value/clinical relevance of the content:
☐ Just Right ☐ Too Advanced ☐ Too Basic

7. Commercial Support and Disclosure	**Yes**	**No**
Disclosure of faculty relationships was made available.	☐	☐
The commercial supporter was acknowledged in the newsletter.	☐	☐
If trade names were used, trade names of all products discussed were used.	☐	☐

If you answered "No" to any of the above questions, please provide details:

_____

_____

8. Based upon the topic of this case series, "When Medications Fail: The Ketogenic Diet," please list additional topics that you would like to hear about that will better help you manage your patients.

1.) _____

2.) _____

9. Are you interested in the following modalities of learning?
(Check all that apply)
☐ Podcast/downloadable audio files ☐ Publications ☐ Webcast ☐ Case Studies
☐ Audioconference ☐ Interactive CD-ROM/DVD ☐ Monograph ☐ Live Events

10. Would you like to continue receiving this publication?
☐ Yes ☐ No

11. Please send me AES membership information.
☐ Yes ☐ No

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How long did you participate in this activity?

☐ I participated in the entire activity and claim _____ credit hours. (maximum 0.5)

☐ I participated in only part of the activity and only claim partial credit hours based on _____hours of instruction. (e.g., 0.25)

☐ By submitting this request, I certify the above is true and correct.

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Signature

Thank you for your participation.