



The Present and Future of the Ketogenic Diet as it Approaches its Second Century!



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Disclosures

- Consultant: Nutricia, Atkins Nutritionals, Bloom Science, VitaFlo, Greenwich
- Data Safety Boards: NIH, BioPharm, Greenwich
- Royalties: UpToDate, Demos, Oxford Press

Dr. Kossoff is a world-renowned neurologist who has been invited to speak for his expertise on the ketogenic diet. The opinions reflected in this presentation are solely those of Dr. Kossoff and independent of Nutricia North America.

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19 September 2019 : Baltimore!

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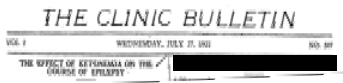
July 27, 1921

FASTING AS EPILEPSY CURE.

Osteopaths Hear That 22 Days on Water Usually End Fits.

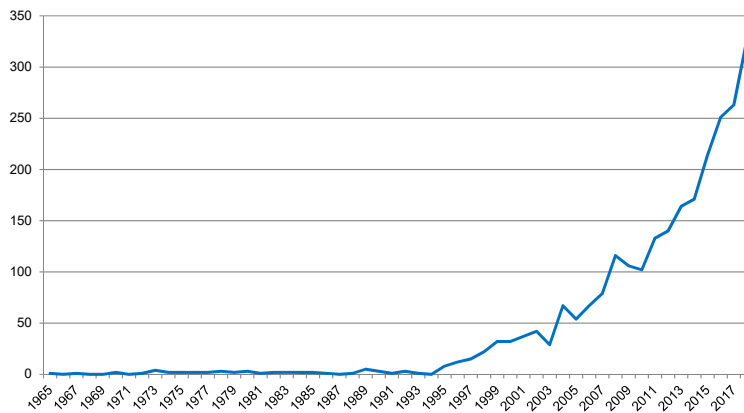
LOS ANGELES, July 5.—Epilepsy may be cured by fasting, Dr. Hugh Conklin told the twenty-sixth annual convention of the American Osteopathic Association, now in session here. Epilepsy, according to Dr. Conklin, is caused by the improper functioning of certain glands in the bowels. By fasting for twenty-two days, taking only water, a cure may be effected, he said.

Dr. Wilder at Mayo Clinic, Rochester, MN creates a high fat, low carbohydrate diet to mimic fasting state



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PubMed: "Ketogenic"



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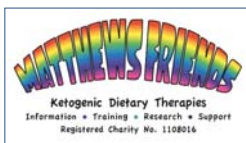
Epilepsia Open The Open Access Journal of the International League Against Epilepsy Open Access

SPECIAL REPORT

Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group

¹Eric H. Kossoff, ²Beth A. Zupce-Kania, ³Stéphane Auvin, ⁴Karen R. Ballaban-Gil, ⁵A.G. Christina Bergqvist, ⁶Robyn Blackford, ⁷Jeffrey R. Buchhalter, ⁸Roberto H. Caraballo, ⁹J. Helen Cross, ¹⁰Maria G. Dahlin, ¹¹Elizabeth J. Donner, ¹²Orkide Guzel, ¹³Rana S. Jehle, ¹⁴Joerg Klepper, ¹⁵Hoon-Chul Kang, ¹⁶Danielle A. Lambrechts, ¹⁷Y.M. Christiana Liu, ¹⁸Janak K. Nathan, ¹⁹Douglas R. Nordli Jr., ²⁰Heidi H. Pfeifer, ²¹Jong M. Rho, ²²Ingrid E. Scheffer, ²³Suvasini Sharma, ²⁴Carl E. Stafstrom, ²⁵Elizabeth A. Thiele, ²⁶Zahava Turner, ²⁷Maria M. Vaccarella, ²⁸Eliens J.T.M. van der Louw, ²⁹Pierangelo Veggiotti, ³⁰James W. Wheless, ³¹Elaine C. Wirrell, The Charlie Foundation, Matthew's Friends, and the Practice Committee of the Child Neurology Society

Epilepsia Open, 3(2):175-192, 2018
doi: 10.1002/epi4.12225



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7TH GLOBAL SYMPOSIUM
ON MEDICAL KETOGENIC DIETARY THERAPIES
COLLABORATIVE SCIENCE AND CLINICAL CARE
#KETO2021 **WWW.GLOBALKETO.COM**

19TH-23RD OCTOBER 2021
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Topics

1. Latest research towards clinical use and flexibility in 2020
2. Keto in Covid-19 pandemic?
3. Future directions in the next century

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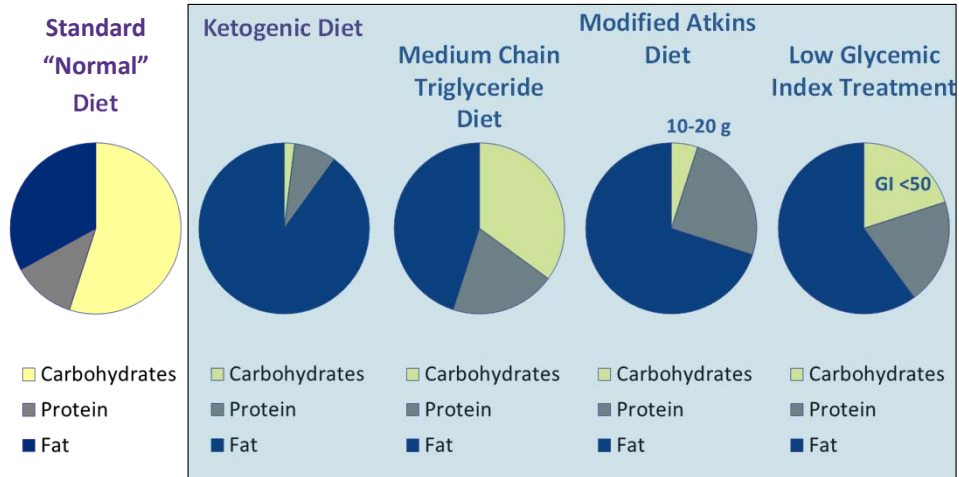
The Traditional Method of Starting the Ketogenic Diet

- Traditionally started in the hospital over 2-4 days, following a 24 hour fast
- Dietitians calculate ratio (fat: protein and carbs), calories, fluids
- Foods weighed and measured



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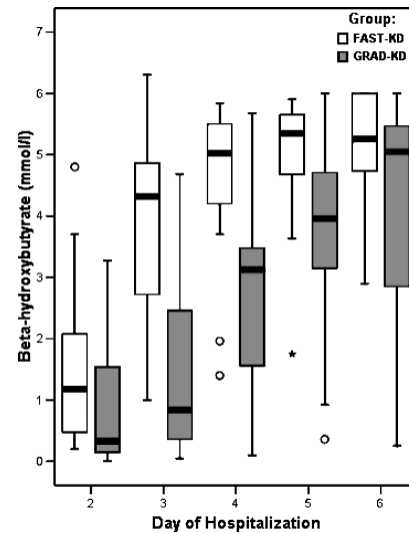
Four Ketogenic Diets



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Flexibility !

- Seminal paper by Dr. Christina Bergqvist published in *Epilepsia* in **2005**
- No difference in a randomized trial between fasting and “gradual” onset
 - Outcomes identical at 3 months



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- No reason to fluid or calorie restrict
- All 4 diets equally valid: you choose!
 - *KD for < 2 years, MAD/LGIT for > 12 years*
- Admission? 92% believe it's optional
- Fasting? 68% believe it's optional
 - *Not in infants < 2 years*

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Major Changes: Revised Consensus

- **New “true” indications (>70% response rates)**
 - Angelman syndrome, Complex 1 mitochondrial disease, FIRES, Ohtahara syndrome, super-refractory status epilepticus
- **Remaining on the list:**
 - Dravet syndrome, Doose syndrome, Glut-1, formula-fed children, infantile spasms, pyruvate dehydrogenase deficiency, tuberous sclerosis complex
- **Helpful (40-70% response, but not “indications” currently):**
 - Adenylosuccinate lyase deficiency, CDKL5 encephalopathy, Childhood absence epilepsy, Cortical malformations, Epilepsy of infancy with migrating focal seizures, ESES, Glycogenosis type V, Juvenile myoclonic epilepsy, Lafora body disease, Landau-Kleffner syndrome, Lennox-Gastaut syndrome, Phosphofructokinase deficiency, Rett syndrome, Subacute sclerosing panencephalitis (SSPE)

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“Hot” Indications in 2020

Status epilepticus

TPN

Infants and infantile spasms

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*There are no nutritionally complete ketogenic formulas approved for infant use in the United States of America.

Author	Population	Diet	Etiology	Response (days (%))
Francois (2003)	6 children	EN KD	RSE	50%
Mikaeloff (2006)	1 child	EN KD	RSE	Yes
Cheuret (2008)	1 child	EN KD	RSE	No
Bodenant (2008)	1 adult	EN KD	Focal epilepsy	7
Strader (2009)	1 child	EN KD	Focal cortical dysplasia	No
Vileneuve (2009)	5 children	EN KD	SWS, encephalitis, cryptogenic	1-10
Kumada (2009)	2 children	Oral MAD	Frontal lobe, heterotopia	5-10
Wusthoff (2010)	2 adults	EN KD	Rasmussen, head trauma	8-10
Nabbout (2010)	9 children	EN KD	Febrile infection-related syndrome*	4-6
Cervenka (2011)	1 adult	EN KD	Idiopathic, possible autoimmune	7
Ismail (2012)	1 child	EN KD	*FIREs	10
Nam (2012)	4 children, 1 adult	EN KD	Encephalitis	1-19
Vaccarezza (2012)	5 children	EN KD	*FIREs, partial status	2-3
Martikainen (2012)	1 adult	Oral LGIT	POEG	4
Sort (2013)	3 children	EN KD	HHES, mitochondrial, FIREs	66%
Carballo (2013)	3 children	EN KD	FIREs	66%
Gedik (2013)	1 child	EN KD	Meningoencephalitis	No
Barros (2014)	1 child	EN KD	NMDA encephalitis	No
O'Connor (2014)	5 children	EN KD	POEG, mitochondrial, cryptogenic	1-5
Cobo (2014)	4 children	EN KD	Tuberous sclerosis, cryptogenic	2-8 (75%)
Thakur (2014)	10 adults	EN KD	Encephalitis, anoxia, partial	1-6
Incecik (2015)	1 child	EN KD	CP	No
Amer (2015)	1 adult	EN KD	NMDA encephalitis	14
Liu (2015)	1 child	IV KD → enteral	Focal epilepsy	3
Carballo (2015)	2 children	EN KD	Refractory myoclonic status epilepticus	75-90% and 50% reduction
Chiusolo (2016)	1 child	IV KD → enteral	Focal epilepsy	No
Appavu (2016)	10 children	TPN, EN KD	Rasmussen, NMDA encephalitis, mycoplasma, LGS, NORSE, FIREs, PCDH19, genetic	90%
Uchida (2017)	1 adult	KD + strip enteral	NMDA encephalitis	60 days
Cervenka (2017)	15 adults	EN KD	SISE-5 NORSE, 3 ICH, 2 LGS, 2 anoxic, 1 GBM, 1 TBI, 1 encephalitis	0-10 (73%)
Farias-Moeller (2017)	9 children	EN KD	7 FIREs, 1 epileptic encephalopathy, CNS HLH	66%
Arya (2018)	11 children	EN KD	RSE	79%
Frazier (2018)	11 adults	EN KD	RSE	0-3 (73%)

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ICU Protocol

Remove dextrose from intravenous fluids

D/C current enteral formula

Remove carbohydrates from medications and parenteral fluids

Check fasting lipid profile, CMP, CBC, selenium levels, urine ketones

Nutrition consult

Begin 4:1 formula at half RDA of calories for first 24 hours then advance to full calories

Begin multivitamin and calcium via GT/NG crushed and mixed in water

Document baseline weight and height

Check glucose every 6 hours

Consider wean of pentobarbital drip after 1 week

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Courtesy Mackenzie Cervenka, MD

2 Important Guidelines

Elles van der Louw¹, Vanessa Aldaz², Jessica Harvey³, Marian Roan⁴, Dorine van den Hurk⁵, J Helen Cross⁶, Stéphane Auvin⁷, Review Group

2020 Jan;62(1):48-56. **Optimal Clinical Management of Children Receiving Ketogenic Parenteral Nutrition: A Clinical Practice Guide**
[Survey of 150 centers, 35 patients in the literature reported](#)

Elles van der Louw, Dorine van den Hurk, Elizabeth Neal, Barbel Leindecker, Georgiana Fitzsimmon, Laura Dority, Lindsey Thompson, Maddelena Marchio, Magdalena Dudzinska, Anastasia Dressler, Joerg Klepper, Stephane Auvin, J Helen Cross.

2016 Nov;20(6):798-809. **Ketogenic diet guidelines for infants with refractory epilepsy.**
[15 expert review, consensus guideline format, best evidence](#)

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*There are no nutritionally complete ketogenic formulas approved for infant use in the United States of America.

Breastfeeding?

- Frequent posters at AES and the biannual keto meetings
- Le Pichon et al. *Seizure* 2019
 - 9 infants
 - Breastmilk expressed and mixed with 4:1 ketogenic or a soy-based formula
- Dressler et al. *Breastfeed Med* 2020
 - 16 infants
 - Similar protocol to Le Pichon, but several breastfed after bottle feed

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Prezioso G et al. Efficacy of ketogenic diet for infantile spasms: A systematic review. *Acta Neurologica Scand.* 2018

- 13 studies, 341 patients selected for analysis
 - 65% with >50% spasm reduction
 - 35% spasm-free
 - IS due to unknown etiology higher chance of seizure-freedom (RR 1.72)

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The Carson Harris Foundation

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What is the keto diet?
It is a high fat, low carbohydrate diet that has been in use since 1921.

JHH KETOGENIC DIET PARENT SUPPORT GROUP
Held monthly during the keto admission week at Johns Hopkins Hospital.

Our Mission
To increase awareness on the issues that affect individuals with epilepsy and raise funds in support of clinical and research efforts on the diagnosis of epilepsy and its treatment including, but not limited to, diets, surgery, and anticonvulsant medications.

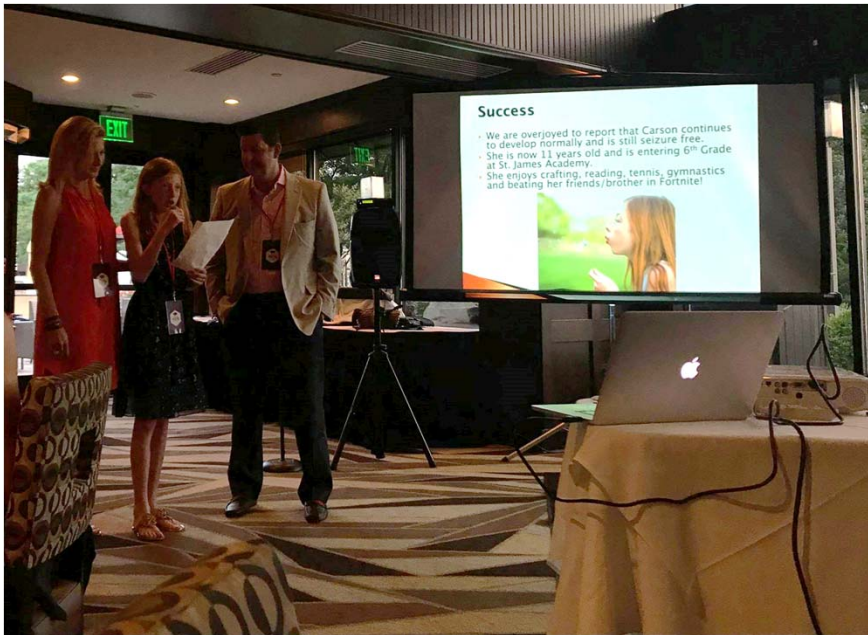
Watch our last webinar!
"New Developments in the Ketogenic Diet for Infantile Spasms"

DONATE TODAY
Donations provide support of clinical and research efforts on the diagnosis

Carson's Story
In January of 2007, we took our 5-month old daughter, Carson, to Johns Hopkins Hospital because she was having what appeared to be seizures. Twelve hours, a spinal tap and an EEG scan of her brain later we were told that she has a rare form of Epilepsy called "Infantile Spasms". [READ MORE](#)

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KetoU 2018

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Dressler A, et al. Efficacy and Tolerability of the Ketogenic Diet Versus High-Dose Adrenocorticotrophic Hormone for Infantile Spasms: A Single-Center Parallel-Cohort Randomized Controlled Trial. *Epilepsia* 2019.

- 101 infants, RCT and parallel-cohort, *included those treated with vigabatrin before*
- All infants: 47% KD vs. 48% ACTH
 - Relapse rate 16% KD vs. 43% ACTH (p=0.09)
- For New Onset (no prior vigabatrin):
 - At 1 month: 80% ACTH vs. 47% KD (p=0.02)
 - At last visit: 21% ACTH vs. 48% KD (p=0.05)

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KD for New-onset Spasms Today

- I will offer it when infants present within 2 weeks of onset
- 13/28 patients tried (**46%**)
 - When not successful, parents still very appreciative
- Need an eager team
- Most common reasons for refusal:
 - Ease of oral steroids and I'm not on call

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Management of infantile spasms (IS) during the COVID19 pandemic

Treatment

- Select from among ACTH (adrenocorticotrophic hormone), high dose prednisolone (6-8mg/kg/day), and vigabatrin, unless contraindications to all three.
- For etiologies other than tuberous sclerosis complex, prefer outpatient initiation of prednisolone.³
- For tuberous sclerosis complex, prefer vigabatrin if immediately available. If anticipating a treatment delay, consider initiating prednisolone until vigabatrin can be obtained.
- **Avoid non-standard therapy as first treatment choice (i.e., avoid topiramate, ketogenic diet, etc.).**
- For prednisolone or ACTH, consider GI prophylaxis with a proton pump inhibitor or H2 blocker.
- For prednisolone or ACTH, write one prescription with 2 weeks at a high dose *and* a 2-week taper.

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Ketogenic Diets and COVID-19: Is there an interaction?

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RELATED LINKS:

- More Keto News



Epilepsy News From: Tuesday, April 7, 2020

I hope everyone is staying safe and staying home! I have been receiving lots of emails from patients, parents, neurologists and dietitians asking if there are particular issues for people on ketogenic diets for epilepsy in this COVID-19 crisis. I personally hadn't heard of any unique keto-related problems, but I asked members of the 2018 International Ketogenic Diet Study Group (who helped create the consensus statement), along with other experts like Dr. Mackenzie Cervenka, Emma Williams from Matthew's Friends; Stacey Bessone RD; Liz Neal RD, PhD; Susan Wood RD; and Marisa Armeno MD.

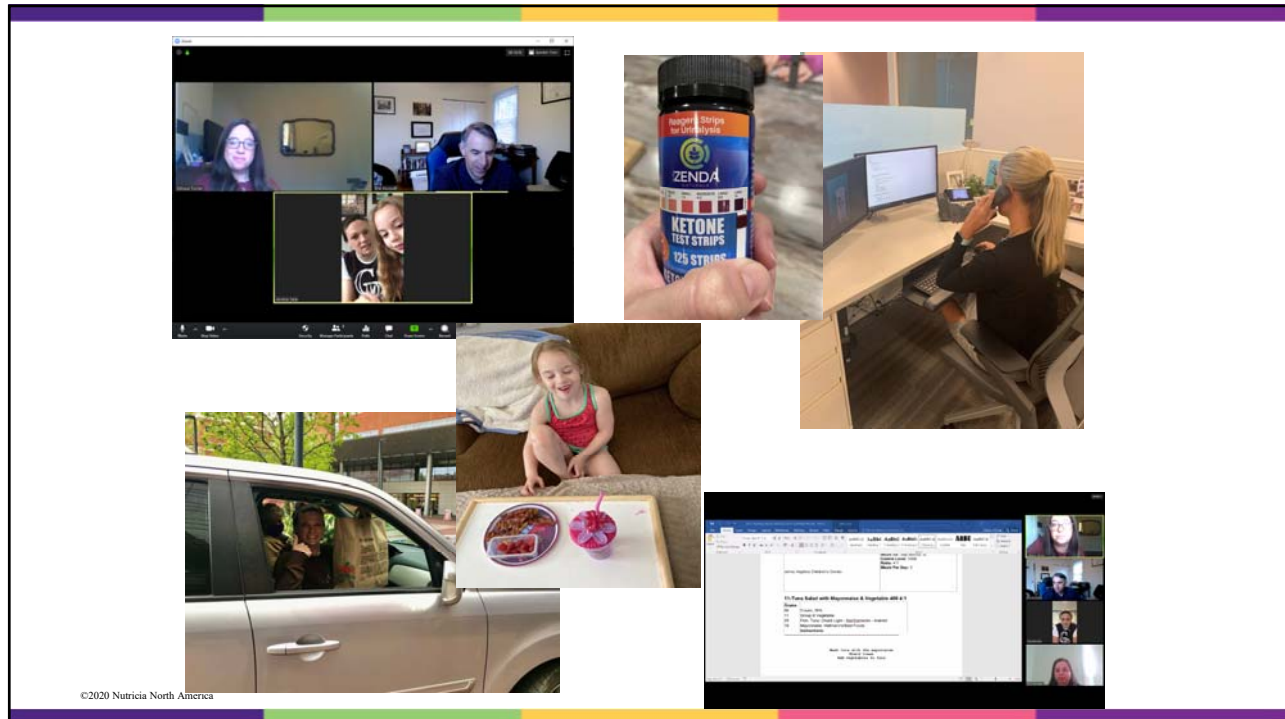
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Several potential options!! It's Possible!

1. Classic KD by Zoom as an outpatient
2. Modified Atkins Diet (with information emailed, video links given)
3. Admit anyway with in-person, Zoom, or phone education
 - Abbreviated admits

Ketogenic diet therapy provision in the COVID-19 pandemic: Dual-center experience and recommendations. *Epilepsy Behav*, online early 2020.



Continuing KDT in a pandemic

Telemedicine!

Make sure there's a home scale

High fat, canned foods with long shelf-lives

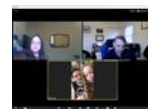
- Oils, tuna, mayo, nuts
- May need special notes for milk, eggs, meat

Food delivery services?

90 day supplies of vitamins, formulas, supplements (and medications)

Lock away high carb foods...

Don't worry as much about labs



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JHH Adult Epilepsy Diet Center

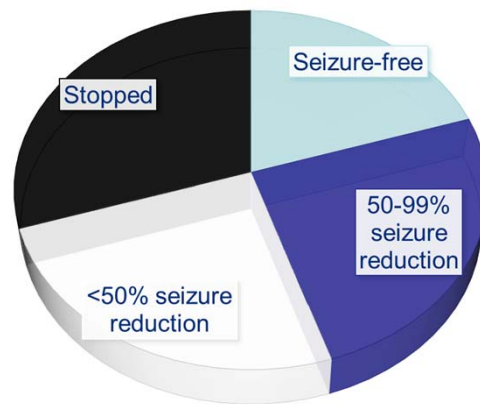
- Approaching the 10 year anniversary!
- >300 adults seen in clinic to date
 - ~20% were already on diet therapies at initial visit
 - ~80% were **not** started on modified Atkins diet



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Slide courtesy Dr. Mackenzie Cervenka

3-month Seizure Outcomes in Adults



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Cervenka et al. *Epilepsy & Behavior*, 2016.

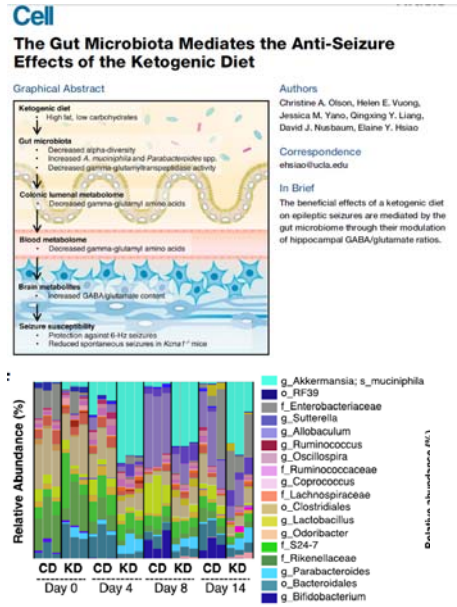
Select Unanswered Questions in Adults

- How do we improve compliance?
 - Ketone esters, MCT, set recipes, pre-made foods
- What are the ramifications of elevated lipid profiles in adults?
- Is the diet safe in pregnancy?
- Many more!

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Gut Microbiome

- Akkermansia muciniphila and Parabacteroides together
 - Changes within 4 days in mice on the KD
 - Providing these bacteria after antibiotics restored seizure protection
- Under active study in humans



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About MHS

Metabolic Health Summit - Formerly the Conference on Nutritional Ketosis and Metabolic Therapeutics - was founded with a mission to revolutionize science and medicine by refocusing attention on the importance of nutrition and metabolism in treating disease, extending life, and improving human performance.

This event is a four-day Immersive experience that will bring you groundbreaking scientific research, paradigm-shifting clinical reports, thought-provoking panel discussions, inspirational success stories, gourmet low-carb cooking classes, and incredible networking opportunities for both the professional and lay-person with interest in ketogenic nutrition and metabolic therapies! The summit is attended by a diverse group of individuals with significant personal, professional, and social influence in the health and nutrition space. Attendees include scientists, physicians, keto enthusiasts, educators, biohackers, content creators, dietitians, naturopaths, entrepreneurs, and industry experts.

We are proud to be hosting MHS 2019 at the beautiful Renaissance Long Beach Hotel! In the heart of the artistic-urban Long Beach community, this stunning space will open your senses and allow you to experience Los Angeles at its finest. Relax in the eclectic lobby, enjoy ocean-to-fork dining, or simply soak in the hotel's perfect blend of beach and city sophistication. Unwind with a refreshing swim or craft keto-friendly cocktail on the third-floor deck, and enjoy unbelievable views of the Pacific Ocean and the legendary Queen Mary from this deluxe Long Beach hotel.

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Neurologic Uses Other than Epilepsy

Hypoxia-anoxia	2001
Autism	2003
Brain tumors	2003
Depression	2004
Narcolepsy	2004
Glycogenosis Type V	2005
Alzheimer's	2005
Traumatic brain injury	2005
Parkinson's	2005
ALS	2006
Migraine	2006
Sleep disorders	2007
Post hypoxic myoclonus	2007
Schizophrenia	2009
Spinal cord injury	2009
Pain	2009
Sandhoff disease	2010
Huntington's disease	2011
Bipolar disorder	2012
Multiple Sclerosis	2012
Diving CNS toxicity	2014
Alternating hemiplegia of childhood	2015
Kabuki syndrome	2016
Pelizaeus-Merzbacher disease	2019

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Ongoing research continues in these areas

Klement RJ. The emerging role of ketogenic diets in cancer treatment. *Clinical Nutrition* 2019.

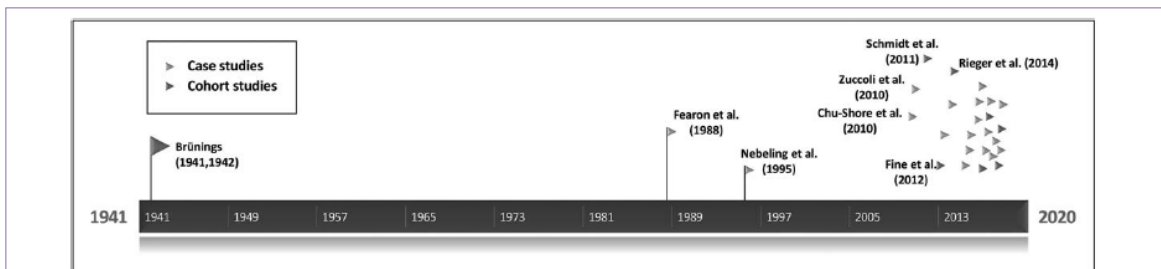


FIGURE 1. Timeline of studies utilizing a ketogenic diet for cancer treatment. After Wilhelm Brünings' pioneering studies, it took 70 years until interest in the ketogenic diet re-emerged as exemplified by an increasing number of published studies beginning in 2011. Reproduced from ref. [2*], which was published under a creative commons license CC BY-NC-ND 4.0.

130 www.co-clinicalnutrition.com

Volume 22 • Number 2 • March 2019

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Ongoing research continues in this area

Table 1. Hypothesized mechanisms through which ketogenic therapies influence neurological disease.

Ketogenic Mechanisms	Epilepsy	Malignant Glioma	Alzheimer's Disease
Metabolic Regulation			
↓Glucose uptake & glycolysis	+	+	
↓Insulin, IGF1 signaling		+	+
↑Ketones/ketone metabolism	+		+
Altered gut microbiota	+		
Neurotransmission			
Altered balance of excitatory/inhibitory neurotransmitters	+		
Inhibition of AMPA receptors	+		
↓mTOR activation & signaling	+	+	
Modulation of ATP-sensitive potassium channels	+		
Oxidative Stress			
↓Production of reactive oxygen species	+	+	
↑Mitochondrial biogenesis/function	+		+
Inflammation/Neuroprotection			
↓Inflammatory cytokines	+	+	
NLRP3 inflammasome inhibition	+	+	
↑cytotoxic T cell function		+	
↓peritumoral edema		+	
↓amyloid-β levels			+
Genomic Effects			
Inhibition of HDACs	+	+	
↑PPARγ	+		
↓Expression of angiogenic factors in tumor cells		+	

AMPA—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; IGF1—insulin-like growth factor 1; HDACs—histone deacetylases; mTOR—mammalian target of rapamycin; NLRP3—NOD-like receptor protein 3; PPAR—peroxisome proliferator-activated receptor. ↓—decreased; ↑—increased; +—mechanism shown in *in vitro* or *in vivo* studies.

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Table from
McDonald TJW, Cervenka MC. The Expanding Role of Ketogenic Diets in Adult Neurological Disorders. *Brain Sci.* 2018;8.

Ongoing research continues in these areas

Unanswered questions for alternative indications?

- Are the mechanisms of action different for each indication?
- Will they truly be effective?
- Will patients stick to the diet for a chronic illness without distinct calendar “events”?
- Who will do the research?

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Consensus Guided Future Research: 2028



- Supplements
- Children with surgically-accessible lesions
- DEXA and monitoring for long-term risks?
- Value of EEG
- Serum ketones? Necessary?
- First-line use before medications

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The screenshot shows a web browser displaying the website for Matthew's Friends Keto College. The page is titled "Online Introductory Course for Families, Carers and Patients". The navigation menu includes Home, About Us, Medical Section, Health & Wellbeing, Keto News, Fundraising, Keto Therapies, Keto Kitchen, Shop, and Contact Us. The main content area features a yellow sidebar with "Keto Training" links and a pink header for the "Online Introductory Course for Families, Carers and Patients". The text in this section states: "In this section you will find a list of links to various films we have made to help you with preparing and managing a medical ketogenic diet. We have put these all in an 'easy to find' list which you can view at your leisure. All these are freely available on our YouTube channel and there are many other recipes and interviews that you can watch on this channel which you can also subscribe to and receive alerts as to when new films have been added." Below this text is a photo of a woman and a paragraph expressing gratitude for donations and support.

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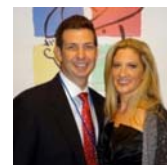
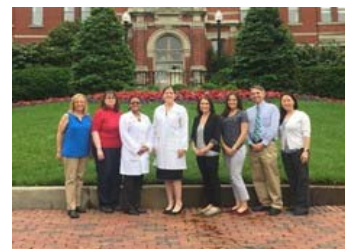
Epilepsy Research KD Special Issue 2020

- Dressler A, Trimmel-Schwahofer P. The ketogenic diet for infants: How low can you go?
- Armeno M, Caraballo R. The evolving indications of KD therapy.
- Blackford R. Not your parents' ketogenic diet: flexibility in 2020.
- Husari KS, Cervenka MC. The ketogenic diet all grown up: Ketogenic diet therapies for adults.
- *(and 4 basic science articles courtesy of Dr. Jong Rho coming soon!)*

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