Diet therapies, Hormonal therapies, & IVIG

Eric H. Kossoff, MD
Professor, Neurology & Pediatrics
Medical Director, Ketogenic Diet Program
Johns Hopkins Hospital
Baltimore Maryland

2023 GW Epilepsy Board Review & Best Practices

26 August 2023

JOHNS HOPKINS MEDICINE

Disclosures

- Consultant: Simply Good Foods, Nutricia, Cerecin, Bloom Science, LivaNova, Biocodex

- Royalties: Springer, UpToDate, Oxford, Elsevier, JHU Press

JOHNS HOPKINS MEDICINE

Why do we need options besides drugs?

The New England Journal of Medicine

EARLY IDENTIFICATION OF REFRACTORY EPILEPSY

PATRICK KWAN, M.D., AND MARTIN J. BRODIE, M.D.

- 2000 : 47% with 1st drug, 14% with 2nd, 1% with 3rd

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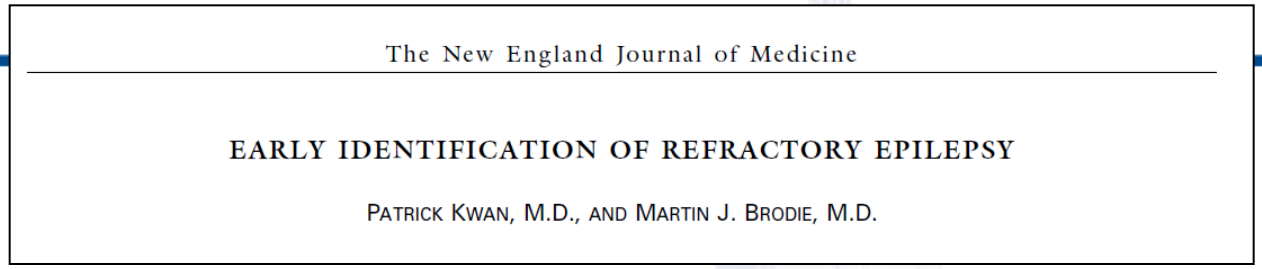
Why do we need options besides drugs?


The New England Journal of Medicine

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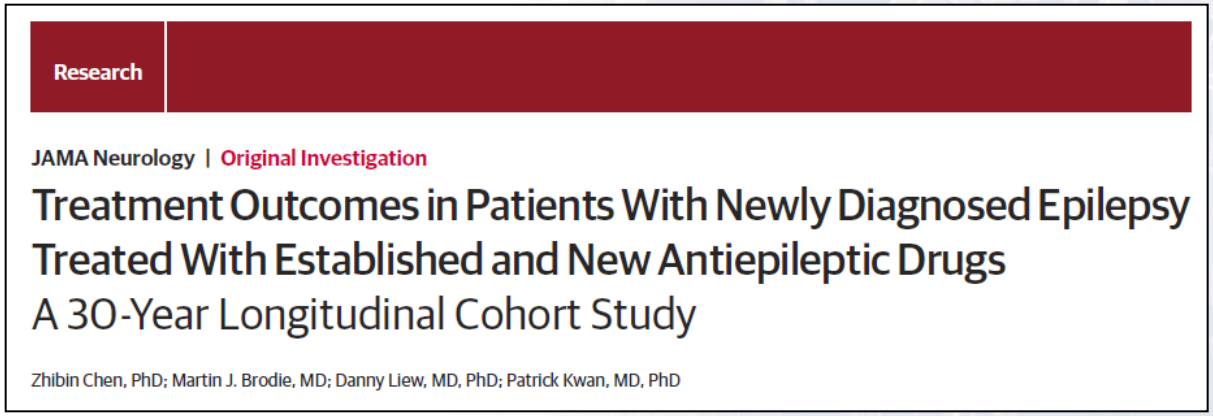
Research

JAMA Neurology | Original Investigation

Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs

A 30-Year Longitudinal Cohort Study

Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD

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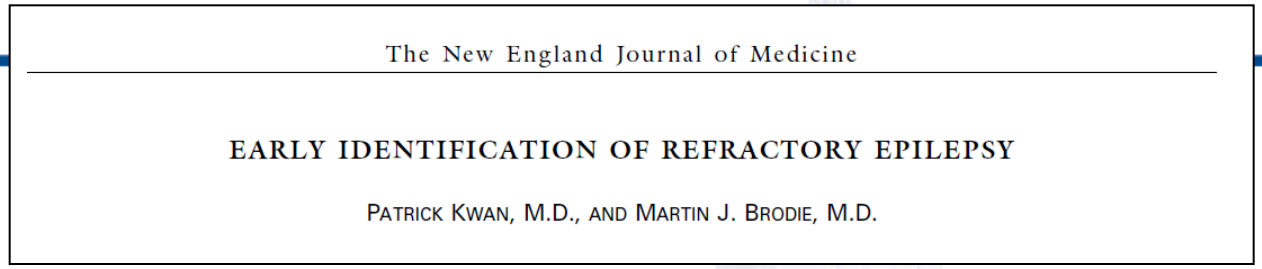
Why do we need options besides drugs?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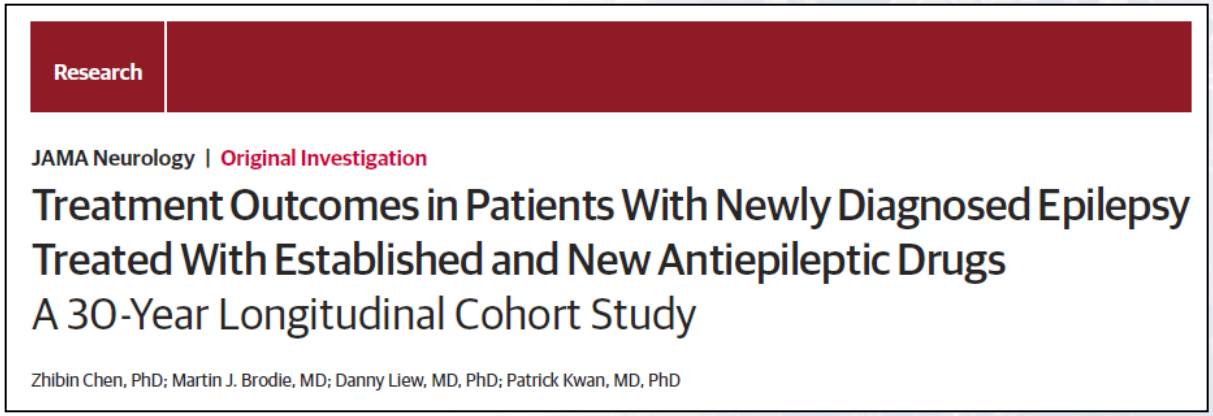
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Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs

A 30-Year Longitudinal Cohort Study

Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD

- 2018 : 50% with 1st drug, 12% with 2nd, 1% with 3rd

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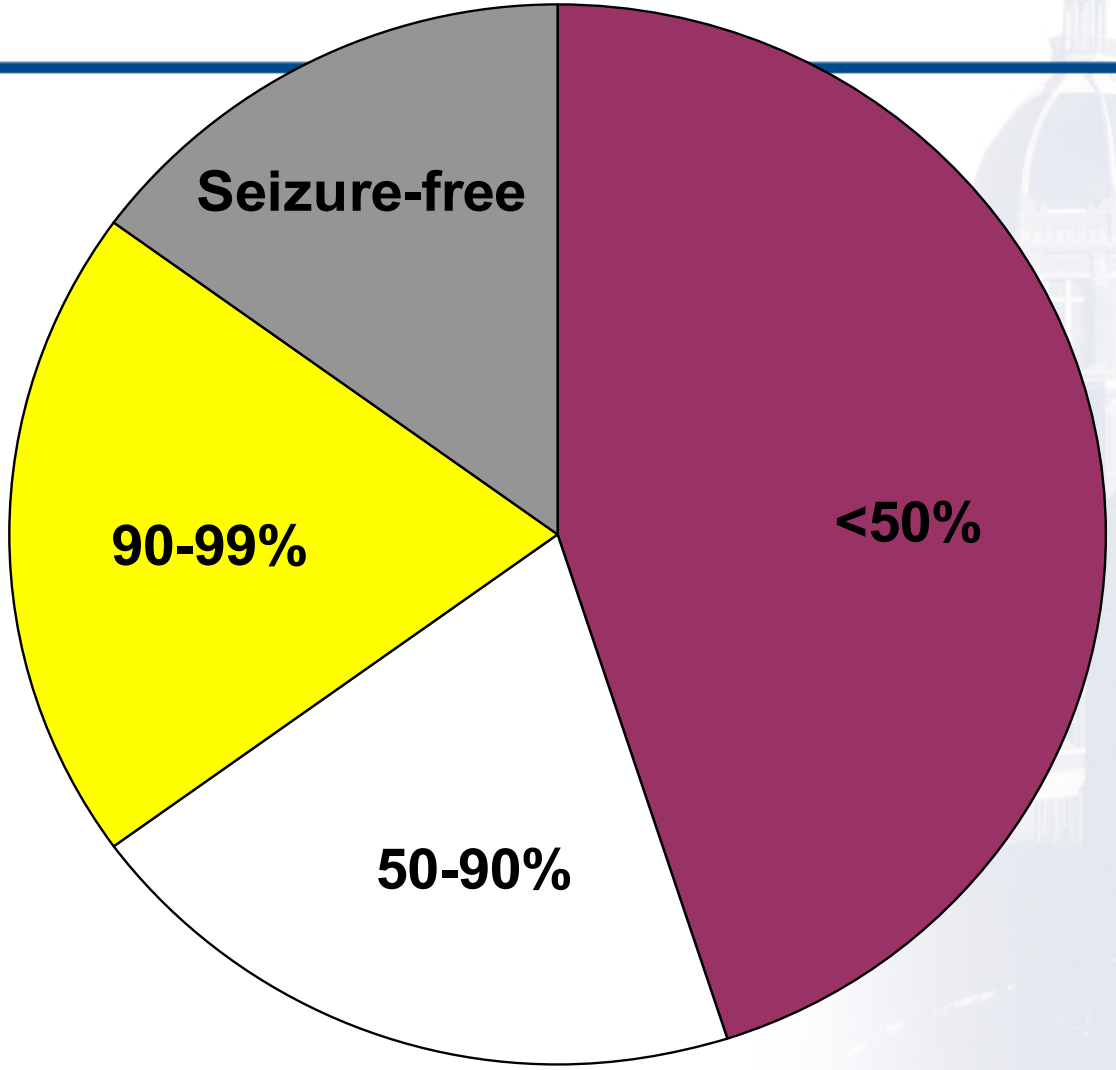
6-Month Seizure Reduction

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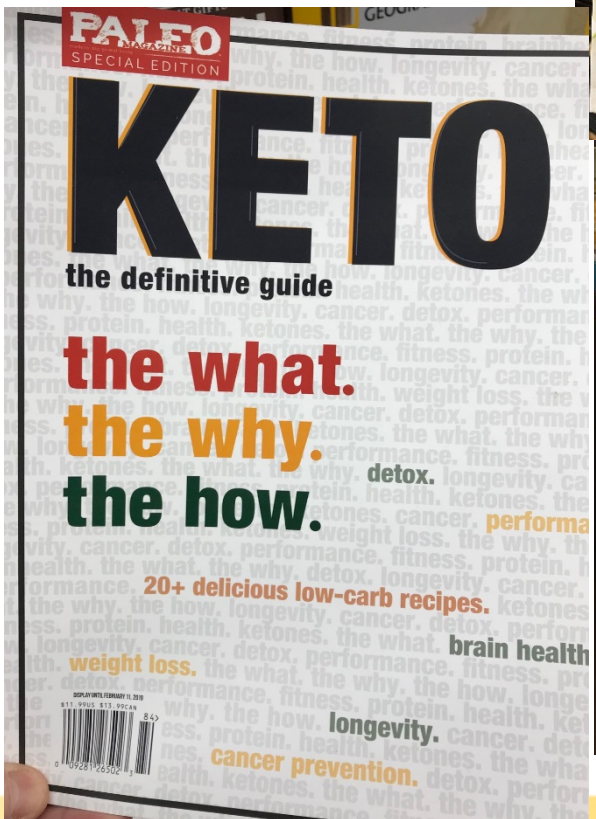
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TIME Healthland
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DIET

Sometimes a 90% Fat Diet Is Good For You

By MEREDITH MELNICK | @meredithcm | November 19, 2010 | 17

This weekend, the *New York Times Magazine* has an article written by Fred Vogelstein, a contributing editor to *Wired* and father to a young boy with epilepsy. Sam's condition is severe: at one point, the boy was having up to 130 seizures a day and was not responsive to medication. To treat him, the family has put Sam on a special diet: a typical breakfast consists of eggs mixed

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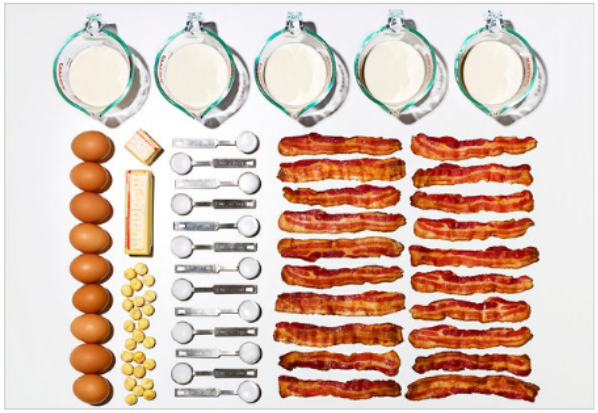
Epilepsy's Big Fat Miracle



Stephen Lewis for The New York Times; Food Stylist: Brett Kurzwell

What's Popular Now

The Yankees, a Summer Symphony in 9 Innings

Seeing Trends, Coalition Works to Help a River Adapt

JOHNS HOPKINS MEDICINE

A blinded, crossover study of the efficacy of the ketogenic diet

*John M. Freeman, *Eileen P.G. Vining, *Eric H. Kossoff, *Paula L. Pyzik, *Xiaobu Ye, and †Steven N. Goodman

Modified Atkins diet in adult with refractory epilepsy: A controlled randomized clinical trial

Mohammad Zare[1], Ali Asghar Okhovat[2], Ahmad Esmaillzadeh[3], Jafar Mehvari[1], Mohammad Reza Najafi[1], Mohammad Saadatnia[1]

The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial

Elizabeth G Neal, Hannah Chaffe, Ruby H Schwartz, Margaret S Lawson, Nicole Edwards, Geogianna Fitzsimmons, Andrea Whitney, J Helen Cross

Efficacy of low glycemic index diet therapy (LGIT) in children aged 2–8 years with drug-resistant epilepsy: A randomized controlled trial

Kannan Lakshminarayanan [a], Anuja Agarawal [b], Prateek Kumar Panda [c,d], Manjari Tripathi [e], Ravindra M. Pandey [f], Sheffali Gulati [c,*]

Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial

*[1]Suvasini Sharma, *[2]Naveen Sankhyan, *Sheffali Gulati, and †Anuja Agarwala

Acta Neurologica Scandinavica
Acta Neurol Scand DOI: 10.1111/ane.12137

ACTA NEUROLOGICA SCANDINAVICA

Modified Atkins diet vs classic ketogenic formula in intractable epilepsy

El-Rashidy OF, Nassar MF, Abdel-Hamid IA, Shatla RH, Abdel-Hamid MH, Gabr SS, Mohamed SG, El-Sayed WS, Shaaban SY.
Modified Atkins diet vs classic ketogenic formula in intractable epilepsy.
Acta Neurol Scand: DOI: 10.1111/ane.12137.

O. F. El-Rashidy[1], M. F. Nassar[2], I. A. Abdel-Hamid[1], R. H. Shatla[1], M. H. Abdel-Hamid[2], S. S. Gabr[1], S. G. Mohamed[1], W. S. El-Sayed[2], S. Y. Shaaban[2]

Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: A randomized clinical trial

Magnhild Kverneland[1,2,3] | Ellen Molteberg[1] | Per O. Iversen[2,3,4] | Marit B. Veierød[3,5] | Erik Taubøll[3,6] | Kaja K. Selmer[1,3,7] | Karl O. Nakken[1]

Improving compliance in adults with epilepsy on a modified Atkins diet: A randomized trial☆

Tanya J.W. McDonald[a], Bobbie J. Henry-Barron[b], Elizabeth A. Felton[c], Erie G. Gutierrez[a], Joanne Barnett[a], Rebecca Fisher[a], MonYi Lwin[a], Amanda Jan[a], Diane Vizthum[b], Eric H. Kossoff[a,d], Mackenzie C. Cervenka[a,*]

Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: A single-center parallel-cohort randomized controlled trial

Anastasia Dressler[1] | Franz Benninger[2] | Petra Trimmel-Schwahofer[1] | Gudrun Gröppel[1] | Barbara Porsche[1] | Klaus Abraham[1] | Angelika Mühlebner[1] | Sharon Samueli[1] | Christoph Male[1] | Martha Feucht[1]

Evaluation of the Modified Atkins Diet for the Treatment of Epileptic Spasms Refractory to Hormonal Therapy: A Randomized Controlled Trial

Suvasini Sharma, MD, DM[1], Shaiphali Goel, MSc[1], Dipti Kapoor, MD, DM[1], Divyani Garg, MD, DM[2], Isha Panda, MD[1], Aman Elwadhi, MD[1], [illegible], MD[3], Sharmila B. Mukherjee, MD[3], and Harish Pemde, MD[3]

A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy

Lambrechts DAJE, de Kinderen RJA, Vles JSH, de Louw AJA, Aldenkamp AP, Majoie HJM.
A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy.
Acta Neurol Scand: DOI: 10.1111/ane.12592.

D. A. J. E. Lambrechts[1], R. J. A. de Kinderen[2,3,4], J. S. H. Vles[1,2,5], A. J. A. de Louw[1,6], A. P. Aldenkamp[2,5,6], H. J. M. Majoie[1,2,5,6]

Efficacy of the ketogenic diet on ACTH- or corticosteroid-resistant infantile spasm: a multicentre prospective control study

Jie Zhang [1], Guohong Chen [2], Juan Wang [3], Yuwu Jiang [1], Zhixian Yang [1], Kaili Xu [2], Jing Peng [4], Shuizhen Zhou [5], Li Jiang [3], Baomin Li [6], Dongqing Zhang [6], Zhisheng Liu [7], Lijuan Huang [7], Chunhong Chen [8], Fang Fang [8], Yanhui Chen [9], Yi Wu [9], Jianmin Zhong [10], Jian Zha [10], Fei Yin [4], Lifei Yu [5], Ye Wu [1]

Affiliations + expand

PMID: 33772508 DOI: 10.1684/epd.2021.1256

Contents lists available at ScienceDirect
Seizure: European Journal of Epilepsy
journal homepage: www.elsevier.com/locate/seizure

Modified Atkins diet versus levetiracetam for non-surgical drug-resistant epilepsy in children: A randomized open-label study☆

Archna [a], Divyani Garg [b], Shaiphali Goel [a], Sharmila B Mukherjee [a], Harish K Pemde [a], Puneet Jain [c], Suvasini Sharma [a,*]

JAMA Pediatrics | Original Investigation

Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy
A Randomized Clinical Trial

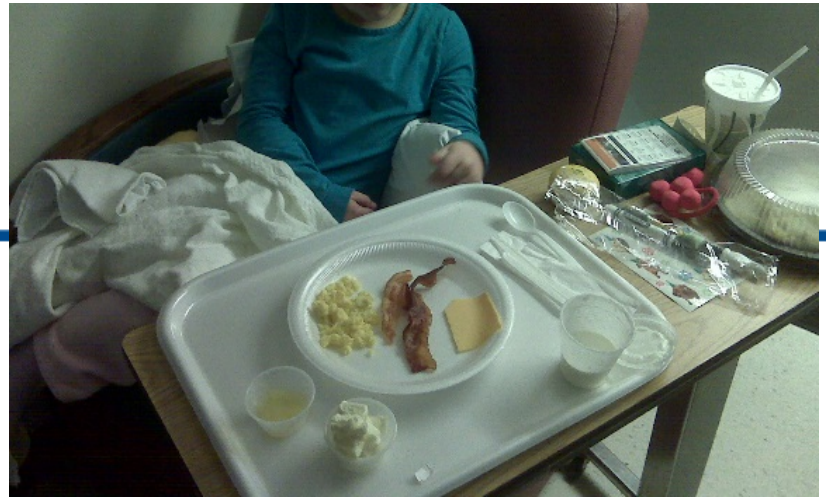
Vishal Sondhi, DM; Anuja Agarwala, MSc; Ravindra M. Pandey, PhD; Biswaroop Chakrabarty, DM; Prashant Jauhari, DM; Rakesh Lodha, MD; Gurudyal S. Toteja, PhD; Shobha Sharma, PhD; Vinod K. Paul, MD; Eric Kossoff, MD; Sheffali Gulati, MD

RESEARCH ARTICLE

Safety, Efficacy, and Tolerability of Modified Atkins Diet in Persons With Drug-Resistant Epilepsy
A Randomized Controlled Trial

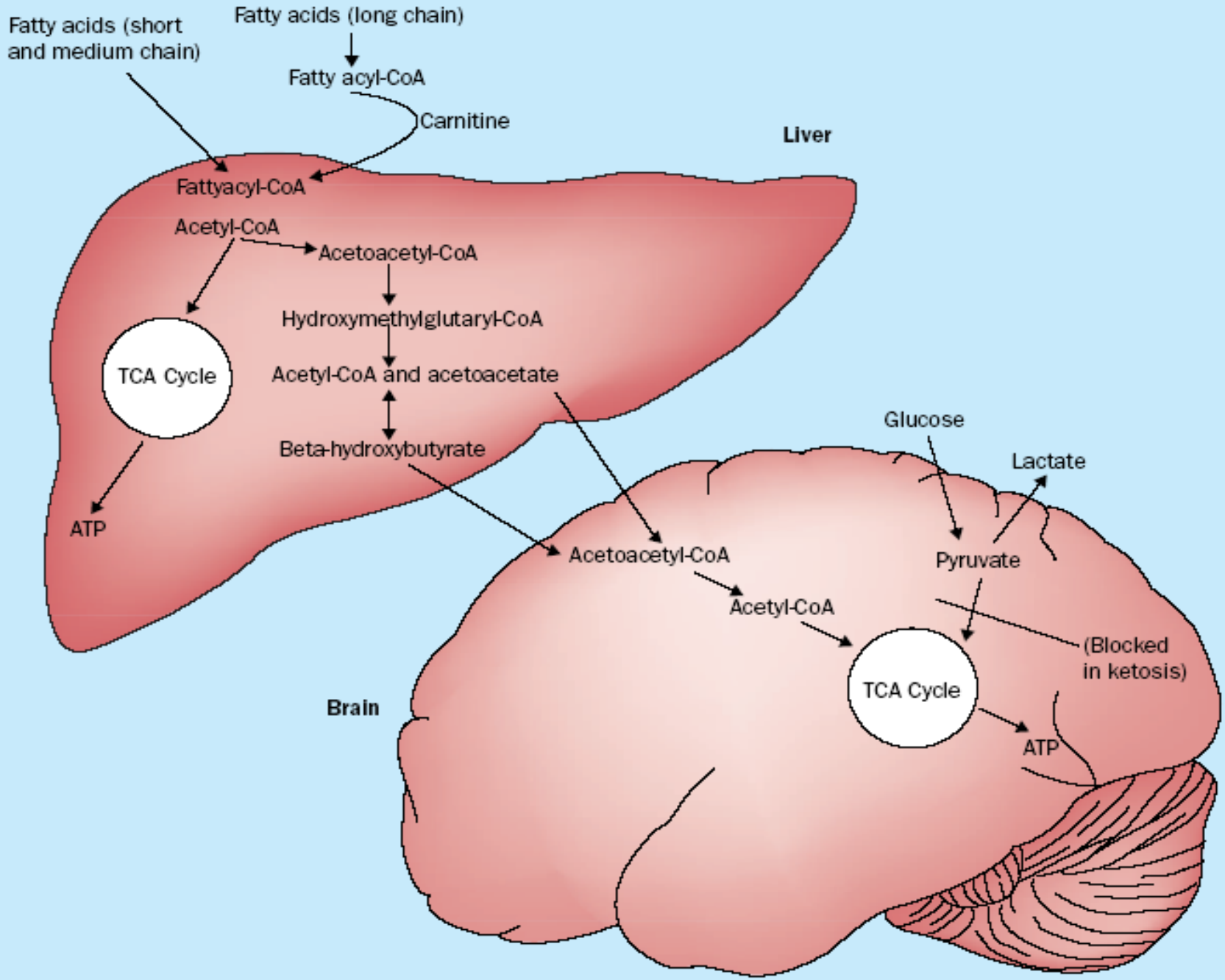
Mala Manral, PhD, Rekha Dwivedi, PhD, Sheffali Gulati, MD, DM, Kirandeep Kaur, PhD, Ashima Nehra, PhD, Ravindra Mohan Pandey, PhD, Ashish Datt Upadhyay, PhD, Savita Sapra, PhD, and Manjari Tripathi, MD, DM

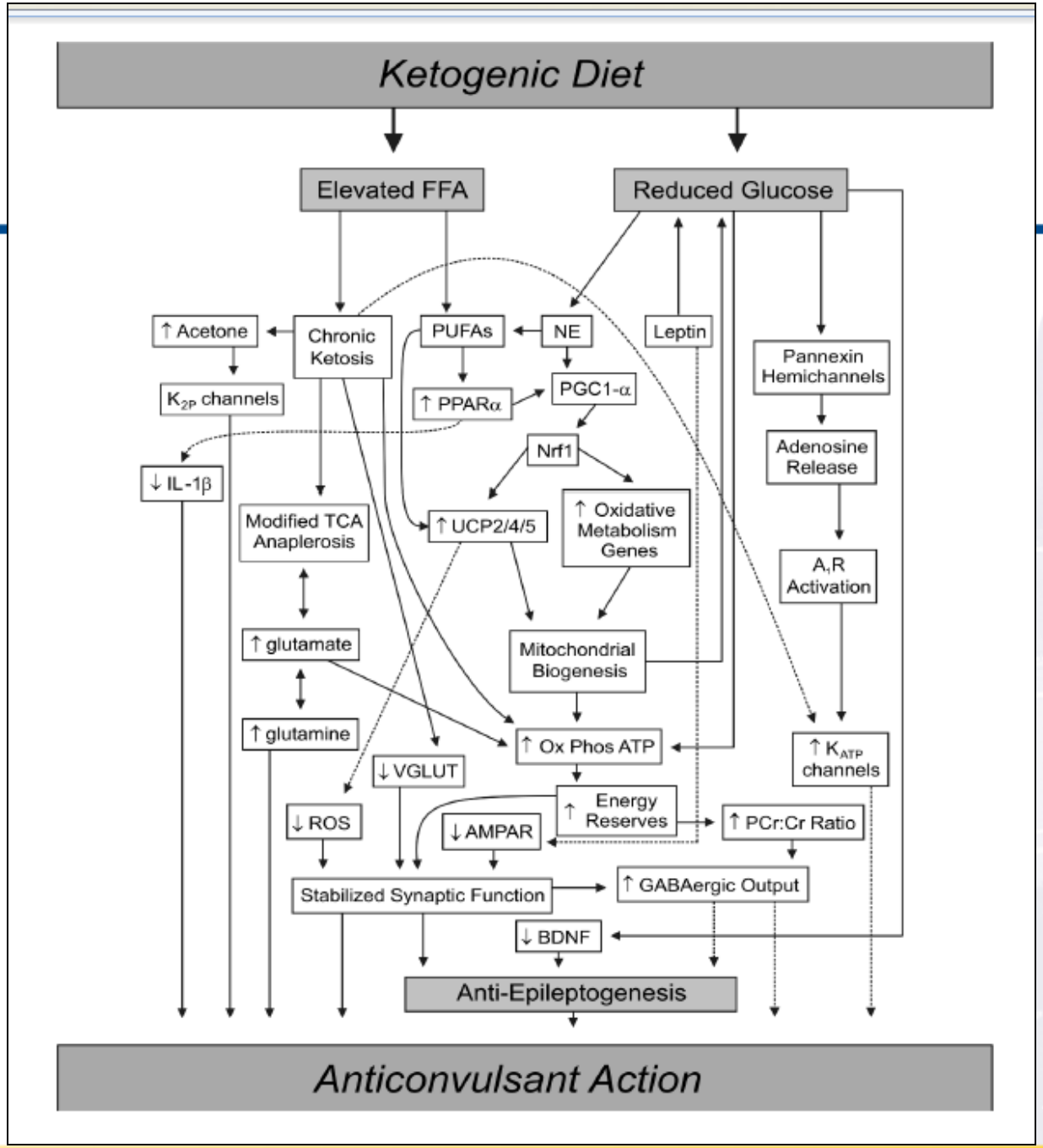
Correspondence
Dr. Tripathi



JOHNS HOPKINS
MEDICINE


NUTRICIA
KetoCal 3:1
NUTRICIA
KetoCal 4:1
Liquigen
Microlipid
MN MEDICA NUTRITION
KetoGEN 4:1
Medical Food
KetoGEN is designed to promote therapeutic ketosis in individuals managing cancer with a ketogenic diet or other medical conditions where a ketogenic diet is indicated.
Contains a proprietary fatty acid profile approved by leading researchers
NON GMO
Net Weight 520 g (18.5 oz)
SOL CARB
When extra calories are needed.
Pour un apport supplémentaire en calories.
Net 227 g
奇酮
KETOGENIC DIET
Net:250ml
CAMBROOKE THERAPEUTICS
KetoVie
vanilla
LIQUID
8.5 FL OZ (250 ML)
CAMBROOKE THERAPEUTICS
KetoVie
PEPTIDE
LIQUID
Peptide-Based 100% Whey Protein
Contains MCT, Carnitine, DHA
8.5 FL OZ (250 ML)
kanso
MCT OIL
100% MCT
0,5 L
A nutritionally complete, ketogenic supplement in a 4:1 ratio
KetoKid
Ketogenic Diet Specially Formulated For Epilepsy
Natural Vanilla Flavor
Sugar Free
Enriched with DHA & EPA
Gluten Free
Lactose Free
Net Wt. 200g
Nutentar
CetogenikK
4:1
berri quik
RCF
Extra Carbohydrate Free
SOY FORMULA BASE WITH IRON
Concentrated Liquid
13 FL OZ (384 mL)
Nampang
Namyang
KETONIA
180 mL
MEIJI
特殊ミルク
No.817-B
ケトンフォーミュラ
general population of
KetoVOLVE
4:1 Ratio Powder
Medical Food
SAMPLE
日清 MCT パウダー
たんぱく質ゼロ
加えるだけで エネルギーアップ!
(764kcal/100g) 250g
MEDICINE


Fatty acids (short and medium chain)
Fatty acids (long chain)
Fatty acyl-CoA
Carnitine
Liver
Fattyacyl-CoA
Acetyl-CoA
Acetoacetyl-CoA
Hydroxymethylglutaryl-CoA
TCA Cycle
Acetyl-CoA and acetoacetate
Beta-hydroxybutyrate
ATP
Glucose
Lactate
Acetoacetyl-CoA
Pyruvate
Acetyl-CoA
(Blocked in ketosis)
TCA Cycle
Brain
ATP



Masino & Rho 2013

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

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SPECIAL REPORT

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

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

Epilepsia Open, **(*):1–18, 2018
doi: 10.1002/epi4.12225

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When? Guidelines:

- Use KDT after 2.6 (SD 0.9) drugs have been tried

- "Consider earlier use for certain situations or indications?"
  - 88% of the consensus group voted YES

Table 1. Epilepsy syndromes and conditions (listed alphabetically) for which KDT has been consistently reported as more beneficial (>70%) than the average 50% KDT response (defined as >50% seizure reduction).

Angelman syndrome[56,57]
Complex I mitochondrial disorders[51,55]
Dravet syndrome[35,36]
Epilepsy with myoclonic–atonic seizures (Doose syndrome)[34,37,38]
Glucose transporter protein 1 (Glut-1) deficiency syndrome (Glut1DS)[27,29–32]
Febrile infection–related epilepsy syndrome (FIRES)[44–47]
Formula-fed (solely) children or infants[48,49]
Infantile spasms[10,39,40]
Ohtahara syndrome[50–52]
Pyruvate dehydrogenase deficiency (PDHD)[28]
Super-refractory status epilepticus[44,46,53,54]
Tuberous sclerosis complex[41–43]

Accepted: 17 August 2017
DOI: 10.1111/ane.12830

REVIEW ARTICLE

WILEY Acta Neurologica Scandinavica

Efficacy of ketogenic diet for infantile spasms: A systematic review

G. Prezioso[1] | G. Carlone[2] | G. Zaccara[3] | A. Verrotti[2]

- 65% with >50% spasm reduction
  - 35% spasm-free
- IS due to unknown etiology higher chance of spasm-freedom (RR 1.72)

JOHNS HOPKINS MEDICINE

Dietary Management of Children With Super-Refractory Status Epilepticus: A Systematic Review and Experience in a Single UK Tertiary Centre

Natasha E. Schoeler[1], Zoe Simpson[2], Runming Zhou[1], Suresh Pujar[3], Christin Eltze[3] and J. H. Cross[1,3,4]*

- 85/141 (60%) responded
- No relationship to the age, ketogenic ratio
- More likely to respond if female, shorter period of status epilepticus

Frontiers in Neurology, 2021

JOHNS HOPKINS MEDICINE

Important Board Questions

- The KD is very effective for adults, but compliance and long-term lipid abnormalities remain of concern
- It is the treatment of choice for Glut1 deficiency syndrome
- It is not a substitute for drugs (80% are on both)

Table 2 – “OK”

- **Helpful (40-70% response, but not “indications” currently) – Table 2:**
  - 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)

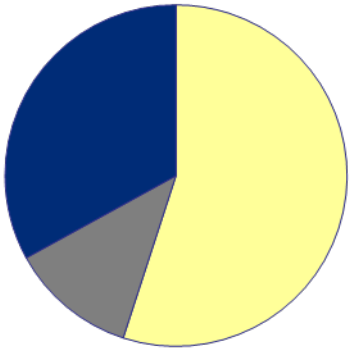
Table 3. Contraindications to the use of KDT

Absolute
- Carnitine deficiency (primary)
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- Carnitine translocase deficiency
- β-oxidation defects
- Medium-chain acyl dehydrogenase deficiency (MCAD)
- Long-chain acyl dehydrogenase deficiency (LCAD)
- Short-chain acyl dehydrogenase deficiency (SCAD)
- Long-chain 3-hydroxyacyl-CoA deficiency
- Medium-chain 3-hydroxyacyl-CoA deficiency.
- Pyruvate carboxylase deficiency
- Porphyria

Relative
- Inability to maintain adequate nutrition
- Surgical focus identified by neuroimaging and video-EEG monitoring
- Parent or caregiver noncompliance
- Propofol concurrent use (risk of propofol infusion syndrome may be higher)

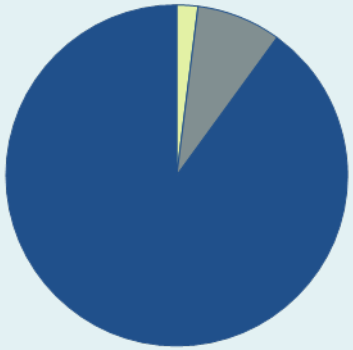
Four Ketogenic Diets

Standard "Normal" Diet



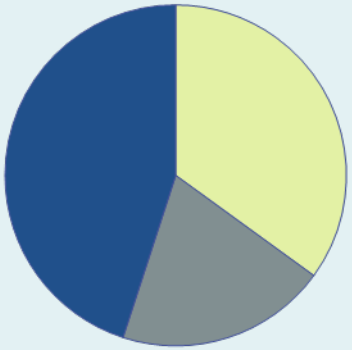
- Carbohydrates
- Protein
- Fat

Ketogenic Diet



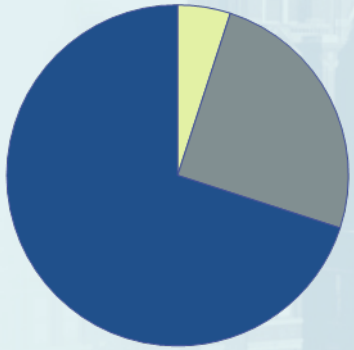
- Carbohydrates
- Protein
- Fat

Medium Chain Triglyceride Diet



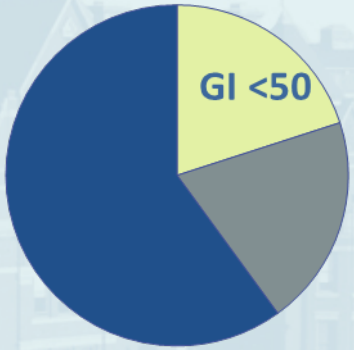
- Carbohydrates
- Protein
- Fat

Modified Atkins Diet



- Carbohydrates
- Protein
- Fat

Low Glycemic Index Treatment



- Carbohydrates
- Protein
- Fat

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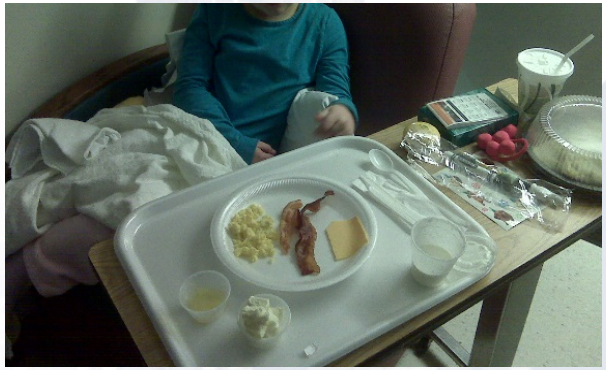
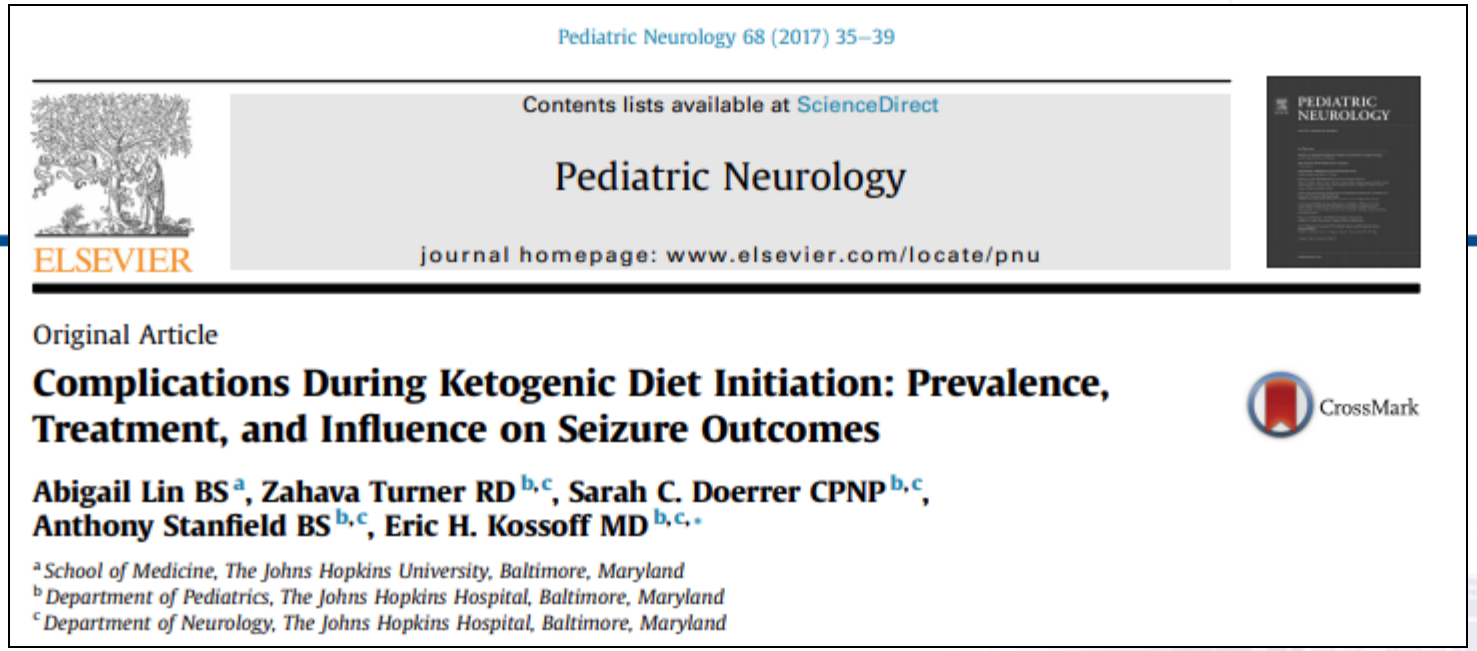
Admission “week”



- Monday
  - Fasting till 5pm (in half)
  - ½ calories, set ratio
  - Follow blood sugars
  - Meds left unchanged
  - Classes begin
- Tuesday
  - Parents start checking ketones
  - Classes continue
  - Full calories at 5pm (Solid foods)
- Wednesday
  - Final classes and wrap-up
  - Appointments and prescriptions
  - Discharge at 12pm



Pediatric Neurology 68 (2017) 35–39

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Original Article

Complications During Ketogenic Diet Initiation: Prevalence, Treatment, and Influence on Seizure Outcomes

Abigail Lin BS [a], Zahava Turner RD [b,c], Sarah C. Doerrer CPNP [b,c], Anthony Stanfield BS [b,c], Eric H. Kossoff MD [b,c,*]

[a] *School of Medicine, The Johns Hopkins University, Baltimore, Maryland*
[b] *Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, Maryland*
[c] *Department of Neurology, The Johns Hopkins Hospital, Baltimore, Maryland*

- Younger children had more issues
- Higher chance of a single low glucose and lethargy if fasted
- NO correlation between more issues and eventual seizure control

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TABLE 2.

Interventions Administered During Inpatient Ketogenic Diet (KD) Initiation

Orange Juice (30 mL)	38 (24%)
Enema or Miralax	9 (6%)
Admission extended at least 24 hours	8 (5%)
Medication for nausea or gastroesophageal reflux	5 (3%)
Advance to solid foods more quickly	5 (3%)
Rescue seizure medication (rectal diazepam, intravenous lorazepam, or oral clonazepam)	4 (3%)
Advance to full calories more quickly than protocol	3 (2%)
Intravenous fluids provided	3 (2%)
Readmitted to hospital within 48 hours postdischarge	3 (2%)
Cancel KD (family preference)	1 (1%)

Values are given as n (percentage).

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

[1]Eric H. Kossoff, [2]Beth A. Zupec-Kania, [3]Stéphane Auvin, [4]Karen R. Ballaban-Gil, [5]A.G. Christina Bergqvist, [6]Robyn Blackford, [7]Jeffrey R. Buchhalter, [8]Roberto H. Caraballo, [9]J. Helen Cross, [10]Maria G. Dahlin, [11]Elizabeth J. Donner, [12]Orkide Guzel, [13]Rana S. Jehle, [14]Joerg Klepper, [15]Hoon-Chul Kang, [16]Danielle A. Lambrechts, [17]Y.M. Christiana Liu, [18]Janak K. Nathan, [19]Douglas R. Nordli Jr, [20]Heidi H. Pfeifer, [21]Jong M. Rho, [22]Ingrid E. Scheffer, [23]Suvasini Sharma, [24]Carl E. Stafstrom, [20]Elizabeth A. Thiele, [25]Zahava Turner, [26]Maria M. Vaccarezza, [27]Elles J.T.M. van der Louw, [28]Pierangelo Veggiotti, [29]James W. Wheless, [30]Elaine 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

- No reason to fluid or calorie restrict
- All 4 diets equally valid: you choose!
  - *KD for < 2 years, MAD/LGIT for > 12 years*
- 80% admit for the diet (but 92% say it's optional)
- 28% fast at the start (but 68% say it's optional)
  - *Not in infants < 2 years*

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Side Effects

- Constipation
- Gastroesophageal reflux
- Acidosis

COMMON

- Renal stones
- Growth slowing
- Hyperlipidemia
- Vitamin D deficiency

SPORADIC

- Carnitine deficiency
- Pancreatitis
- Bone fractures
- Cardiomyopathy (due to selenium deficiency)

RARE

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Table 5. Supplementation recommended for children receiving KDT

Universal recommendations
- Multivitamin with minerals (including trace minerals, especially selenium)
- Calcium and vitamin D (meeting daily RDA requirements)

Optional extra supplementation
- Vitamin D (above RDA)
- Oral citrates (eg, CitraK or PolycitraK)
- Laxatives: Miralax, mineral oil, glycerin suppository
- Additional selenium, magnesium, zinc, phosphorus, iron, copper
- Carnitine
- MCT oil or coconut oil (source of MCT)
- Salt (sodium to add to RCF formula if used for greater than age 1 year)

All supplements listed should be provided as carbohydrate-free preparations whenever possible.

Maintenance

- Children at 1, 3, 6, 12, 18, 24 months
- Labs, dietitian, neurologist evaluation to assess efficacy and safety
- After 1-2 years if successful (3 months if not), the ketogenic diet is slowly weaned back to previous foods
  - Return to their referring neurologist

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Table 6. Recommendations for aspects of a follow-up KDT clinic visit

Nutritional assessment (registered dietitian)
Height, weight, ideal weight for stature, growth velocity, BMI when appropriate
Head circumference in infants
Review appropriateness of KDT prescription (calories, protein, and fluid)
Review vitamin and mineral supplementation
Assess compliance to KDT
Adjust KDT if necessary to improve compliance and seizure control
Medical evaluation (neurologist)
Efficacy of the diet (is the KDT meeting parental expectations?)
Side effects of KDT
Antiseizure drug reduction (if applicable)
Should KDT be continued?
Laboratory assessment
Complete blood count with platelets
Electrolytes to include serum bicarbonate, total protein, calcium
Serum liver and kidney profile (including albumin, blood urea nitrogen, creatinine)
Vitamin D level
Fasting lipid profile
Free and total carnitine
Urinalysis
Selenium level
Anticonvulsant drug levels (if applicable)
EEG (at KDT discontinuation consideration)
Optional
Serum beta-hydroxybutyrate (BOH) level
Urine calcium and creatinine
Zinc, copper levels
Renal ultrasound
ECG
Bone mineral density (DEXA scan) after 2 years on the KD

Visits should be at least every 3 months for the first year of KDT, with a visit 1 month after starting KDT also advised.

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Long-term Use (>6 years)

- 21% with bone fractures
- 25% with kidney stones
- 82% were <10th percentile for both height and weight
- *Mean cholesterol normal*

Groesbeck DK,et.al. *DMCN* 2006

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Reasonable Reasons to Stop

- “Time to move on to other options”
- “Side effects are outweighing benefits”
- “The diet may have done it’s job”

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When: Consensus Statements

- Minimum diet duration: 3.5 months (SD 2.2)
  - 2018: 3.2 months (1.3)
- Stop immediately if seizures worsen for 1-2 weeks
- Discuss at each visit but definitely after 2 years
  - At each visit, start to weigh the risks vs. the benefits of the diet
- 64% obtain an EEG before discontinuation

Unique Conditions?

- Infantile spasms – 6 months
- Status epilepticus – 6 months
- Glut1 DS, PDHD – indefinitely
- Adults - ? indefinitely

Epilepsy Research (2011) 95, 232–236

journal homepage: www.elsevier.com/locate/epilepsyres

Is there an ideal way to discontinue the ketogenic diet?

Lila T. Worden[a], Zahava Turner[b], Paula L. Pyzik[c], James E. Rubenstein[c], Eric H. Kossoff[c,*]

183 children who stopped the KD
Mean age 5.3 years

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Relapse?

- 26 (14%) of 183 had increased seizures
  - 15 were still able to come off the diet with anticonvulsant changes made
  - 9 had diet changes made (8 regained control)
  - 2 lost to follow-up

Worden L, et.al. *Epilepsy Res* 2011

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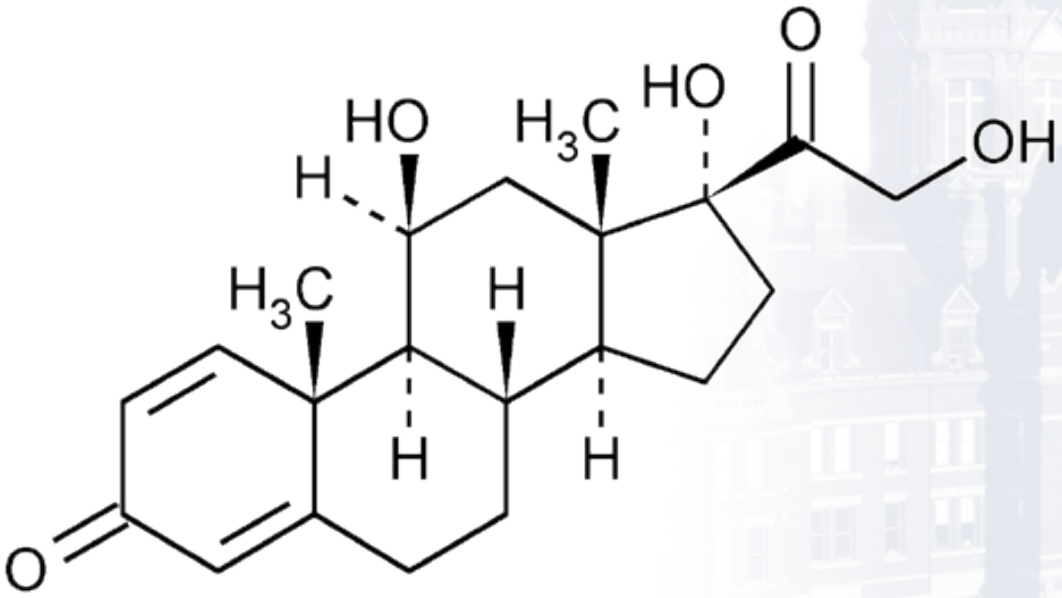
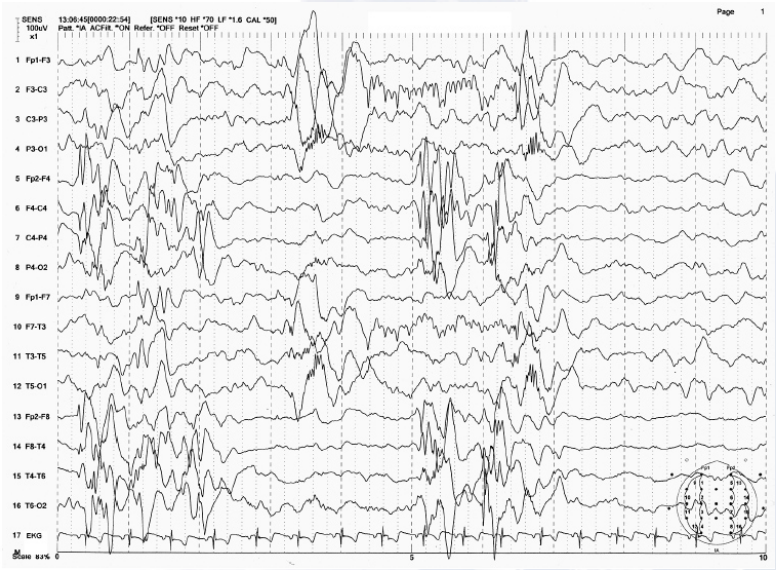


Infantile spasms

- Highly effective with copious publications
- Often excluded from reviews on the topic due to this high level of evidence
- Stops IESS in 1-2 weeks in 60-70% of patients



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Options

- ACTH
  - Injections (80U vial) IM
  - 150 units/m2 twice daily for 2 weeks

- Prednisolone
  - Liquid (20mg/5ml) – 20mg TID-QID
  - 4-6 mg/kg/day
  - Tastes terrible
  - Cheap

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Problems

- Side effects
  - Gastrointestinal side effects
  - Irritability, edema, weight gain
  - Hypertension in 34/77 (44%) ACTH and 4/11 (36%) with prednisolone (McGarry JCN 2020)
- 33% recurrence risk

The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial

*Andrew L Lux, Stuart W Edwards, Eleanor Hancock, Anthony L Johnson, Colin R Kennedy, Richard W Newton, Finbar J K O'Callaghan, Christopher M Verity, John P Osborne, the trial steering committee on behalf of participating investigators**

Lancet Neurol 2005; 4: 712–17

Published online October 6, 2005
DOI:10.1016/S1474-4422(05)70199-X

*See Lancet Online for webappendix

Royal United Hospital Bath NHS Trust and the School for Health, University of Bath, Bath, UK (A L Lux BMBS, S W Edwards PhD, E Hancock MD, F J K O'Callaghan PhD, J P Osborne MD); **Department of Paediatric Neurology, Frenchay Hospital and the Bristol Royal Hospital for Children, Bristol, UK** (A L Lux BMBS, F J K O'Callaghan PhD); **Medical Research Council Biostatistics Unit, University of Cambridge Institute of Public Health, Cambridge, UK** (A L Johnson PhD); **Paediatric Neurology, Child Health, University of Southampton, Southampton, UK** (C R Kennedy MD); **Department of Paediatric Neurology, Royal Manchester Children's Hospital, Manchester, UK** (R W Newton MD); **Department of Paediatrics, Addenbrooke's Hospital, Cambridge, UK** (C M Verity MA)

Correspondence to:
Professor John P Osborne, Children's Centre, Royal United Hospital, Combe Park, Bath BA1 3NG, UK
mpsjpo@bath.ac.uk

Summary

Background Infantile spasms is a severe infantile seizure disorder that is difficult to treat and has a high morbidity. Absence of spasms on days 13 and 14 after randomisation is more common in infants allocated hormone treatments than in those allocated vigabatrin. We sought to assess whether early control of spasms is associated with improved developmental or epilepsy outcomes.

Methods Infants enrolled in the United Kingdom Infantile Spasms Study (UKISS) were randomly assigned hormone treatment (n=55) or vigabatrin (n=52) and were followed up until clinical assessment at 12–14 months of age. We assessed neurodevelopment with the Vineland adaptive behaviour scales (VABS) at 14 months of age on an intention to treat basis.

Findings Of 107 infants enrolled, five died and 101 survivors reached both follow-up assessments. Absence of spasms at final clinical assessment (hormone 41/55 [75%] *vs* vigabatrin 39/51 [76%]) was similar in each treatment group (difference 1·9%, 95% CI −18·3% to 14·4%; χ^2=0·05; p=0·82). Mean VABS score did not differ significantly (hormone 78·6 [SD 16·8] *vs* vigabatrin 77·5 [SD 12·7]; difference 1·0, 95% CI −4·9 to 7·0; t_{99}=0·35, p=0·73). In infants with no identified underlying aetiology, the mean VABS score was higher in those allocated hormone treatment than in those allocated vigabatrin (88·2 [17·3] *vs* 78·9 [14·3]; difference 9·3, 95% CI 1·2 to 17·3; t_{97}=2·28, p=0·025).

Interpretation Hormone treatment controls spasms better than does vigabatrin initially, but not at 12–14 months of age. Better initial control of spasms by hormone treatment in those with no identified underlying aetiology may lead to improved developmental outcome.

Introduction

Infantile spasms, a rare form of epilepsy, presents in infancy with ictal episodes consisting of spasms that usually occur in clusters.[1,2] The associated chaotic and high-voltage interictal EEG pattern is called hypsarrhythmia, although this term is not always used because it is poorly defined and the EEG can vary with the underlying aetiology of the spasms and can change as the disorder progresses.[2] More than half of infants who develop infantile spasms have an underlying neurological disorder, such as periventricular leucomalacia, hypoxic ischaemic encephalopathy, Down's syndrome, or tuberous sclerosis.[3] Onset of spasms is often associated with developmental arrest or regression and, even among those without an identified underlying [illegible] was more likely in infants allocated hormone treatments than in those allocated vigabatrin.[4] Observational studies suggest that a reduced interval between onset and cessation of spasms results in improved development[5] in infants with no underlying aetiology and in those with Down's syndrome.[5,6] Additionally, the degree of brain involvement in tuberous sclerosis is not sufficient to account for the reduction in intelligence quotient, and the presence of infantile spasms is independently associated with a reduced intelligence quotient.[7] Better control of spasms might improve development, but no previous assessment of treatment for spasms has systematically measured this outcome.[8]

We hypothesised that if a treatment was initially successful in controlling spasms it might result in [illegible]

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY SYSTEMATIC REVIEW

Prednisolone/prednisone as adrenocorticotropic hormone alternative for infantile spasms: a meta-analysis of randomized controlled trials

SHAOJUN LI[1,2,3,4,5] | XUEFEI ZHONG[2,3,4,5,6] | SIQI HONG[2,3,4,5,7] | TINGSONG LI[2,3,4,5,7] | LI JIANG[2,3,4,5,7]

1 Department of Emergency, Children's Hospital of Chongqing Medical University, Chongqing; **2** Ministry of Education Key Laboratory of Child Development and Disorders, Children's Hospital of Chongqing Medical University, Chongqing; **3** National Clinical Research Center for Child Health and Disorders (Chongqing), Children's Hospital of Chongqing Medical University, Chongqing; **4** China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing; **5** Chongqing Key Laboratory of Paediatrics, Children's Hospital of Chongqing Medical University, Chongqing; **6** Department of Electroneurophysiology, Children's Hospital of Chongqing Medical University, Chongqing; **7** Department of Neurology, Children's Hospital of Chongqing Medical University, Chongqing, China.

Correspondence to Tingsong Li, Department of Neurology, Building 6, Zhongshan Er Road 136, Yuzhong District, Chongqing 400014, China. E-mail: litscq@126.com

Table 1: Descriptive characteristics of the included studies

Study	Country	Study set	Time frame	Cases (*n*)	Age (mo)	Sex (M/F)	Patients	Interventions	Study outcomes	Follow up	Attrition (%)
Hrachovy et al.[13]	USA	Double-blind, RCT	NA	24	3.5–24	NA	IS with HS	ACTH (20–30U/d) vs PRD (2mg/kg/d) for 2wks, then tapered over 1wk for responders	Cessation of spasms and disappearance of HS	12–33mo	0
Baram et al.[6]	USA	RCT	NA	29	2–21	12/17	IS with HS	ACTH (150U/m^2/d) vs PRD (2mg/kg/d) for 2wks, then tapered over 15d	Cessation of spasms and elimination of HS by the end of the 2wk treatment	2–48mo	0
Lux et al.[14]	UK	Multi-centre, RCT	Jun 1999–Dec 2002	55	4–9	32/23	IS with HS or similar	PRDL (40–60mg/d) vs tetracosactide (40–60IU/ alternated) for 2wks, then tapered over 15d	Cessation of spasms for at least 48h including day 13; resolution of HS on day 12–19 after treatment	29d	0
Wanigasinghe et al.[17]	Sri Lanka	Single-blind, RCT	2010–2014	97	2–30	56/41	IS with HS	Synthetic ACTH (40–60IU/ alternated) vs PRDL (40–60mg/d) for 2wks, then tapered over 3wks	Remission of IS by end of day 14 and electroclinical remission by end of day 14; other secondary outcomes	42d	6
O'Callaghan et al.[15]	Five countries	Multi-centre, RCT	Mar 2007–May 2014	377	2–14	210/167	IS with HS or similar	The protocol for hormone treatment is the same as that in Lux et al.[17]	Freedom from spasms on and between day 14 and day 42 from trial entry; cessation of spasms and resolution of HS EEG; other secondary outcomes	6wks	0
Wanigasinghe et al.[16]	Sri Lanka	Randomized, single-blind, parallel trial	2010–2014	97	2–24	56/41	IS with HS	The same as that in Wanigasinghe et al.[17] The same hormone treatment was repeated and other anti-convulsants were introduced for relapsed patients during follow-up	The proportion of freedom from spasms at 3, 6, and 12mo	12mo	22
Gowda et al.[12]	India	Single centre, RCT	Oct 2013–Oct 2015	34	2–60	21/13	IS (no detailed EEG)	ACTH (100IU/body surface area/d vs PRDL 4mg/kg/d for 2wks, then tapered over 3–4wks)	Cessation of spasms at day 14, day 28	6mo	3

RCT, randomized controlled trial; NA, not available; IS, infantile spasms; HS, hypsarrhythmia; ACTH, adrenocorticotropic hormone; U, unit; PRD, prednisone; PRDL, prednisolone; EEG, electroencephalogram.

- Identical EEG and clinical responses
- Similar adverse effects too…
- High dose > low dose prednisolone

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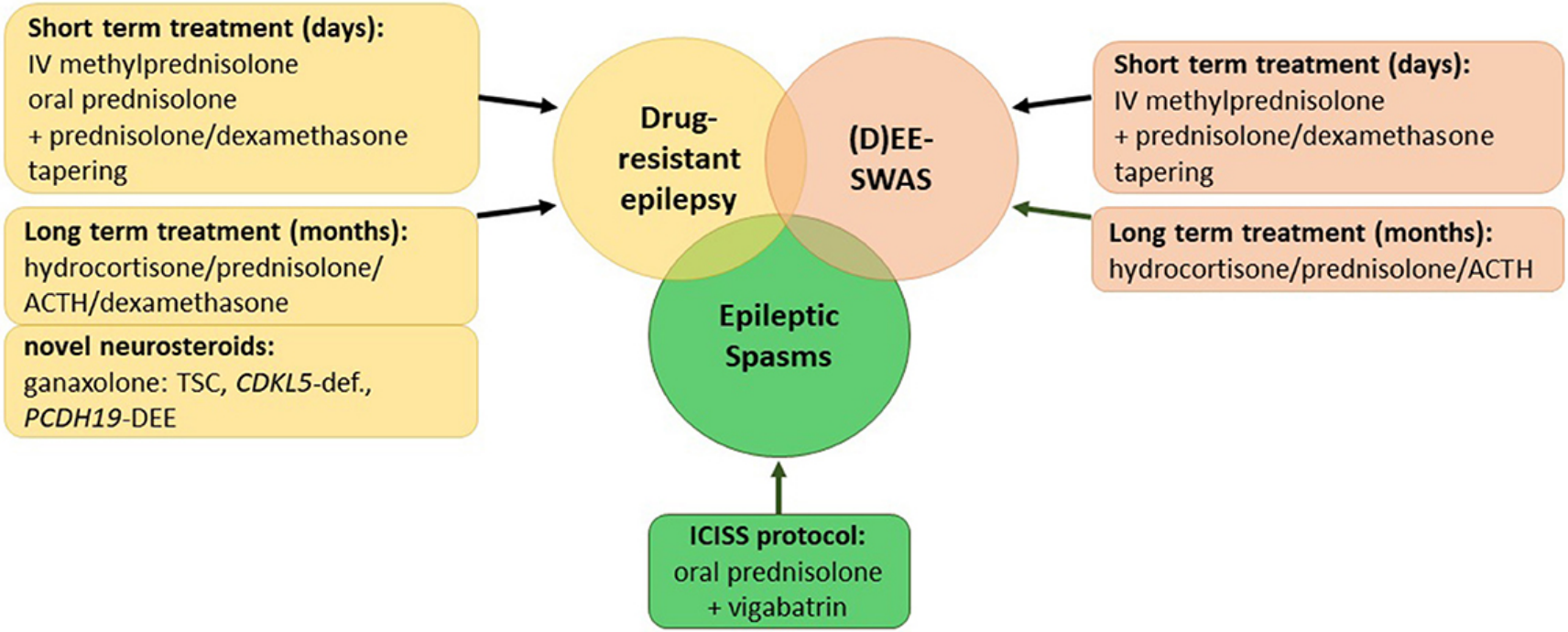
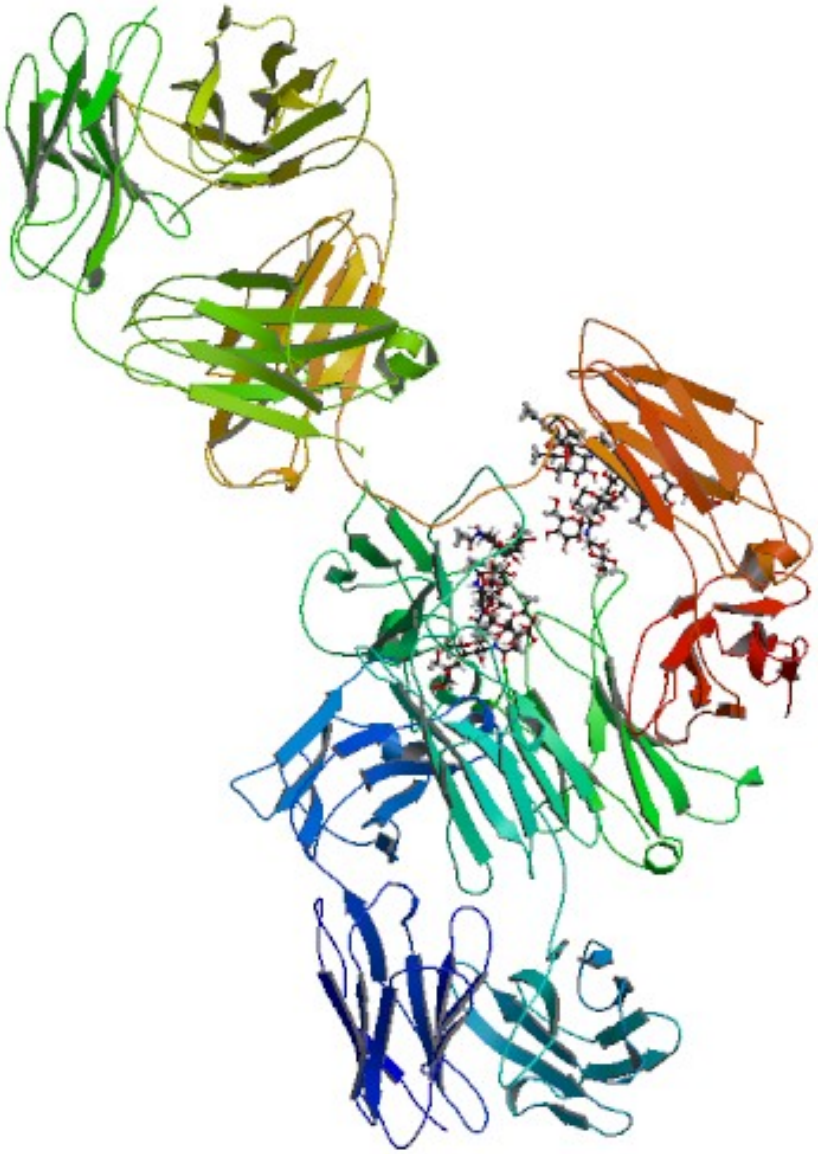
Outside of IESS?

- Evidence (limited) for:
  - ESES
  - Landau Kleffner syndrome
    - 50-60% efficacy, but 75% relapse rates
  - Status epilepticus
    - Limited case reports (NORSE/FIRES) only
  - “Other” drug-resistant epilepsy
    - 40-50% efficacy, but high recurrence again



"there is a lack of results from RCT providing clear evidence for the use of specific steroid regimens in epilepsies other than epileptic spasms. Therefore, no recommendations or statistics including a meta-analysis could be performed."

Becker & Kaindl Front Neurol 2023
review



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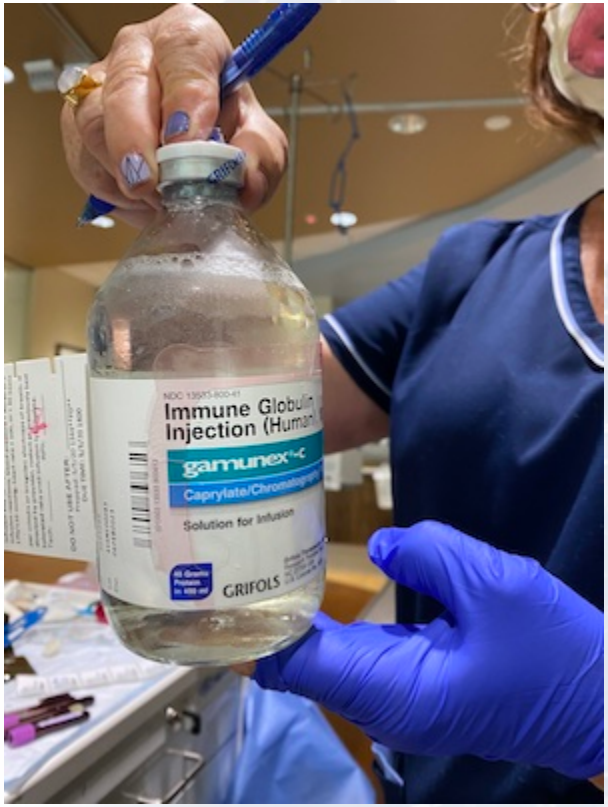
Immunoglobulin therapy

- 400 mg/kg – 1 g/kg given IV over 5 days
  - Some protocols with monthly infusions
- Commonly used for epilepsy due to encephalitis or immune-related



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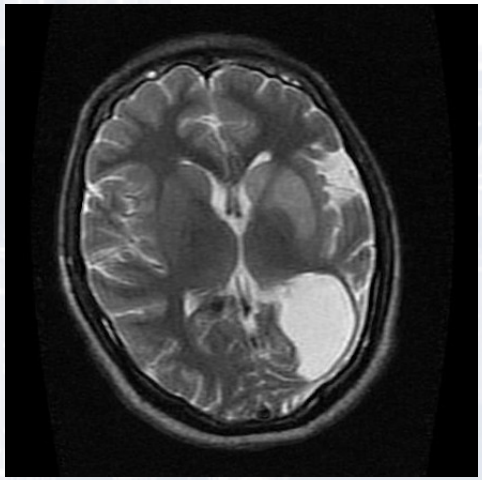
- Van Rijckevorsel-Harmant 1994
  - 61 participants
  - IVIG vs. placebo
    - 21/40 vs. 5/18 (not significant)

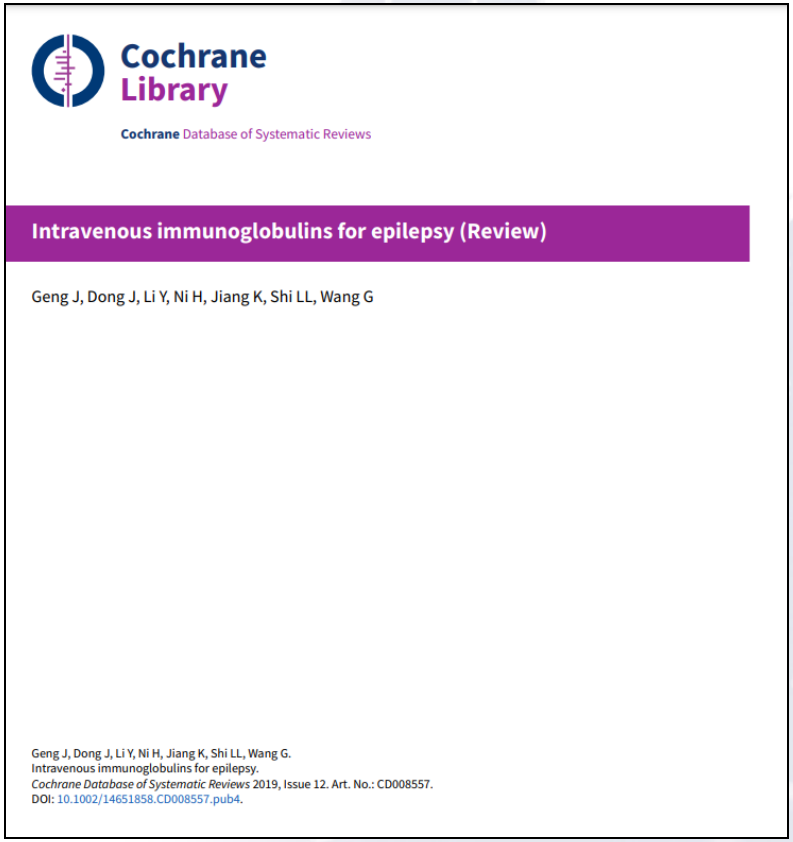


- LGI-1 75% (6 of 8) – Mayo

- Rasmussen syndrome
  - Bien 2013
  - Temporizes before hemispherectomy

Cochrane Review 2019

- 1 study included
  - 7 case reports also
    - 4 with **Rasmussen**
- "We cannot draw any reliable conclusions regarding the efficacy of IVIg as a treatment for epilepsy"


Cochrane Library

Cochrane Database of Systematic Reviews

Intravenous immunoglobulins for epilepsy (Review)

Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, Wang G

Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, Wang G.
Intravenous immunoglobulins for epilepsy.
Cochrane Database of Systematic Reviews 2019, Issue 12. Art. No.: CD008557.
DOI: 10.1002/14651858.CD008557.pub4.

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Summary

- Ketogenic diet therapy is a well-established, nonpharmacologic therapy for refractory epilepsy
- Steroids – infantile spasms
- IVIG – Rasmussen, LGI-1?, other encephalitis cases?

References

- Kossoff et al. Optimal clinical management of children receiving dietary therapies for epilepsy. **Epilepsia Open** 2018

- Becker, Kaindl. Corticosteroids in childhood epilepsies: A review. **Front Neurol** 2023

- Geng et al. IVIG for epilepsy **Cochrane Database Syst Rev** 2019

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Johns Hopkins Ketogenic Diet Center

Eric Kossoff MD

Babitha Haridas MD

Carl Stafstrom MD

Mackenzie Cervenka MD

Tanya McDonald MD PhD

Megan Reiter RN

Zahava Turner RD

Sofie Wicker Velez RD

Bobbie Henry RD

Diane Vitzhum RD

Stacey Bessone RD

Beth Bounds MSW

Jaimie Lansinger

Kelley Ercole CCLS

Gerry & Mike Harris

Christina Megiel, PharmD

Haley Rue, BS, CCRP

Sapana Edwards, RN

Rebecca Fisher, RN