Ketogenic diet therapy in infants with epilepsy

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Introduction

Epilepsy affects 0.5 to 1% of children, of which approximately 25% are drug-resistant – they continue to have seizures despite having trialled at least two tolerated and appropriately chosen antiepileptic drugs (AEDs), either as monotherapy or in combination. Incidence of epilepsy is greatest in the first two years of life, a population who are most at risk for long-term neurodevelopmental compromise.

Ketogenic diet therapy (KDT) is a group of high-fat, low-carbohydrate, adequate protein diets designed to mimic the effects of starvation on the body, whereby fat is utilised as the principle energy source through production of ketones. KDT is the treatment of choice for certain neurometabolic disorders (glucose transporter type 1 deficiency syndrome [GLUT1-DS] and pyruvate dehydrogenase complex deficiency [PDHD]) and are recommended in National Institute for Health and Care Excellence guidelines (CG137) as a possible treatment option for children and young people with drug-resistant epilepsy.

Randomised controlled trials (RCTs) have shown KDT to reduce seizure frequency by ≥50% in 35-56% children and young people, with approximately 10-15% becoming seizure free (1). KDT has also been shown to lead to quicker recovery from seizures, shorter seizures, reduced use of emergency medication, improve mood and cognition, and increase energy and ‘interest in life’ in older children and adults. High-quality evidence is mounting for clinical effectiveness in adults.

This article aims to outline the basics on use of KDT in infants (defined here as aged <2 years of age) with epilepsy.

History of ketogenic diets as a treatment for epilepsy

As early as the Hippocrates era, there were reports of starvation associated with a reduction or cessation of seizures in people with epilepsy. In the Gospels, Mark (9.29, King James Version) described a boy with seizures, which only ‘prayer and fasting’

could cure. In the 1920s, Wilder first proposed a ‘ketogenic diet’ (KD), which restricted carbohydrate and increased fat intake to mimic starvation, as a treatment for seizures. This led to the introduction of the classical KD, which is based on a ratio of grams of fat to grams of protein and carbohydrate (usually up to 4:1), as a treatment for people with epilepsy.

The initial enthusiasm for the classical KD was ousted by the discovery of phenytoin in the 1930s and the advent of other new, easy-to-administer AEDs. Although widely used, concerns were quickly raised regarding adverse side effects of these drugs.

In the 1970s, the Medium Chain Triglyceride (MCT) KD was introduced. Based on the premise that MCTs are more ketogenic per calorie, the MCT KD included 60% calories from MCT fats, allowing greater freedom in protein and carbohydrate intake compared to the predominantly long-chain classical KD. A modified MCT KD was later developed, which derived 30% calories from MCT and 41% from long-chain fats, designed to minimise gastrointestinal side effects.

KDT experienced a new lease of life in 1994 following NBC-TV’s Dateline report on Charlie Abrahams, who became seizure-free with KDT. In the early 2000s, Dr Eric Kossoff from Johns Hopkins Hospital proposed a more liberal KD variant, the Modified Atkin’s Diet (MAD), where fats were ‘encouraged’ rather than specifically measured, and protein was ‘unlimited’ to aid compliance and reduce the burden of traditional KDs. There have since been further advances in alternative KD types. For example, the Low Glycaemic Index Treatment was introduced in 2005 in Boston, which allows up to ~50g carbohydrates per day, but limits the type of carbohydrate to those with a glycaemic index of <50. Another KD variant offered in UK centres is the modified KD, a hybrid between the classical KD and MAD.

Epilepsy and infancy

Over 50% of infants presenting with seizures will have infantile spasms; this affects approximately 1 in 2000 infants. First-line treatment options lead to seizure control in up to 70% of individuals with infantile spasms, but side effects limit how long they can be used and relapse rates are up to 40%. There is limited evidence regarding further AED options in those who do not achieve seizure freedom with first-line treatment. For infants with other forms of epilepsy, such as Ohtahara syndrome, early myoclonic encephalopathy or epilepsy of infancy with migrating focal seizures, or those without a definitive epilepsy syndrome, there are few data to guide optimal treatment. Early control of seizures is associated with better developmental outcome, but many infancy-onset epilepsies are highly drug-resistant. Infants with epilepsy, in particular those who remain resistant to medication, therefore place a large burden on NHS services, with a need for regular clinical review, ongoing medication and therapy support on a long-term basis.

For families of infants with epilepsy, in particular drug-resistant epilepsy, this is an extremely stressful and emotional time, fraught with concerns regarding long-term

prognosis, perceived stigma and potential social and financial impacts. This adds to the complexity of clinical management and limits the extent to which this patient group can be included in clinical trials, with consequent limitations on published data available to guide treatment options.

Why consider infants for ketogenic diet treatment?

Due to the long-term impacts of uncontrolled seizures in this age group, early exploration of non-pharmacological treatment options is warranted in infants presenting with drug-resistant seizures. There is mounting evidence showing safety and efficacy of KDT in infants. The first report of infants aged <2 years treated with KDT was published in 2001. 19.4% of 32 infants became seizure-free and an additional 35.5% had >50% seizure reduction. KDT was generally well-tolerated: adverse events were all reversible, with renal stones, gastritis, colitis, alteration of mentation, and hyperlipidemia occurring in one patient each. 96.4% maintained appropriate growth parameters.

Use of KDT in infants has since been increasingly reported, including two RCTs with age-specific diet efficacy data. Kim et al. (2016) compared classical KD to MAD treatment in children aged 1-18 years, including 27 infants (2). At 3 months, 9/17(53%) infants aged 1 to <2 years on classical KD were seizure-free and 10/17(59%) achieved >50% seizure reduction, compared to 4/20(20%) seizure-free and 8/20(40%) with >50% seizure reduction on MAD. At 6 months, 9/17(53%) on classical KD were seizure-free and 10/17(59%) achieved >50% seizure reduction, compared to 5/20(25%) seizure-free and 9/20(45%) with >50% seizure reduction on MAD. Dressler et al. (2019) compared classical KD to standard adrenocorticotropic hormone (ACTH) treatment in infants with West syndrome (3). 10/16 (62%) in the KD group and 11/16 (69%) in the ACTH group achieved the primary endpoint of electroclinical seizure remission at 28 days. 6/16 (38%) in the KD group and 7/16 (44%) in the ACTH group remained seizure-free at last follow-up.

No prospective controlled studies have published on adverse side effects in infants. From uncontrolled, mostly retrospective studies, adverse side effects seem mild and transient, and rarely lead to diet discontinuation, as in older children. Most commonly reported are gastrointestinal symptoms, in particular constipation and reflux, with lipid profile changes, renal stones and acidosis also reported. Nutritional deficiencies, such as vitamin D, selenium, magnesium and vitamin C, have also been reported, as well as impaired growth, with younger children potentially at increased risk. Catch-up growth post diet discontinuation, however, has been seen.

The importance of obtaining seizure control and the role of KDT in this age group is being increasingly recognised. Reports thus far are encouraging but high-quality evidence is needed. An RCT of Ketogenic Diet in Infants with Epilepsy (KIWE) is underway, led by Professor Helen Cross at UCL Great Ormond Street Institute of Child Health, London, UK (ClinicalTrials.gov Identifier: NCT02205931).

Indications/contra-indications for dietary treatment

European guidelines (4) outline the following indications (Table 1) and contra-indications (Table 2) for KDT in infants. In the absence of a clear metabolic disorder for which KDT is the treatment of choice, KDT can be considered for infants who have failed two standard AEDs; this includes infantile spasms/West syndrome, where standard first line treatments remain vigabatrin and steroids. There is also emerging evidence about optimal AED treatment for epilepsies associated with certain genetic mutations, such as sodium channel blockers in *SCN8A*, or *KCNQ2* mutations, which should be taken into consideration.

Table 1: Indications for KDT in infants

Epilepsy:	Metabolic diseases:
- Refractory epilepsy after use of 2 AEDs: i.e. West syndrome, Ohtahara syndrome - Adverse effects of AEDs - Waiting for epilepsy surgery	- Glucose transporter type 1 deficiency syndrome - Pyruvate dehydrogenase complex deficiency - Mitochondrial diseases (optional)

From 'Ketogenic Diet guidelines for infants with refractory epilepsy', 2016

Table 2: Contra-indications for KDT in infants

Absolute:	Relative:
- Fatty acid oxidation deficiencies (VLCAD, LCHAD, MCAD, OCTN2, CPT1, CPT2) - Pyruvate carboxylase deficiency and other gluconeogenesis defects (fructose 1,6 diphosphatase deficiency) - Glycogen storage diseases (except type 2) - Ketolysis defects - Ketogenisis defects - Porphyria - Prolonged QT syndrome or other cardiac diseases - Liver, kidney or pancreatic insufficiency - Hyperinsulinism	- Inability to maintain adequate nutrition - Surgical focus identified by neuroimaging and video EEG monitoring - Parent or caregiver noncompliance - Growth retardation - Severe gastrointestinal reflux - Familiar hypercholesterolemia

From 'Ketogenic Diet guidelines for infants with refractory epilepsy', 2016

Preparing suitable candidates for dietary treatment

Referral and patient selection

In addition to appropriate medical indication for KDT, parent/carer motivation must be ascertained by the multidisciplinary team (paediatric neurologist, dietitian and specialist nurse, with close cooperation with pharmacy) and a realistic picture presented of the practicalities and social impact of KDT, risks of potential short- and long-term adverse effects, and anticipated timelines for the trial period and dietary treatment if clinically effective.

Counselling

If the patient is deemed an appropriate candidate, clear treatment objectives should be set together with the multidisciplinary team. Psychosocial aspects of KDT should be continually discussed alongside medical and dietetic review.

Investigations
A full medical history is completed by the neurologist, including history of epilepsy treatment, neurodevelopmental assessment and physical examination.

Baseline biochemical monitoring is essential, including metabolic screening (Table 3).

Dietary assessment includes growth history, feeding difficulties, presence of food allergies and a three day food diary.

Social circumstances should also be discussed with the multidisciplinary team, including family composition, educational levels of parents/carers and expected compliance.

If applicable, medications should be changed to low-carbohydrate versions.

Table 3: Recommended baseline biochemical monitoring of infants considering KDT

Essential	**Recommended**
Blood:	Blood:
Full blood count Renal profile (includes sodium, potassium, urea, creatinine, bicarbonate and albumin) Liver profile Calcium, phosphate, magnesium Glucose Vitamin D Lipid profile (repeat with fasting if elevated) Free and acylcarnitine profile	Vitamins A, E, B12 Zinc, selenium, copper Folate, ferritin
Urine:	
Calcium:creatinine ratio Haematuria, organic acids	

From 'Ketogenic Diet guidelines for infants with refractory epilepsy', 2016

Ketogenic diet type
An individual diet prescription is calculated by a paediatric dietitian to ensure energy, protein, fluid, vitamins and mineral requirements are met. Consideration is made of the infant's usual feeding pattern and parent/carer preferences.

The classical KD is generally used, both for oral and enteral feeding, based on studies reporting efficacy and tolerance in this age group. Most centres use a 3:1 ratio in order to meet protein requirements, but this ratio may be increased or decreased, depending on ketone levels and/or tolerance.

The formula Ketocal®3:1 (Nutricia Ltd) is specifically developed to meet the nutritional requirements of infants and young children on KDT. Ketocal®4:1 (Nutricia Ltd) may be used on an individual basis, for example, as part of a bespoke prescription, with appropriate assessment of micronutrient intake. Ketogenic formula can be combined with breastfeeding, either mixed with expressed milk or offered prior to a breastfeed. When weaning off a milk diet or for infants who have started complementary feeding, micronutrient intake should be assessed and supplementation commenced as necessary. Age- and developmentally-appropriate recipes using the prescribed diet ratio are calculated for oral feeders. Blended KD recipes can be calculated and used for enteral feeders, providing centre-specific guidance is followed.

Diet initiation

KDT is usually started during a 3-5 day inpatient stay for infants aged <1 year or those aged 1-2 years who are clinically unstable. Otherwise, following a face-to-face education session, older infants may be started at home, whilst maintaining close communication with the KDT team.

A non-fasting protocol is usually adopted to minimise the risk of complications such as hypoglycaemia and dehydration. KDT is initiated gradually, depending on centre practice and individual tolerance. For example, the ratio may be increased from 1:1 to 2:1 to 3:1, with increments made daily, every two days or more slowly, depending on individual tolerance. Alternatively, a 3:1 ratio may be used at the onset, with the amount of daily calories coming from the 3:1 formula or recipes gradually introduced (for example, 33%, 66%, then 100% of daily calories).

Blood glucose and blood or urine ketone levels are monitored twice daily, both for inpatients and those starting at home (for outpatient, blood glucose testing may only be recommended if symptomatic, depending on local centre practice). Symptoms of hypoglycaemia or excess ketosis are treated with 2-4 grams of carbohydrate from breast milk, formula milk, 10% glucose solution or pure fruit juice. Persistent hypoglycaemia or excess ketosis requires amendment of the introduction schedule and, potentially, the KDT prescription. Persistent hypoglycaemia is rare as a complication of KDT alone and therefore, in its presence, a full metabolic assessment should be undertaken.

Gastrointestinal symptoms, such as vomiting, nausea, diarrhoea, and abdominal discomfort, can usually be managed by amending the introduction schedule. Medication may be needed to help constipation and gastro-oesophageal reflux, particularly if pre-existing, if not helped by dietary manipulation.

Monitoring and Management

Frequent (often daily) telephone or email contact is needed with the dietitian and/or nurse during the first two weeks post diet initiation. Communication may then reduce to once or twice a week, and then less frequently, depending on the age of the patient, diet tolerance and clinical efficacy.

Home monitoring of the following is required:

- Seizure frequency and duration, for each seizure type. A paper or electronic seizure diary may be used to facilitate recording.
- Other benefits from KDT, such as improvements in cognition, motor development and quality of life. Age- and developmentally appropriate existing tools may be used to assess these benefits on an individual basis, but none are validated for use in epilepsy KDT patients. Otherwise, data are based on parental report.
- Adverse effects
- Ketones: twice daily (morning and evening) for the first few weeks, then reduced to once daily. After approximately 3 months, testing may be even less frequent, subject to discussion with the multidisciplinary team. Blood ketone levels of 2-5mmol/l or urine ketone levels of 8-16mmol/L (3-4+) may be aimed for, but optimal ketone levels should be determined on an individual basis, based on tolerance and clinical efficacy.
- Weekly or bi-weekly weights, depending on the growth history and current trajectory of the individual.

Frequency of reviews with the neurologist and multidisciplinary team is centre-dependent. European guidelines suggest clinical review at 2 weeks, 6 weeks and 3 months post diet initiation, then every 3 months until aged 2 years, with more frequent visits recommended for infants with additional medical or nutritional needs. Children aged over 2 years can be seen 6-monthly.

At reviews, assessment of KDT efficacy in terms of seizures and other benefits, diet tolerance, laboratory tests (Table 4), medication review, growth and dietary assessment are conducted. Renal ultrasound may be requested for individuals on KDT for >12 months; an EEG and/or ECG may be requested if clinically indicated.

Table 4: Recommended following biochemical monitoring of infants on KDT

Investigation	Frequency of monitoring
Essential	
Blood:	
Full blood count Renal profile (includes sodium, potassium, urea, creatinine, bicarbonate and albumin) Liver profile Calcium, phosphate, magnesium Glucose	6 weeks, 3 months, 6 months, then every 6 months
Vitamin D Lipid profile (repeat with fasting if elevated) Free and acylcarnitine profile	After 3 months, 6 months, then every 6 months
Urine:	
Calcium:creatinine ratio Haematuria	6 weeks, 3 months, 6 months, then every 6 months

Recommended	
Blood:	
Vitamins A, E, B12 Zinc, selenium, copper Folate, ferritin	6 months, then every 12 months

From 'Ketogenic Diet guidelines for infants with refractory epilepsy', 2016

A low dose of MCT emulsion may be incorporated into the classical KD, either to enhance ketosis or liberalise the amount of carbohydrate and/or protein foods

How long should infants continue ketogenic diet therapy?

Infants with GLUT1-DS and PDHD deficiency are usually recommended to continue KDT life-long, as KDT is the treatment of the underlying metabolic defect as well as presenting seizures and other neurological symptoms. However, a reduced ratio or more liberal types of KDT may be tolerated and still be clinically effective in the longer term.

For other infants with epilepsy, in the first instance, KDT should be followed for 2-3 months to determine efficacy. One exception is use of KDT as first, second or third line treatment for infantile spasms, in which case, alternative treatments may be considered after 1 month of KDT if seizures continue. When effective, most patients show signs of improvement within the first 14-23 days of dietary treatment.

At the end of the trial period, a discussion should be had between the family and multidisciplinary team, weighing up the benefits and disadvantages to continuing KDT. If effective, KDT is usually continued for at least 2 years, but there is no limit as to how long KDT can be followed. In infants and children who achieve seizure freedom on KDT, there is evidence that seizure control is maintained by 75-80% of patients after returning to a normal diet. Patients with infantile spasms who achieve seizure freedom on KDT may discontinue the diet after approximately 8 months, with no difference in relapse rates compared to those who discontinue after 2 years.

For infants who remain on KDT after they reach 2 years of age, changing to another type of KDT, such as the modified KD, may be considered.

If the decision is made to discontinue KDT, this should be done in a stepwise fashion, both for oral and enteral feeders. For non-responders, the diet may be discontinued within 2 weeks, depending on individual tolerance. For those who have followed KDT for longer, weaning may take up to 3-4 months, with daily, weekly or even monthly ratio reductions, particularly for those who achieved seizure freedom. In the case of deterioration in seizure control, a return to the previous ratio can be made.

Ketone levels can be monitored during diet discontinuation and, once no longer present, a return to normal diet expedited. Food and drinks high in refined carbohydrate can be

cautiously reintroduced once the normal diet is fully established, within healthy eating guidelines.

Further support

Support organisations:
Matthew's Friends: www.matthewsfriends.org (for information, recipes, online tutorials, support forms and cookery channel)
The Daisy Garland: www.thedaisygarland.org.uk (for information and online support forum)
The Charlie Foundation: www.charliefoundation.org (for information, recipes and blog)

Industry:
Nutricia: https://www.myketocal.com/history.aspx (for prescribable product information, recipe booklets, cookery and education days)
Vitaflo: https://www.nestlehealthscience.co.uk/vitaflo/conditions/ketogenic%20diet/home and www.myketogenicdiet.co.uk (for prescribable product information, healthcare professional guidelines, recipe booklets and ketogenic diet calculator app)
Ketocare; http://ketocarefoods.com (for prescribable product information and recipe ideas)

Electronic diet calculators:
My Keto Planner: www.myketoplanner.co.uk
Electronic Ketogenic Manager (EKM): https://www.matthewsfriends.org/keto-kitchen/keto-recipes/ketogenic-mealplanner-electronic-ketogenic-manager-ekm
Keto Diet Calculator: https://www.ketodietcalculator.org/ketoweb/KetoStart

Professional organisations
Ketogenic Dietitians Research Network: @KDRN_online, kdrn_online@outlook.com
KetoPAG (Professional Advisory Group) mailing list

Conferences:
Ketocollege: http://www.mfclinics.com/keto-college/ketocollege-uk-2020
Global Symposium on Ketogenic Dietary Therapies: https://globalketo.com
Nutricia KetoConference
Vitaflo European Ketogenic Symposium

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Further reading

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