

Refractory Epilepsy Patients: Management Options when Drugs Fail

December 14, 2017

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

Disclosures

- 1. I received funding from the Epilepsy Foundation of Greater Los Angeles and The Charlie Foundation to establish our program at U.S.C.
- 2. We are currently receiving funding for our Dietary Program from The Carley Eissman Foundation
- 3. I received funding from Nutricia to prepare these slides

Objectives

DINLC

- 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

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

Diagnosis of an epilepsy syndrome

2017 ILAE Classification of the Epilepsies	
Seizure Types Focal Generalized Unknown Epilepsy Types Focal Ceneralized Unknown Epilepsy Syndromes Epilepsy Syndromes Adapted from: Scheffer et al. E	

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

Recogniz paramou	zing drug-resistant epil nt	epsy is
antiepilep achieve s In a the la perc than Cons	f adequate trials of 2 tolerated, approp. tic drug schedules (whether as monot sustained seizure freedom community-based survey, patients with sat 2 years had higher levels of anxiety eived stigma and impact of epilepsy, ai did those who were seizure-free (Jac sensus is that seizure-free duration sho sees the longest inter-seizure interval	herapies or in combination) to o one or more seizures over / and depression, greater nd lower employment rates oby et al., 1996).
Some Reasons for Pseu	doresistance to Antiepileptic Drug Therapy	
Some Reasons for Pseu Reason	Examples	
Reason	Examples syncope, cardiac arrhythmia or other conditions;	
Reason Wrong diagnosis	Examples syncope, cardiac arrhythmia or other conditions; psychogenic non-epileptic seizure Inappropriate for seizure type; pharmacokinetic or	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."

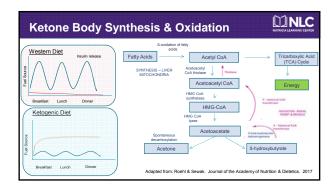
J. Wheless. "History and Origin of the Ketogenic Diet" in Epilepsy and the Ketogenic Diet edited by Stafstrom & Rho, 2004

Early	stud	ies of	fasting	
irst Author	Year	Diet	Seizure Type	Success Rate
Seyelin R	1921	Fasting	PG, GM	87% Seizure free
Veeks DR	1923	Fasting	PM, GM	47% Seizure free during fast
albot	1926	Fasting	UN	Seizure free during fast
ennox WG	1928	Fasting	UN	50% had marked reduction in seizures during the fast
			Adpated fro	om: J. Wheless. "History and Origin of the Ketogenic Diet"
1921, Dr.	Wilder	at Mayo (Clinic proposed	d & coined the term ketogenic diet:
exists be in the tiss ketogene . If this is	tween t sues. In sis by f the me	he amoui n any cas feeding di echanism	nt of fatty acid e, as has long ets which are responsible fo	a fat and protein whenever a disproportion and the amount of sugar actually burning been known, it is possible to provoke very rich in fat and low in carbohydrate r the beneficial effect of fasting, it may be tal procedure [fasting] a dietary therapy

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

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- 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 \rightarrow 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..."



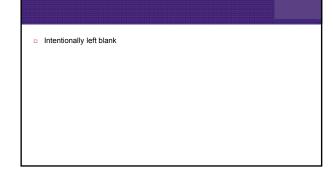


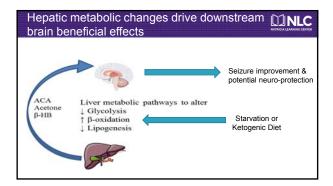
MNLC Mechanism of Action of ketogenic diets

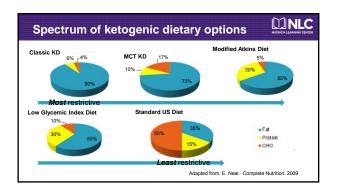
- Direct anticonvulsant effects
 - BHB can slow spontaneous neuronal firing by opening ATP-dependent K⁺ channels
 - ↑ GABA inhibition, ↓Glutamate excitation
- Anti-inflammatory
 - decreases proinflammatory cytokine levels after an immune challenge. Polyunsaturated fatty acids (PUFAs): omega-3s in particular
 - directly decrease inflammatory cytokines, ROS, & expression of adhesion molecules. EPA & DHA
 - Indirectly by altering expression 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
- Anti-inflammatory Models Species Type of diet 6.6:1 KD 3 weeks before Exp. Made by the lab 2 weeks before Exp. Anti-inflammatory effect of KD Decrease both swelling and plasma extravasation Decrease of activated microglis (Ibai stairing); Decrease of IL-4β, IL-6, TNF-α (ELISA of SN) Model us injection of complete juvant into one hind paw Freund's adju MPTP model C57BL/6J Mice 2-2.5-fold reduction in CNS-derived CD4+ cells and CD1 lib+CD45+ cells (macrophage and microgial tendency toward increased CD4+ CD25+ Fouz3+ Treg cells Lymph node & CNS reduction in cytokines (IL-1 §I, IL-5, TN-C, IL-12, IL-17) and chemokines (IFN-r, MCP-I, MIP-Ia, MIP-Ib) 6.3:1 KD (Bio-Serv F3666 diet) 7 days before Exp. C57BL/6 Mice Experimental autoimmune encephalomyellits S.C. myelin oligodendrocyte glycoprotein (MO(3)35-55 peptide + complete Freund's adjuvant (CFA) I.V.20 ng of pertussis toxin 6.3:1 KD (Bio-Serv F3866 diet) C57BL/6 Mice 4 weeks before Exp. Liver: Increase of expression of Trifa, II-6, Emr I, Cd68, Itgam, Nirp3 WAT: Decrease of expression of Trifa, II-6, Emrl, Cd68, Itgam, Nirp3 Liver and white adipose tissue (WAT) 3:1 KD (Ketocal) 2 weeks before Exp. Wistar rats Fever model Modulate raise of body temperature 50 ug/kg of KPS (*Escherichia coli* 0.55:85) Blood: Reduce IL-I β, TNF-α Brain: Reduce IL-I β mRNA

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

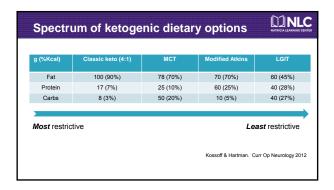














Spectrum of ketogenic diets

- 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.
- 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.
- 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
- 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

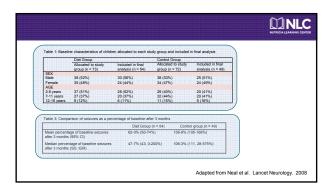
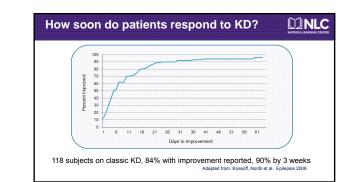
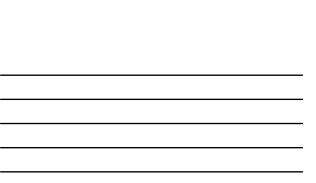




Table 4: Number of children in e reduction at 3 months	ach group who achi	leved 50% and 90%	s seizure		NUTRICIA LEARNING CE
		achieved cut-off	P value	No one withdrew	after 3 mo due
		pints		to those side offe	ata: diatan/
	Diet group (n = 73)	Control group		to these side effe	cis, uleialy
>90% reduction in seizures	(n = 73) 5 (7%)	(n = 72) 0 (0%)	0.0582	adjustment helpe	d but $\approx 1/4$
>50% reduction in seizures*	28 (38%)	4 (6%)	<0.0082	aujusiment neipe	u, but - 1/4
<50% reduction in seizures [†]	45 (62%)	68 (94%)	<0.0001	required meds fo	r constination
who reported >90% reduction. 1 did not receive treatment, 10 dis			inknown (16	Table 5: Side-effects reported after 3 mp	
No. differences			. (Table 5. Side-ellects reported aller 5 mo	Patients who reported
No difference w	nether syr	npiomatic	;		side effects'
focal vs. genera	lizod coiz	uroc in to	me	Vomiting	13 (24%)
			1115	Diarrhea	7 (13%)
of response to o	tiat			Abdominal pain	5 (9%)
or response to t	not			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 2

	Numb	ers (%) of children achieving o	utoff points
Time	Classical diet group (n = 73)	MCT diet group (n = 72)	p-value
3 months			
Greater than 90% seizure reduction Greater than 50% seizure reduction ^a	5 (6.8%) 18 (24.7%)	2 (2.7%) 21 (29.2%)	0.442
6 months	10 (24.7 10)	21 (23.2.14)	0.510
Greater than 90% seizure reduction	6 (8.2%)	4 (5.6%)	0.745
Greater than 50% seizure reduction ^a	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).	





So which epilepsies respond to KD?

Australian study consecutively enrolling individuals with drugresistant 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 Tharmongkol et al. Epilepsia 2012

Final outcomes Current seture status Current seture status Time Patients with follow-up Data (n = 61) Patients memaring Discontinued def (%) Current seture status Time Patients with follow-up Data (n = 61) Patients memaring Discontinued def (%) Current seture status 3membre def 30 37 49 71(2) 2 24(2) 10(20) 10(20) 10(20) 10(20) 10(20) 20(20) 10(20) 20(20) 10(20) 20(20)

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
- 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

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Author (Year)	Subjects, n	Diet	Duration, mo	Compliant, n (%)	≥90% sz reduction	>50% sz reduction
irven et al. (1999)	11	4:1 KD	8	7 (64%)	3/11 (27%)	6/11 (55%)
Aosek et al. (2009)	9	4:1 KD	3	2 (22%)	0/9 (0%)	2/9 (22%)
Jein et al. (2010)	12	3-4:1 KD	4	8 (67%)	2/12 (17%)	5/12 (42%)
ervenka and Kossoff (2013)	27	KDa	2-118	9 (33%)	52% ²	70%5
lei et al. (2014)	28	4:1 KD	24	5 (18%)	1/28 (4%)	13/28 (46%)
choeler et al. (2014)	23	2-2.5:1 KD	12	9 (39%)	2/23 (8%)	9/23 (39%)
ambrechts et al. (2012)	15	KD+/MCT	12	5 (33%)	0/15 (0%)	2/15 (13%)
oppola et al. (2011)	6	LGIT	2	5 (83%)	0/6 (0%)	3/6 (50%)
lossoff et al. (2003)	3	MAD	3	3 (100%)	1/3 (33%)	1/3 (33%)
arrette et al. (2008)	8	MAD	6	3 (38%)	0/8 (3%)	1/8 (12%)
lossoff 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%)
ervenka et al. (2012)	22	MAD	3	14 (64%)	4/22 (18%)	6/22 (27%)
lossoff et al. (2013a,b,c)	6	MAD	2	5 (83%)	2/6 (33%)	4/6 (67%)
amm-Pettersen et al. (2013)	3	MAD	12	3 (100%)	2/3 (67%)	2/3 (67%)
verneland et al. (2015)	13	MAD	3	6 (46%)	1/13 (8%)	4/13 (31%)
ervenka et al. (2016a.b)	87°	MAD	12	33 (38%)	13/87 (15%)	29/87 (33%)

Adapted from: Williams & Cervenka. Clinical Neurophysiology Practice 2, 2017
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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 KO-MCT
 Efficacy rates of 52% for classic KD and 34% for MAD
 Compliance rate of 38% for classic KD and 56% for MAD

	op-out rat Il anti-epi	tes but leptogenic i	mpact?			NUTRE	
About h	alf of individu	als will drop out o	of dietary thera	oy befo	re 3-6	months	
	rm (<1 year)	s study shows that predicts & perhap					
1/3 rd sz im	provement ver	ad >50% sz reducti sus 2/3 rd of those w discontinued the diet prior		oonse to	he diet <1	year who di	
1/3 rd sz im	of those who h provement ver on of the group who of ar with the initial coho Entire 150-	ad >50% sz reducti sus 2/3 rd of those w discontinued the diet prior rt 67 who discontinued	TABLE 3. Outcomes of surgery or v	oonse to of those on t agal nerve s	he diet <1 stimulator (N = 41)	year who di implantation	d not undergo
1/3 rd sz im rABLE 1. Comparis to one ye	of those who h provement ver an of the group who of ar with the initial cohor Entire 150- Patient cohort	ad >50% sz reducti sus 2/3 rd of those w discontinued the diet prior rt 67 who discontinued The diet before 1 year	TABLE 3. Outcomes of surgery or w	of those on t agal nerve a %	he diet <1 stimulator i (N = 41) Seizure red	year who di implantation uction at folic	d not undergo
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Ketogenic diets for epilepsy: synopsis

- DINLC
- 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 1.
- 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

DINLC

- 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

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

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Summary

MNLC

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

Questions?

Feedback, Please! Certificate of Attendance

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