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Refractory Epilepsy Patients: Management Options when Drugs Fail

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The opinions reflected in this Webinar are those of the speaker and independent of Nutricia North America.

Disclosures

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Objectives

1. Understand alternative management options when AEDs fail
2. Discuss existing clinical evidence and MOA of the ketogenic diet
3. Identify best candidates for the ketogenic diet
4. Evaluate how the ketogenic diet could benefit your patients

Conceptual definition of Seizures & Epilepsy

- An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain. (ILAE 2005)
- Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

Fisher et al. Epilepsia, 55(4). 2014

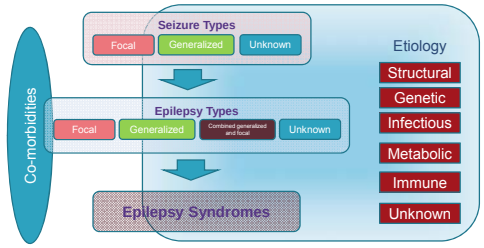
Operational Definition of Epilepsy

Epilepsy is a *disease* of the brain defined by any of the following:

- At least two unprovoked (or reflex) seizures occurring >24 h apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome

RS Fisher et al. Epilepsia, 55(4), 2014

2017 ILAE Classification of the Epilepsies



Adapted from: Scheffer et al. Epilepsia, 58(4). 2017

Epilepsy Epidemiology: the *stark reality*

65 MILLION people around the world who have epilepsy.
3.4 MILLION people in the United States who have epilepsy.
1 IN 26 people in the United States will develop epilepsy at some point in their lifetime.
150,000 new cases of epilepsy in the United States each year
ONE-THIRD: Number of people with epilepsy who live with uncontrollable seizures because no available treatment works for them.

www.Epilepsy.com

Recognizing drug-resistant epilepsy is paramount

- Failure of adequate trials of **2** *tolerated, appropriately chosen and used* antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom
  - In a community-based survey, patients with one or more seizures over the last 2 years had higher levels of anxiety and depression, greater perceived stigma and impact of epilepsy, and lower employment rates than did those who were seizure-free (Jacoby et al., 1996).
  - Consensus is that seizure-free duration should be at least 12 months or 3 times the longest inter-seizure interval

Some Reasons for Pseudoresistance to Antiepileptic Drug Therapy

Reason	Examples
Wrong diagnosis	syncope, cardiac arrhythmia or other conditions; psychogenic non-epileptic seizure
Wrong drug (or drugs)	Inappropriate for seizure type; pharmacokinetic or pharmacodynamic interactions
Wrong does	Too low (overreliance on "therapeutic" blood levels); side effects preventing drug increase
Lifestyle issues	Poor compliance with medication; alcohol or drug abuse

Kwan et al. Epilepsia, 51(6), 2010
Kwan, Schachter, & Brodie. NEJM 2011

When drugs fail: alternative management

- Surgical treatment:
  - surgically remedial syndrome: unilateral hippocampal sclerosis or other resectable lesions
    - Anterior temporal lobectomy is superior to continued medication in providing long-term relief from seizures in up to 70% of adults with drug-resistant temporal-lobe epilepsy (class I evidence)
  - Other potentially curative procedures include resection of structural lesions/lesionectomy such as glial tumors and vascular malformations (class III evidence).
  - Palliative procedures: Corpus callosotomy, Multiple subpial transection, Hemispherectomy or functional hemispherotomy, new minimally-invasive techniques

Kwan et al. Epilepsia, 51(6), 2010

When drugs fail: alternative management (cont'd)

- Devices: vagus-nerve stimulator, reactive neurostimulation
- **Dietary**

Kwan et al. Epilepsia, 51(6), 2010

History of ketogenic diets

- Complete abstinence from food and drink was prescribed and was successful for an epileptic man by Hippocrates in 5th century B.C.
- In King James version of the Bible, when asked about healing an epileptic child, Jesus responds that "this kind can come out by nothing but prayer and fasting."

J. Wheless. "History and Origin of the Ketogenic Diet" in *Epilepsy and the Ketogenic Diet* edited by Stafstrom & Rho, 2004

Early studies of fasting for seizures

First Author	Year	Diet	Seizure Type	Success Rate
Geyelin R	1921	Fasting	PG, GM	87% Seizure free
Weeks DR	1923	Fasting	PM, GM	47% Seizure free during fast
Talbot	1926	Fasting	UN	Seizure free during fast
	1928	Fasting		50% had marked reduction in seizures during the fast
Lennox WG			UN	

Adpated from: J. Wheless. "History and Origin of the Ketogenic Diet"

In 1921, Dr. Wilder at Mayo Clinic proposed & coined the term **ketogenic diet**:

- "The ketone bodies . . . Are formed from fat and protein whenever a disproportion exists between the amount of fatty acid and the amount of sugar actually burning in the tissues. In any case, as has long been known, it is possible to provoke ketogenesis by feeding diets which are very rich in fat and low in carbohydrate . . . If this is the mechanism responsible for the beneficial effect of fasting, it may be possible to substitute for that rather brutal procedure [fasting] a dietary therapy . . . "

Wilder RM. Mayo Clinic Bull 1921;2:307-308

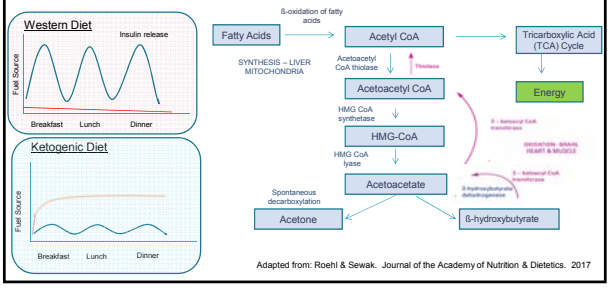
History of ketogenic diets

Dr. Peterman of Mayo Clinic first reported the calculation & effectiveness of the ketogenic diet in 1924: composed of 1 gm/kg of protein, 10-15 gm/day of carbohydrates, and remainder fat ➔ 4:1 ratio ketogenic diet used today!

- Noted nausea/emesis with excess ketosis & relief with orange juice
- "In all the children treated with the ketogenic diet there was marked change in character, concomitant with the ketosis, a decrease in irritability, and an increased interest and alertness . . ."

Peterman MG. JAMA 1925 & Am J Dis Child 1924

Ketone Body Synthesis & Oxidation



Adapted from: Roehl & Sewak. Journal of the Academy of Nutrition & Dietetics. 2017

Mechanism of Action of ketogenic diets

- Direct anticonvulsant effects
  - BHB can slow spontaneous neuronal firing by opening ATP-dependent K^+ channels
  - ↑ GABA inhibition, ↓Glutamate excitation
- Anti-inflammatory
  - decreases proinflammatory cytokine levels after an immune challenge.
  - Polyunsaturated fatty acids (PUFAs): omega-3s in particular
    - directly decrease inflammatory cytokines, ROS, & expression of adhesion molecules. EPA & DHA
    - Indirectly by altering expressino of pro-inflammatory genes & bind to and activiate PPAR's
- Neuro-regenerative/reparative
  - Mimics in utero & infantile metabolic condition, with KBs being major source for normal brain development
    - Repair epileptogenisis-related neuronal injury?
    - Possible therapeutic role in neurodegenerative disease, TBI, etc.

NA Youngson et al. Seizure, 52, 2017

Anti-inflammatory Models

Type of diet	Species	Model	Anti-inflammatory effect of KD
6.6:1 KD 3 weeks before Exp. Made by the lab 2 weeks before Exp.	Rats C57BL/6J Mice	Subcutaneous injection of complete Freund's adjuvant into one hind paw MPTP model	Decrease both swelling and plasma extravasation Decrease of activated microglia (Iba1 staining) Decrease of IL-1β, IL-6, TNF-α (ELISA of SN)
6.3:1 KD (Bio-Serv F3666 diet) 7 days before Exp.	C57BL/6 Mice	Experimental autoimmune encephalomyelitis S.C. myelin oligodendrocyte glycoprotein (MOG)35-55 peptide + complete Freund's adjuvant (CFA) I.V.20 ng of pertussis toxin	2-2.5-fold reduction in CNS-derived CD4+ cells and CD11b+ CD45+ cells (macrophage and microglia tendency toward increased CD4+ CD25+ Foxp3+ Treg cells Lymph node & CNS reduction in cytokines (IL-1 β, IL-6, TNF-α, IL-12, IL-17) and chemokines (IFN-γ, MCP-1, MIP-1a, MIP-1b)
6.3:1 KD (Bio-Serv F3666 diet) 4 weeks before Exp.	C57BL/6 Mice	Liver and white adipose tissue (WAT)	Liver: Increase of expression of Tnfα, Il-6, Emr I, Cd68, Itgam, Nlrp3 WAT: Decrease of expression of Tnfα, Il-6, Emr1, Cd68, Itgam, Nlrp3
3:1 KD (Ketocal) 2 weeks before Exp.	Wistar rats	Fever model 50 ug/kg of KPS (*Escherichia coli* 0.55:B5)	Modulate raise of body temperature Blood: Reduce IL-1 β, TNF-α Brain: Reduce IL-1 β mRNA

JA French et al. Epilepsia 58 (Supp 3), 2017

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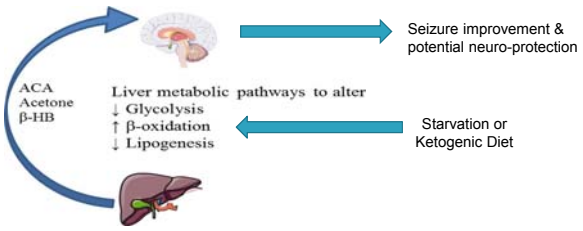
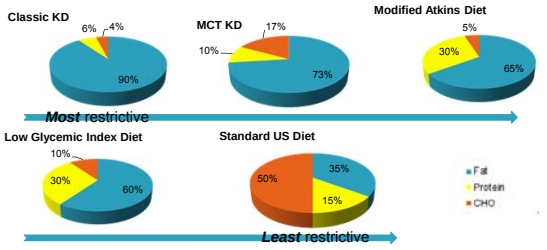
Hepatic metabolic changes drive downstream brain beneficial effects



Spectrum of ketogenic dietary options



Adapted from: E. Neal. Complete Nutrition. 2009

Spectrum of ketogenic dietary options

g (%Kcal)	Classic keto (4:1)	MCT	Modified Atkins	LGIT
Fat	100 (90%)	78 (70%)	70 (70%)	60 (45%)
Protein	17 (7%)	25 (10%)	60 (25%)	40 (28%)
Carbs	8 (3%)	50 (20%)	10 (5%)	40 (27%)

Most restrictive ***Least*** restrictive

Kossoff & Hartman. Curr Op Neurology 2012

Spectrum of ketogenic diets

1. Classical KD: fat mainly provided from long chain foods (butter, mayo, margarine, oil, cream) or a prescribed supplement. Carb intake severely limited mainly to fruits & veggies. Protein intake based on minimum requirements.
2. MCT diet: started in 1971, produces higher ketone yield per KCal of energy than long-chain fatty acids. Therefore incorporate less fat and allows for more carbs and proteins. In practice, a starting MCT level somewhere between 40-50% (plus some classical long chain fat sources) to produce best balance b/w tolerance & ketosis.

Both diets require food calculations & weighing, with prescribed balance of ketone-producing foods/MCT oil to non-fats.

Spectrum of ketogenic diets

3. MAD diet: started 2003, restricts carbs to 10-20g daily for children & adults, encourages high fat foods but does not limit or measure protein or total calories.
4. LGID, started 2005, allows 40-60g carbs but only those with low glycemic index < 50, aim being to minimize spikes in blood glucose. Specific meal plans are usually not provided, and food is not weighed but based on portion sizes.

First prospective, multi-center trial

1. Seven epilepsy centers prospectively entered 51 children, classic keto diet
   - All with intractable epilepsy, avg 230 sz/mo
   - Sz frequency evaluated at 3, 6, & 12 mo
2. Results: 10% sz free & 40% > 50% decrease in sz frequency at one year. Using intention-to-treat analysis, 47% remained on diet at one year. Of 53% who discontinued, half due to poor tolerance & half poor sz control
3. No effect of pt's age, sz type, or EEG results
4. Demonstrated KD efficacy across centers Vining et al. Archives Neurology. 1998

Randomized controlled trial-2 Aims

1. Test efficacy (& tolerability) of ketogenic vs. regular diet at 3 months in first randomized controlled trial
2. Compare efficacy & tolerability of classical vs. MCT versions of ketogenic diet at 3, 6, & 12 months
   - 5 years of enrollment (2001-2006)
   - Inclusion criteria: children 2-16 yrs with at least daily sz's or > 7 szs/week, lack of response to at least 2 AEDs, naïve to keto diet
   - Exclusion criteria: h/o hyperlipidemia, renal stones, or organic acid deficiency

Randomized controlled trial-Methodology

1. After education & baseline medical screening, Ketogenic diets started at home
   - Classical gradually increased to 3:1 or 4:1 ratio over 1-2 weeks
   - MCT diets titrated over 7-10 days to achieve MCT fat content of ~45% of total dietary energy, 30% long-chain fat, 10% protein, 15% carbs
2. Subjects reviewed as outpatients at 6 weeks & 3 mo, plus close monitoring via telephone calls
3. Urine ketones twice daily, plus blood ketones during visits

Neal et al. Lancet Neurology. 2008

Table 1: Baseline characteristics of children allocated to each study group and included in final analysis

	Diet Group		Control Group	
	Allocated to study group (n = 73)	Included in final analysis (n = 54)	Allocated to study group (n = 72)	Included in final analysis (n = 49)
SEX				
Male	38 (52%)	30 (56%)	38 (53%)	25 (51%)
Female	35 (48%)	24 (44%)	34 (47%)	24 (49%)
AGE				
2-6 years	37 (51%)	28 (52%)	29 (40%)	20 (41%)
7-11 years	27 (37%)	20 (37%)	32 (44%)	20 (41%)
12-16 years	9 (12%)	6 (11%)	11 (15%)	9 (18%)

Table 3: Comparison of seizures as a percentage of baseline after 3 months

	Diet Group (n = 54)	Control group (n = 49)
Mean percentage of baseline seizures after 3 months (95% CI)	62·0% (50·74%)	136·9% (105·169%)
Median percentage of baseline seizures after 3 months (SD, IQR)	47·7% (43, 0·200%)	106·3% (111, 28·575%)

Adapted from Neal et al. Lancet Neurology. 2008

Table 4: Number of children in each group who achieved 50% and 90% seizure reduction at 3 months

	Patients who achieved cut-off points		P value
	Diet group (n = 73)	Control group (n = 72)	
>90% reduction in seizures	5 (7%)	0 (0%)	0.0582
>50% reduction in seizures*	28 (38%)	4 (6%)	<0.0001
<50% reduction in seizures*	45 (62%)	68 (94%)	<0.0001

Percentages based on numbers allocated to each intervention. *Includes patients who reported >90% reduction. †Includes 71 patients with data and 42 unknown (16 did not receive treatment, 10 discontinued treatment, 16 with no data)

No difference whether symptomatic focal vs. generalized seizures in terms of response to diet

No one withdrew after 3 mo due to these side effects; dietary adjustment helped, but ~1/4 required meds for constipation

Table 5: Side-effects reported after 3 months on the ketogenic diet

	Patients who reported side-effects*
Vomiting	13 (24%)
Diarrhea	7 (13%)
Abdominal pain	5 (9%)
Constipation	18 (33%)
Medication for constipation needed	13 (24%)
Lack of energy	13 (224%)
Hunger	12 (22%)

*Data are number (%) of the 55 children who continued on the diet for 3 months

Adapted from:Neal et al. Lancet Neurology. 2008

RCT: classic vs. MCT ketogenic diet

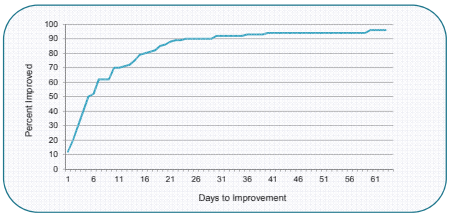
Time	Numbers (%) of children achieving cutoff points		
	Classical diet group (n = 73)	MCT diet group (n = 72)	p-value
3 months			
Greater than 90% seizure reduction	5 (6.8%)	2 (2.7%)	0.442
Greater than 50% seizure reduction*	18 (24.7%)	21 (29.2%)	0.578
6 months			
Greater than 90% seizure reduction	6 (8.2%)	4 (5.6%)	0.745
Greater than 50% seizure reduction*	18 (24.7%)	14 (19/4%)	0.549
12 months			
Greater than 90% seizure reduction	7 (9.6%)	7 (9.7%)	1.000
Greater than 50% seizure reduction*	13 (17.8%)	16 (22.2%)	0.539

*Includes those reporting >90% reduction (n, number who were allocated to intervention).

- ➔ No differences in sz refuction between two dietary groups at any time point. Serum acetoacetate & BHB levels were significantly higher on classical KD at 3 & 6 months.
- ➔ Only differences in tolerability: increased reports of lack of energy & vomiting at different time points on classic KD. No difference in drop-out/inefficacy rates overall.

Apapted from: Neal et al. Epilepsia. 2009

How soon do patients respond to KD?



118 subjects on classic KD, 84% with improvement reported, 90% by 3 weeks

Adapted from :Kossoff, Nordli et al. Epilepsia 2008

So which epilepsies respond to KD?

Australian study consecutively enrolling individuals with drug-resistant chronic epilepsy over span of 7 years

- 64 children & 4 adults
- 7 excluded (1 failed to keep sz diary, 1 became sz-free prior to KD, & 5 did not comply with KD
- all underwent inpatient initiation of 2:1 to 4:1 KD
- 13 of 61 (21%) did not complete 3-month trial: 2 due to acute illness, 11 with inefficacy dropped out
- "responders" experienced >50% reduction in sz frequency

Thammongkol et al. Epilepsia 2012

Final outcomes

Time	Patients with follow-up Data (n = 61)	Patients remaining on diet	Discontinued diet (%)	Current seizure status		
				Seizure-free	Responders (>50% reduction)	Nonresponders (<50% reduction)
3 months	61	48	13 (21)	2	29 (48)	19 (31)
6 months	57	37	7 (12)	2	24 (42)	13 (23)
12 months	55	24	11 (20)	2	19 (35)	5 (9)
24 months	49	11	8 (16)	2	7 (14)	4 (8)

1. 1/3rd overall were responders at 12 months
2. Excellent response in most genetic and primary generalized forms of epilepsy (JME, CAE, Doose, Dravet) but small #'s of pts
3. Good response with structural etiologies due to malformations or acquired pathologies
4. Good response in 3/8 with LGS & 1/5 with West syndrome

Adapted from: Thammongkol et al. Epilepsia, 2012

2016 Cochrane Review for Pediatric Dietary Trials

- 7 RCTs, with total n=427
- 55% with sz freedom and 85% having significant sz reduction in a 4:1 KD group after 3 months
- Studies using MAD reported 10% sz freedom rate with 60% achieving significant sz reduction
- High attrition rates, mainly due to GI side effects & perceived inefficacy
- No data on impact on cognition, behavior, or QOL

Martin et al. Cochrane Database Syst Rev. 2016

Responder Rates in Adults

Author (Year)	Subjects, n	Diet	Duration, mo	Compliant, n (%)	≥90% sz reduction	≥50% sz reduction
Sirven et al. (1999)	11	4:1 KD	8	7 (64%)	3/11 (27%)	6/11 (55%)
Mosek et al. (2009)	9	4:1 KD	3	2 (22%)	0/9 (0%)	2/9 (22%)
Klein et al. (2010)	12	3-4:1 KD	4	8 (67%)	2/12 (17%)	5/12 (42%)
Cervenka and Kossoff (2013)	27	KD[a]	2-118	9 (33%)	52%[b]	70%[b]
Nei et al. (2014)	28	4:1 KD	24	5 (18%)	1/28 (4%)	13/28 (46%)
Schoeler et al. (2014)	23	2-2.5:1 KD	12	9 (39%)	2/23 (8%)	9/23 (39%)
Lambrechts et al. (2012)	15	KD+MCT	12	5 (33%)	0/15 (0%)	2/15 (13%)
Coppola et al. (2011)	6	LGIT	2	5 (83%)	0/6 (0%)	3/6 (50%)
Kossoff et al. (2003)	3	MAD	3	3 (100%)	1/3 (33%)	1/3 (33%)
Carrette et al. (2008)	8	MAD	6	3 (38%)	0/8 (3%)	1/8 (12%)
Kossoff et al. (2008)	30	MAD	6	14 (47%)	1/30 (3%)	10/30 (33%)
Smith et al. (2011)	18	MAD	12	14 (78%)	0/18 (0%)	3/18 (17%)
Cervenka et al. (2012)	22	MAD	3	14 (64%)	4/22 (18%)	6/22 (27%)
Kossoff et al. (2013a,b,c)	6	MAD	2	5 (83%)	2/6 (33%)	4/6 (67%)
Ramm-Pettersen et al. (2013)	3	MAD	12	3 (100%)	2/3 (67%)	2/3 (67%)
Kverneland et al. (2015)	13	MAD	3	6 (46%)	1/13 (8%)	4/13 (31%)
Cervenka et al. (2016a,b)	87[c]	MAD	12	33 (38%)	13/87 (15%)	29/87 (33%)

Adapted from: Williams & Cervenka. Clinical Neurophysiology Practice 2, 2017

Clinical trial data in Adults

- Klein P, et al **Dietary treatment in adults with refractory epilepsy: a review.** Neurology 2014**:**
  - 32% of KD-treated and 29% of MAD-treated patients achieved ≥ 50% seizure reduction
  - Including 9% and 5% (KD and MAD) of patients with >90% seizure frequency reduction
  - The 3:1 and 4:1 [fat]:[carbohydrate + protein] ratio KD variants and MAD are similarly effective.
- Ye F et al. **Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis.** J. Clin. Neurology 2015:
  - Combined 270 adults on classic KD, MAD, or KD-MCT
  - Efficacy rates of 52% for classic KD and 34% for MAD
  - Compliance rate of 38% for classic KD and 56% for MAD

High drop-out rates but potential anti-epileptogenic impact?

- About half of individuals will drop out of dietary therapy before 3-6 months
- But pediatric Hopkins study shows that a favorable response to KD even in the short-term (<1 year) predicts & perhaps impacts favorable response in the long-run 3-6 years out
  - 1/3rd of those who had >50% sz reduction on KD continued to have similar sustained sz improvement versus 2/3rd of those who had poor response to KD

TABLE 1. *Comparison of the group who discontinued the diet prior to one year with the initial cohort*

	Entire 150-Patient cohort	67 who discontinued The diet before 1 year
Male/Female	85:65	40:27
Age: average	5.3 yr	6.6 yr
Range	4 mo-26 yr	6 mo-26 yr
Seizure frequency	410 per mo	921 per mo
Seizure type	Multiple, varied*	Multiple, varied*
No. of medications	1.97	1.89

TABLE 3. Outcomes of those on the diet <1 year who did not undergo surgery or vagal nerve stimulator implantation (N = 41)

% Seizure reduction when discontinued	% Seizure reduction at follow-up			
	Free	>90%	50-90%	<50%
<50% (n = 26)	4 (15%)	2 (8%)	3 (12%)	17 (65%)
50-90% (n = 9)	2 (22%)	1 (11%)	2 (22%)	4 (44%)
>90% (n = 5)	2 (40%)	1 (20%)	1 (20%)	1 (20%)
Free (n = 1)	1 (100%)	--	--	--
Total	9	4	6	22

Adapted from: Marsh et al. Epilepsia 47(2), 2006

Ketogenic diets for epilepsy: synopsis

1. Still mostly reserved for intractable epilepsy since 70% of time, and AEDs can achieve seizure control. Not ideal for good surgical candidates either. Role in refractory status epilepticus
2. Seizure types: meta-analysis of 11 KD studies found no difference in effectiveness for partial vs. generalized onset sz
3. No difference in symptomatic vs. asymptomatic epilepsy
4. Myriad epilepsy syndromes respond
   - Treatment of choice: GLUT1 & pyruvate dehydrogenase deficiency
   - Consider early: LGS, Dravet, Doose (myoclonic-astatic), Landau-Kleffner, other epileptic encephalopathies, infantile spasms, Rett syndrome, Angelman syndrome, TSC
   - Positive trend: JME & symptomatic generalized epilepsies
   - Practicality: formula-fed infants, gastrostomy-fed patients of any age

Ketogenic diets for epilepsy: synopsis

5. Effectiveness across the age spectrum
6. Improved cognition & behavior, allows tapering of AEDs many responders
7. Contra-indications: fatty acid/carnitine transport & β-oxidation defects, pyruvate carboxylase def.,porphyria
8. Relative contra-indications: need for chronic steroids, diuretics & carbonic anhydrase inhibitors, h/o poor compliance/adherence, clear structural lesion with focal epilepsy, h/o nephrolithiasis, liver or pancreatic disease, metabolic/electrolyte abnormalities, pregnant, poor nutritional status

A Bergqvist in *Epilepsy and the Ketogenic Diet* edited by Stafstrom & Rho, 2004
Kossoff & Hartman. Current Opinion Neurology. 2012
Kossoff et al. Epilepsia, 50(2):304–317, 2009

Identifying ideal candidates for KD in your practice

- Drug-resistant → clearly epileptic → not surgical candidate
- Continued impact of epilepsy & treatment side effects on QOL?
- Compliant & Motivated?
- Food secure & adequate social/caretaker support?
- Evidence-based efficacy:
  - Treatment of choice: GLUT1 & pyruvate dehydrogenase deficiency
  - Consider early: LGS, Dravet, Doose (myoclonic-astatic), Landau-Kleffner, other epileptic encephalopathies, infantile spasms, Rett syndrome, Angelman syndrome, TSC
  - Positive trend: JME & symptomatic generalized epilepsies
  - Practicality: formula-fed infants, gastrostomy-fed patients of any age

Evaluating candidates & further workup prior to diet initiation

Concern	Suggested Workup
Inability to maintain adequate nutrition or hydration • **Failure to thrive** • **Dysphagia** • **Gastrointestinal issues (chronic diarrhea, vomiting, reflux)** • **Not able to meet fluid goals** • **Extreme picky eating/limited food acceptance**	• Obtain gastrointestinal consult • Obtain swallow evaluation • Consider need for gastrostomy tube placement • Increase fat/kcal before initiation • Trial of 4:1 ketogenic formula • Provide recipes/foods to trial • Behavioral feeding consult
Concerning medical history • **Extreme dyslipidemia** • **Cardiomyopathy** • **Renal disease/renal calculi** • **Liver disease** • **Baseline metabolic acidosis**	• Obtain cardiology, nephrology, or hepatology consult for clearance • Adjust fluid minimums • Add citrate, consider bicitrate to alkalize urine, avoid/wean drugs like topiramate and zonisamide • Wean insulting medications if possible, increase fluid minimums, consider beginning with lower diet ratio
Social constraints • **Access to food and kitchen** • **Caregiver support and compliance** • **Multiple caregivers/unstable home environment**	• Connect family with social worker to discuss access to services, for example, but not limited to, durable medical equipment, Special Supplemental Program for Women, Infants, and Children, respite care, in home supportive services and/or formula company's assistance programs • Registered dietitian nutritionist can discuss metal/food options feasible for family.

Adapted from: Roehl & Sewak. Journal of the Academy of Nutrition & Dietetics.

Evaluating candidates: Minimum standards & recommendations for initiation of classic KD & MAD

Evaluations	Baseline (pre-diet)	Follow-up (at clinic visited)
Nutrition/Monitoring		
Mandatory:	Basic nutrition counseling Height & weight, calculation of body mass index (BMI) Food allergies/intolerances, food availability/preference	BMI changes Seizure frequency
Recommended:	Three-day food record/calorie count Pre-diet seizure frequency Consider monitoring tart and end date of menses	Food records/compliance Side effects Changes in menses
Laboratory		
Mandatory:	Basic metabolic panel, liver function tests (if on hepatically metabolized anticonvulsants) Urine human chorionic gonadotropin (premenopausal women)	Basic metabolic panel, lipid profile, urinalysis Urine ketones (if patient not doing well and considering stopping diet)
Recommended:	Complete blood count, lipid profile, liver function tests, calcium, vitamin D level Consider free carnitine, selenium, magnesium, phosphorus, anticonvulsant levels, urinalysis and urine calcium and creatinine ratios	Liver function tests, vitamin D lever, complete blood count, calcium, free and total carnitine, urine ketones Consider selenium, zinc, magnesium, phosphorus, and urine calcium and creatinine ratios (especially if not on citrate)
Diagnostic		
Mandatory:	Metabolic testing in children to identify etiology, if suspected high risk based on history	None
Recommended:	EEG/Epilepsy Monitoring Unit evaluation (if diagnosis unclear, patient suspected to be an epilepsy surgery candidate)	Bone density scan (every 5 years, minimum) Renal ultrasound (if nephrolithiasis suspected) Carotid ultrasound (if prolonged fasting lipid elevation)

Williams & Cervenka. Clinical Neurophysiology Practice 2, 2017
Kossoff et al ILAE Epilepsy Task Force for Dietary Therapy. Epilepsia 56, 2017

Ketogenic Diet Find a Ketogenic Diet Center

Where can I find a Ketogenic Diet center?

We have compiled a list of hospitals and medical centers that offer the ketogenic diet for pediatric epilepsy. If you would like to add your hospital or medical center to this list, please send the name, address, website, and phone number of your facility to myketocal@nutricia.com.

- https://www.myketocal.com/kdcenters.aspx
- https://www.epilepsy.com/article/2017/8/ketogenic-diet-trainings-opportunities-dietitians-and-neurologists
- http://www.carleyeissmanfoundation.com

Summary

- Dietary modification represents a safe, effective, & evidence-based therapeutic intervention for drug-resistant epilepsy
- There exists a range of ketogenic diets in clinical practice which confer both direct & indirect anticonvulsant, anti-inflammatory, and likely neuro-protective effects.
- Identify & evaluate appropriate candidates for dietary changes, focusing on epilepsy etiology/syndrome and compliance

Questions?

Feedback, Please!
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