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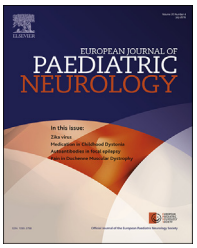

Review article

Ketogenic diet guidelines for infants with refractory epilepsy

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ABSTRACT

Background: The ketogenic diet (KD) is an established, effective non-pharmacologic treatment for drug resistant childhood epilepsy. For a long time, the KD was not recommended for use in infancy (under the age of 2 years) because this is such a crucial period in development and the perceived high risk of nutritional inadequacies. Indeed, infants are a vulnerable population with specific nutritional requirements. But current research shows that the KD is highly effective and well tolerated in infants with epilepsy. Seizure freedom is often achieved and maintained in this specific patient group.

There is a need for standardised protocols and management recommendations for clinical use.

Method: In April 2015, a project group of 5 experts was established in order to create a consensus statement regarding the clinical management of the KD in infants. The manuscript was reviewed and amended by a larger group of 10 international experts in the KD field.

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Consensus was reached with regard to guidance on how the diet should be administered and in whom.

Results: The resulting recommendations include patient selection, pre-KD counseling and evaluation, specific nutritional requirements, preferred initiation, monitoring of adverse effects at initiation and follow-up, evaluation and KD discontinuation.

Conclusion: This paper highlights recommendations based on best evidence, combined with expert opinions and gives directions for future research.

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1. Introduction/background

The ketogenic diet (KD) is a non-pharmacologic treatment for children with drug resistant epilepsy. The efficacy of the KD has been established by several multicenter studies and one randomized controlled trial. The randomized trial that further established the efficacy of KD was conducted in children and adolescents aged 2–16 years.[1] The diet may be administered in one of several ways and each may be valid. An international protocol for its implementation and subsequent follow-up management in children has been published[2] and recently updated (ILAE 2015).[3]

For a long time, the KD was not recommended for use in infancy (under the age of 2 years) in view of it being such a crucial period of development and the perceived high risk of nutritional inadequacies. This was based on the knowledge of immaturity of lipase activity, liver function and lipid metabolism and the difficulty of achieving and maintaining ketosis.

The first reports by Nordli et al. in a small group of infants showed the KD to be effective and safe.[4] A KD formula with ratio 3:1 is now available making the diet easier to administer in this group as first or second line treatment. The most recent study by Dressler et al. showed the KD to be highly effective and well tolerated in infants with epilepsy. Seizure freedom appears to be often achieved and maintained in this age group.[5]

Because international KD guidelines do not contain specific advice for infants, recommendations for optimal practice in this group are needed. Infants are a vulnerable population with specific nutritional requirements. It is therefore desirable that consensus is reached with regard to guidance on how the diet should be administered and in whom.

2. Methods

At the Dietary Management of Inherited Metabolic Diseases (DMIMD) conference 2015 in London an initial meeting was held with the goal of starting a working group of experts in KD treatment in infancy. A group of five experts (i.e two pediatric neurologist and three dietitians, see Appendix I) discussed issues with regard to specific recommendations for this group of patients and designed the framework based on subjects they found applicable. During teleconference calls several subjects were addressed. A larger group of international experts (i.e. 3 pediatric neurologists and 7 dietitians, see Appendix I) on KD treatment in infants were asked to send their guidelines or, in absence of recent published literature on subjects, information based on their professional or centre's experience. These experts also reviewed the full manuscript of the recommendations. After two rounds of review, consensus was reached on the final text.

The questions to be answered were:

- Which epilepsy syndromes in infancy benefit most from KD treatment?
- How should KD initiation be considered in infants?
- Which version of KD is feasible and safe in infancy and how should the KD be initiated?
- What are the dietary prescriptions for infants in respect to their specific nutritional requirements?
- How should the KD be monitored during treatment at baseline and follow up and which are the most important adverse effects to be expected?
- How should the diet be implemented in emergency situations?
- After what period of time should efficacy of KD treatment be evaluated and/or the diet discontinued?
- What are the future directions for research?

3. Epilepsy syndromes in infancy where KD is of benefit

Management of epilepsy in infancy is challenging based on the characteristics of the epilepsy and its impact on neurodevelopment of the child. This implies early, aggressive and optimal treatment is warranted. As a non-pharmacological treatment KD is currently used in infants with refractory epilepsy syndromes (see Table 1) such as infantile spasms (West syndrome) resistant to first line medication,[5–9] Ohtahara syndrome,[10,11] epilepsy of infancy with migrating seizures[12] and resistant epilepsy with focal seizures awaiting epilepsy surgery. There are also other conditions for which the KD is the treatment of choice such as glucose transporter type 1 (GLUT-1) deficiency[13] and pyruvate dehydrogenase complex (PDHC) deficiency.[14]

4. Preparing for treatment

Treatment with the KD is demanding for families and requires a high degree of medical and dietetic monitoring because of possible side effects and restrictiveness. A multidisciplinary team is highly recommended (pediatric neurologist/pediatrician, epilepsy nurse, dietitian and close cooperation with pharmacy).

At baseline detailed information is obtained on the medical, nutritional and biochemical status of the infant. After a positive decision an individualized KD and step by step plan will be designed.

5. Dietary prescription

5.1. *Which diet to choose and how to initiate*

KD is a high fat (71–90% energy) and carbohydrate restricted (5–19% energy) diet that contains adequate amount of protein to support growth. Clinical practice shows the classical version of the KD with a 3:1 ratio is routinely used in infants in order to meet protein requirements. This means that for every 3 g of fat there is 1 g of combined protein and carbohydrate.

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Table 1 – Indications and contra indications of KD in infants.

Indications	Contra-indications
Epilepsy:	*Absolute*:

- Refractory epilepsy after use of 2 anti-epileptic drugs (AEDs): i.e.
  - West syndrome
  - Ohtahara syndrome
  - with focal seizure waiting for epilepsy surgery
	- 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
	- Ketogenesis defects
	- Porphyria
	- Prolonged QT syndrome or other cardiac diseases
	- Liver, kidney or pancreatic insufficiency
	- Hyperinsulinism

Metabolic diseases: - GLUT-1 deficiency - PDHC deficiency optional - Mitochondrial diseases	*Relative* - Inability to maintain adequate nutrition - Surgical focus identified by neuroimaging and video EEG monitoring - Parent or caregiver non compliance - Growth retardation - Severe gastrointestinal reflux - Familial hypercholesterolemia

Several studies show the range of KD ratio used is 2.5–4:1 with respect of tolerance, ketosis and side effects.[5–8]

Information in the literature on how the KD should be initiated in infants is scarce. Raju et al. (2011) showed in a randomized trial of 38 infants that a 2.5:1 ratio KD was as effective as 4:1 ratio KD but less side effects were seen.[15] Pires et al. (2013) showed in a prospective trial of 17 infants receiving a KD during hospitalisation that a 3:1 (some 4:1) ratio was very effective and tolerated well. Diet initiation was performed by a non-fasting protocol with daily steps of increasing calories and ratio.[7]

Information from expert teams show infants are admitted to hospital for diet initiation performed without fasting and by an individualized step by step plan. Most centres start with a 1.0:1 ratio with full calories, increasing the ratio on a daily basis to 3:1 based on tolerance.

Recommendations: all young infants (<12 months) should be admitted to hospital. Diet initiation should be undertaken without fasting and a stepwise start commencing with a 1:1 ratio. A build to a classical KD with 3:1 ratio is recommended. The diet can be adjusted to a lower ratio (2.5 or 2:1) or higher ratio (3.5 or 4:1) based on level of ketosis and tolerance. A KD formula with ratio 3:1 can be used purely or combined with breast milk. Careful calculation to check individual requirements are met is highly recommended especially when a 4:1 ratio is applied.

5.2. *Energy*

The energy requirements of infants with epilepsy may vary greatly. There is no consensus in the literature on how to calculate energy requirements in infants below 6 months of age.

Often a percentage (75%–100%) of the recommended daily allowance (RDA) of energy is used; sometimes an individual calculation is reported based on dietary history.[2,4,16]

For infants with severe disability such as encephalopathy with epilepsy and severe motor involvement, a calculation of the expected energy requirement based only on the Schofield formula is not very accurate below 10 kg and/or age 12 months.

The total energy requirement depends on the physical activity that may be influenced by epileptic seizures, the anti-epileptic drug (AED) used and possibly the degree of spasticity or frequency of muscle spasm during epileptic seizures.[17] The RDAs are recommendations for groups of healthy children, making them less suitable for the individual with epilepsy but still the only validated recommendations available (see Table 2).

Table 2 – Energy requirements for an infant on the KD based on RDA.[a]

Age/months	Weight/kg	Kcal/kg/day
1–3	3.8–5.9	100–95
4–6	6.0–7.9	95–85
7–12	8.0–10.0	85–80

[a] RDA from Austria, France, Germany, The Netherlands, UK, USA.

Recommendations: for infants the energy requirements have to be based on the intake recorded in the food diary, compared with the RDA for age and gender and recent growth.

If there is a recent decline in the growth curve or failure to thrive an additional amount of energy is necessary. Using the ideal weight/age or weight/height should be considered to ensure catch up growth. If infants have gained a large amount of weight (e.g. after adrenocorticotropic hormone (ACTH) use), it is important to determine the most appropriate weight/age or weight/height to be used for an adequate diet calculation. In individual cases resting energy expenditure (REE) can be measured with a ventilated hood

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on which factors for (catch up) growth and physical activity level (PAL) will be multiplied. The energy intake has to be adjusted frequently (sometimes on weekly basis) based on evaluation of growth curve, changes in level of activity and/or illness.

5.3. *Fat*

The classical KD is based on long chain triglyceride (LCT) and works with different ratios. Most infants use the classical KD at a ratio of 3:1. Based on individual tolerance and/or level of ketosis, a different ratio may be used (2:1–4:1).

Use of medium chain triglyceride (MCT) in infants will be limited. In older infants use of MCT 50% emulsion mixed with a (low fat) milk product (50–50) or a little amount of MCT 20% emulsion drink will be possible. The amount of MCT is tailored based on level of ketosis and tolerance.

The amount of total MCT well tolerated by the infant will be around 10–25% of daily energy intake.

5.4. *Protein*

The protein requirements of infants with epilepsy are the same as in healthy infants. There is no consensus in the literature (primarily the classical KD) with respect to protein intake.

Often, 10% energy combined protein and carbohydrate is assumed in which 1 g of protein per kg body weight is recommended; sometimes a protein intake of 5–7% energy is reported or reference is made to the RDAs.

With the classical KD, achieving an adequate protein intake in the ratio is at the expense of the allowed quantity of carbohydrate. Therefore for the young child with psychomotor delay, with a realistic chance of growth retardation, a ratio of 3:1 is usually chosen.[4,18]

Recommendations: for infants the protein intakes based on RDA are advised (see Table 3).

If there is a recent decline in the growth curve or failure to thrive an adequate intake of protein is important. Using the ideal weight/age or weight/height should be considered to ensure catch up growth.

If infants have gained a large amount of weight it is important to determine the most appropriate weight/age or weight/height to be used for adequate diet calculation.

Table 3 – Recommended daily protein intake for an infant on the KD based on RDA or WHO/FAO.

Age/months	Weight/kg (use ideal weight/age)	Protein g/kg/day during KD[a]	Protein/g/kg/day WHO/FAO
1–3	3.8–5.9	2.0–1.6	1.77–1.36[b]
4–6	6.0–7.9	1.5–1.3	1.24–1.12[b]
7–12	8.0–10.0	1.2–1.1	1.12–0.86[c]

[a] Based on average RDA from Austria, France, Germany, The Netherlands, UK, USA.
[b] WHO 2007: safe level for growth +1.96 SD.
[c] FAO 2013.

Aim for the optimal amount of protein and check that the amount of protein is above the minimal World Health Organisation (WHO) recommendation.[19,20]

The diet must be adjusted frequently (sometimes on weekly basis) based on weight gain.

5.5. *Carbohydrate*

The permitted quantity of carbohydrate follows from the calculation of energy and protein requirements and the establishment of the necessary quantity of fat.

The allowed quantity of carbohydrate is divided throughout the day to prevent adverse effects such as hypoglycaemia or excessive ketosis. Artificial sweeteners should be avoided in infants.

Introduction of solid foods, when age and developmentally appropriate, will increase the amount of fibre since constipation is a frequent adverse effect of the KD. The potential presence of resorbable carbohydrate in medication and supplements should not be overlooked.

Recommendations: the treating physician consults the pharmacist for suitable (alternative) sugar free medication.

5.6. *Fluid*

In the past, the KD has been combined with a fluid restriction. It was believed that mild dehydration improved the efficacy of the KD. Theories that a fluid restriction influenced the pH, electrolytes or ketone concentrations of the blood and brain have been abandoned after various studies. According to Homer et al., no mechanism has been found that shows that over hydration has a negative effect on epileptic seizures.[21]

Recommendations: fluid restriction might add to the development of kidney stones so an adequate hydration is required. An age and weight appropriate fluid intake is advised based on RDA, with fluid offered throughout the day. The fluid intake should be individually calculated and adjusted frequently based on weight gain and biochemistry results (e.g. urine calcium: creatinine ratio) (see Table 4).

Table 4 – Recommended daily fluid intake based on RDA.[a]

Age/months	Weight/kg	ml/kg/day
1–3	3.8–5.9	150–140
4–6	6.0–7.9	120–110
7–12	8.0–10.0	100–90

[a] Based on average of RDA from Austria, France, Germany, The Netherlands, UK, USA.

5.7. *Vitamins and minerals*

The classical KD contains insufficient micronutrients.[22,23] The potential presence of absorbable/resorbable carbohydrate in vitamin/mineral supplements however should not be overlooked. It is known that various anticonvulsants have interactions with some minerals and vitamins, for example, influencing the absorption of folic acid and the metabolism of calcium and vitamin D.[21]

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Recommendations: by means of adequate supplementation, the intake of micronutrients should be individually calculated corresponding to reference intakes for age and weight. When starting to wean off a formula diet, micronutrient intake should be assessed and supplementation commenced as necessary (for example when formula intake contributes to less than 80% of energy requirements).

6. Treatment phase

6.1. *Baseline monitoring*

Prior to the start of KD, laboratory and urine checks are strongly advised to ensure there are no pre-existing contra-indications or deficiencies (Table 5).

6.2. *Monitoring during diet initiation*

6.2.1. *General*

During diet initiation weight, nutritional intake, tolerance (i.e gastro intestinal disturbances, vomiting, etc.) are checked on a daily basis. Height and head circumference are measured at baseline.

While on a KD the infant can continue bottle feeding. In daily practice the majority of infants with severe epilepsy have feeding difficulties and may need an enteral tube feed at diet initiation to achieve their requirements.

It is possible to continue using a limited amount of expressed breastmilk combined/mixed with ketogenic 3:1 formula. If there is no expressed breastmilk a limited amount of standard infant formula can be used to combine/mix with the ketogenic formula.

This may be given by bottle and/or tube.

In some cases (i.e. the young infant) breastfeeding may be possible after a controlled amount of ketogenic formula is given, which highly depends on seizure reduction and on level of ketosis. In this situation the use of ketogenic 3:1 formula is recommended. In some of these cases ketogenic 4:1 formula may be necessary, but use this only after careful calculation and monitoring. In some cases (i.e. the young infant) breastfeeding on demand may be possible but this highly depends on seizure frequency and on level of ketosis.

Table 5 – Advised baseline monitoring.[2]

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

6.2.2. *Glucose*

There is a risk of hypoglycaemia during diet initiation although uncommon in the absence of a metabolic disease. During initiation blood glucose should be checked twice daily (or more based on symptoms of hypoglycemia) and frequency must be adjusted based on tolerance. Hypoglycemia is defined as glucose levels below of 2–2.5 mmol/l (approximately 40 mg/dl) and should be treated immediately with 2–4 g of carbohydrates. Infants with blood glucose >3 mmol/l but showing symptoms of hypoglycaemia (see Fig. 1) should also be treated in the same way. Blood glucose should be re-checked after 15–20 min and if not improved treatment should be repeated.

6.2.3. *Ketones*

During transition to a ketogenic feeding regime or ketogenic food, the level of ketone bodies in the blood will increase. Monitoring of ketones will ensure a therapeutic level is reached without risking symptoms of excess ketosis (see Fig. 1). Ketones can be measured in blood or urine. Blood testing using a ketometer is recommended during diet initiation as this is more accurate and unaffected by urine dilution or any possible alterations in water homeostasis that may occur in very young infants. Blood ketones should be checked twice daily using a finger or heel prick. Hyperketosis is defined as 5 mmol/l or higher in blood and should be treated with 2–4 g of carbohydrates. Blood ketones should be re-checked after 15–20 min and if not improved treatment should be repeated.

6.2.4. *Gastro-intestinal complaints*

Gastro-intestinal problems such as vomiting, nausea, diarrhea, and abdominal discomfort are common side effects of the KD,[15,24] however they can usually be alleviated with dietary manipulation and by altering the step by step initiation plan.

There is a risk that children with pre-existing gastro oesophageal reflux will have symptoms exacerbated by a high fat regime in view of delayed gastric emptying. Optimising anti-reflux medication will help alleviate the symptoms.

Constipation is the most common reported complication of the KD and may already be present prior to diet initiation. Despite dietary changes to help lessen the problem many children need additional treatment with medication.

When the amount of fat is increased gradually the risk of adverse effects will be limited.

6.3. *Monitoring and adverse effects during follow up*

6.3.1. *Glucose/ketones*

There is a risk of hypoglycaemia, acidosis, dehydration and high levels of ketones on commencing a KD[24] with increased risk of excess ketosis and metabolic acidosis with concurrent use of carbonic anhydrase inhibitors (for example, topiramate or zonisamide).[25]

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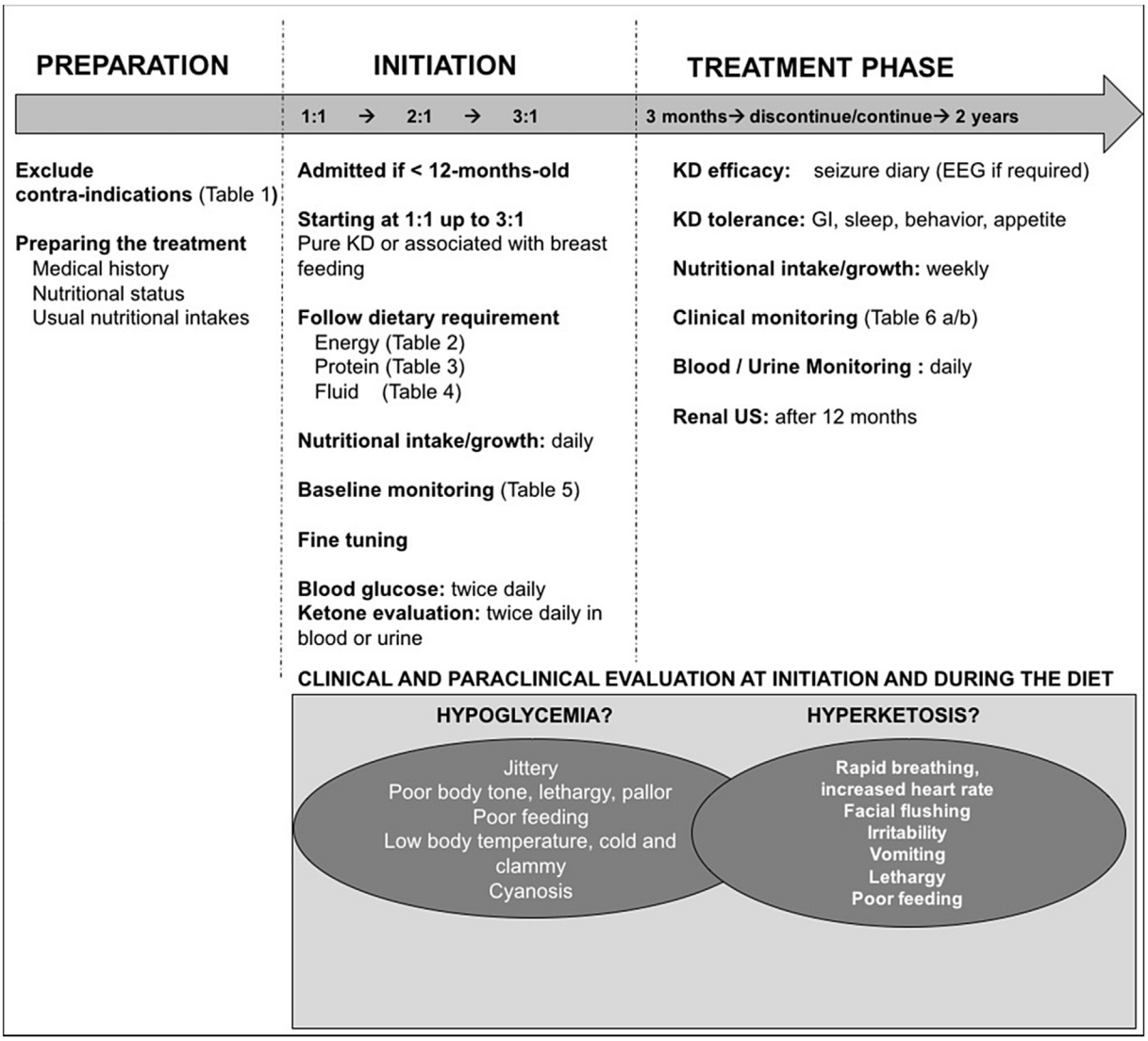

Fig. 1 – Overview of preparation, initiation and treatment of ketogenic diet in infants. EEG: electroencephalogram, GI: GastroIntestinal.

6.3.2. *Gastro intestinal complaints*

Gastro-intestinal problems such as vomiting, nausea, diarrhea and abdominal discomfort are common on-going side effects of the KD however can usually be alleviated with dietary manipulation, see Section 6.2.4.[26,27]

6.3.3. *Growth*

There is evidence of impaired growth in children on the KD[28,29]; younger children may be more at risk.[18] Long-term follow up of children treated with the KD in the past suggests that although growth does improve after the diet is discontinued, height gain can still be below expected.[30] Although growth retardation appears to be a problem in children on both classical and MCT KDs despite the latter providing a significantly higher protein intake,[31] a prescribed protein-to-energy ratio of at least 1.5 g protein/100 kcal has been suggested to help prevent growth faltering.[32]

6.3.4. *Nutritional deficiencies*

Children with drug resistant epilepsy are at risk of insufficient vitamin D status prior to starting a KD[33] and although levels can be normalised on diet therapy with vitamin D supplementation, a decline in both whole body and spine bone mineral content while on the KD has been reported[34] despite reduction in anticonvulsant medication.

Selenium deficiency has been reported in children on the KD[35] with the risk of impaired myocardial function.[36]

Hypomagnesaemia has also been seen,[24] and may be a particular problem in children on the classical KD despite micronutrient supplementation.[22]

Vitamin C deficiency has been reported in one child on the KD[37] but plasma levels of fat soluble vitamins A and E can often be raised as a consequence of a high fat intake.[22] A fall in carnitine status of children and young adults during the first few months of the KD has been seen with some cases

requiring supplementation,[38] although levels tended to normalise with time on diet therapy.

6.3.5. *Cardiovascular*

Plasma lipid levels can often be elevated by the KD and significant increases in atherogenic apoB-containing lipoproteins have been reported in children after 6 months of KD.[39] Although there is evidence of a trend back towards normal with time on the KD,[40] this raises concern about long term adverse effects on vascular function. Studies suggest that while arterial stiffness may increase initially,[41] the changes in arterial function observed within the first year of KD treatment are not significant after 24 months and appear to be reversible.[42] Further studies are required to investigate this issue.

6.3.6. *Kidney stones*

The use of KD in infants might increase the risk of kidney stones compared to older children. In addition to the age factor, the presence of hypercalciuria also increases the risk for the development of kidney stones.[43] Uric acid, calcium oxalate, calcium phosphate or mixed composition stones have been reported in up to 7% of children on the KD.[43–45] Risk may be higher with long-term treatment[28] and concurrent use of carbonic anhydrase inhibitors.[46] The daily oral intake of citrate potassium that theoretically alkalinizes the urine and solubilizes urine calcium can be suggested to prevent kidney stones, in particular in the patients with cumulating risk factors. A retrospective study comparing patients treated by KD with or without daily potassium citrate supplement has suggested a preventive effect.[47]

6.3.7. *Other side effects*

Other reported, but rare, side effects of the KD are increased infection risk, bruising, raised serum uric acid, fractures, pancreatitis, lipid-aspiration pneumonia, and cardiac abnormalities.[24,36,48–50]

6.3.8. *Adverse effects of the ketogenic diet reported in infants*

Most commonly seen in infants were gastro-intestinal disturbances especially constipation and reflux, altered lipid levels, renal stones and acidosis. Most side effects were transient and could be controlled without diet withdrawal by a high level of monitoring as recommended in Table 6 A and B. However Eun et al. reported that 37% of their group of 43 infants discontinued the KD due to complications.[6] Most studies are based on retrospective data, which implies a lower quality assessment of side effects.

For summary of reported side effects in infants see Supplementary material.[4–9,51–53]

6.4. *Fine tuning*

When the ketosis doesn't reach the adequate range (2–5 mmol/l in blood) within 2 weeks after diet initiation and careful calculation, it is important to adjust the diet (ratio) to optimise the diet effect. It is also important to exclude medication, including intravenous (IV) fluid, that may contain significant amounts of glucose or other carbohydrates.

6.5. *Weaning*

To stimulate oral motor activity and to avoid feeding aversion behaviour, solid foods may be introduced at age of 4–6 months (sometimes at 9 months in the event of developmental delay).

Combining ketogenic formula with solid food is possible while maintaining the classical diet. Recipes can be calculated based on the original diet ratio (3:1). This will be suitable for most infants (for example vegetable or fruit purees mixed with oil/margarine or fruit with double cream). At the age of 9–12 months when more carbohydrate containing foods are introduced (such as bread, potatoes) a more liberal KD version with a low-dose of MCT is also possible and well tolerated. The amount of MCT is mixed with a (low fat) milk product and gradually increased.

The full MCT KD (50–60% energy MCT) allows a generous amount of protein and carbohydrates, but is not recommended as it is poorly tolerated in infancy.

7. Diet during emergency situations

The increased risk of hyperketosis should be considered during intercurrent illness. This is caused by reduced energy and carbohydrate intake in combination with elevated metabolism due to illness. Frequent testing of ketosis/blood glucose with use of additional carbohydrate as needed (additional Oral Rehydration Salt (ORS), glucose solution) is then required.

In calculating the allowed quantity of ORS/24 h, the carbohydrate level of the individual KD will initially be assumed. This is a deciding factor for the dosage and use of ORS during periods of illness. When the child recovers the KD formula and/or solid foods may be reintroduced gradually.

In a child established on the KD who needs to be nil by mouth and requires hydration intravenously for this or other reasons, solutions containing glucose should be avoided; 0.45% or 0.9% saline of Ringers-lactate should be utilized. Frequent testing of ketosis/blood glucose is required.

If a child has an enteral feeding tube or PEG and is thought to be absorbing, then a liquid KD diet can be utilized as tolerated. Care needs to be given to avoid aspiration. An enteral tube feed can also be utilized in status epilepticus that has failed first and second line therapy.[54]

8. Evaluation and discontinuation

The overall aim of treatment is to reduce, if not control, epileptic seizures. To monitor this, it is important for seizures to be documented in a form of a diary. Further secondary gains may be aimed for such as reduction of AEDs, as well as increased alertness and attention, although neither of these gains can be predicted.

The aim of the treatment in case of infantile spasms (IS) varies according to the course of the disease. This is the most common seizure type in the first year of life. When the KD is used in IS as first, second or third line treatment, the aim remains to achieve seizure freedom. After one month on KD, a

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Table 6A – Advised clinical monitoring during follow up.

Assessment of KD efficacy by seizure diary and medication review, also any other observed benefits	Every follow up visit.
Assessment of KD tolerance and side effects including questions about bowel function, sleep, behaviour and appetite	Every follow up visit.
Weight, height and head circumference	Every follow up visit
Blood and urine testing	As detailed in Table 6B. Tests should be repeated more frequently if show abnormal results or there are other concerns
Renal ultrasound	After 12 months on the KD. As an extra test if clinically indicated by haematuria in 3 consecutive tests or if an infant shows unexplained irritability (at baseline and during KD).
EEG	When clinically indicated.
ECG	At baseline and if clinically indicated.
Dual Energy X-ray Absorptiometry (DEXA)	Due to the limited reference data for this young age group, routine monitoring with DEXA scans is not recommended in infants

Table 6B – Advised biochemical monitoring during follow up.

Investigation	Frequency of monitoring
Essential:	
Blood:	6 weeks, 3 months, 6 months, then every 6 months
Full blood count	
Renal profile (includes sodium, potassium, urea, creatinine, bicarbonate and albumin)	6 weeks, 3 months, 6 months, then every 6 months
Liver profile	6 weeks, 3 months, 6 months, then every 6 months
Calcium, phosphate, magnesium	6 weeks, 3 months, 6 months, then every 6 months
Glucose	6 weeks, 3 months, 6 months, then every 6 months
Vitamin D	after 3 months, 6 months, then every 6 months
Lipid profile (repeat with fasting if elevated)	after 3 months, 6 months, then every 6 months
Free and acylcarnitine profile	after 3 months, 6 months, then every 6 months
Urine:	6 weeks, 3 months, 6 months, then every 6 months
calcium: creatinine ratio, haematuria	
Recommended:	
Blood:	
Vitamins A, E, B12	6 months, then every 12 months
Zinc, selenium, copper	6 months, then every 12 months
Folate, ferritin	6 months, then every 12 months

child neurologist should then evaluate the patient to discuss the use of an AED in addition to KD.[9] When the KD is used in resistant IS, the overall aims are similar to the other drug resistant epilepsy syndromes (seizure reduction as well as the reduction of AEDs).

A cognitive or psychomotor improvement is frequently observed. This has been reported by several studies using the KD in infants.[4,7,9] This outcome requires further evaluation in the future. The current data are limited by uncontrolled studies with small sample size. The data on cognitive improvement are based on the report of the parents during the clinics or with a questionnaire. The use of validated scales of neurodevelopment or standardized tests that can be repeated to evaluate alertness or attention would permit better assessment in future studies.

8.1. *Evaluation period*

A formal evaluation of the effectiveness of the KD should be made by the ketogenic team (including neurologist and dietitian) in discussion with the family at any time dependent on the severity of the epilepsy and number of other treatment options that have previously been tried. Consideration should also be given to tolerance and the parent or caregiver's ability to comply fully with the dietary restrictions.

There is only one study reporting when the seizures improve in responding patients on the KD.[55] This retrospective study evaluated the time to seizure reduction in 118 epilepsy patients who started on the KD of whom 84% had a seizure reduction. The first sign of improvement was observed after a mean time of 5 days (1–65 days). Seventy-five percent had improvement within the first 14 days of the diet and 90% within 23 days.[55]

Recommendations: the KD should be maintained for 2–3 months to undoubtedly evaluate efficacy. During this time a degree of fine tuning to the diet may have been required. As mentioned, the delay to control seizures has been described as a prognostic factor in IS. The patient with IS treated by KD as first, second or third treatment (aim of treatment is still seizure freedom) should be evaluated by the child neurologist after one month of KD to consider an additional treatment.

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8.2. Discontinuation

The KD is usually continued for at least 2 years in children who have seen effective seizure control. There is evidence that seizure control can be maintained after a return to a normal diet in children who have a positive response to diet therapy.[56] Children with GLUT 1 deficiency and PDHC deficiency do not usually discontinue the KD as this will be treating the underlying metabolic defect. However, there is evidence that they may tolerate a reduced ratio (with increased carbohydrate intake) in a longer term. In the case of IS, a study randomizing the seizure-free patients to either discontinue the diet in the short-term (8 months) or long term (2 years) showed no difference in the rate of seizure relapse between the two groups.[57] Considering the possible occurrence of side effects including growth consequences, a shorter duration of KD in IS might be considered. Further studies are required to confirm or refute this.

Weaning from KD back on to normal diet should be done gradually using a step-wise approach over weeks or months. The longer a child has been on KD the longer the period of withdrawal advised; if seizure-free the process may take 3–4 months. The ketogenic ratio will be slowly reduced, e.g. by 0.25, 0.5 or 1.0 every few days, weeks, or more slowly, e.g. every month. However, if there has been no benefit from the diet a full wean within 2 weeks is possible, especially in the young infant who needs to move quickly to the next treatment option. Ketone levels can be monitored during this time and once they are no longer present in blood or urine tests the transition to normal diet can be made more quickly. This process can be an anxious time for parents or caregivers who may need reassurance and support. If at any point there is deterioration in seizure control the child can go back to the last ratio used. Concentrated sources of refined carbohydrate should only be reintroduced cautiously once the child is fully established on a normal diet without ill effects.

9. Conclusions and remarks for future research

These guidelines represent the first international effort to identify commonalities in the clinical use of the KD in infants. All members of the project and review group agreed on most of the major issues in both choosing the best candidates for the KD, pre-diet counselling, supplementation, and the management of children on the KD in regards to nutrition, laboratory values, potential adverse effects, and eventual discontinuation. Areas of variability included choice of initial diet ratio, how to initiate the KD and how to design the nutritional composition of the KD to reach adequate ketosis, with respect to the specific requirements of the infant.

The creation of these recommendations for use in infants encourages safe and effective implementation of the KD in this vulnerable group of patients.

Future research should focus on effects of seizure reduction in specific underlying conditions, how to minimize adverse effects to prevent discontinuation and how to optimize growth of the infant.

Disclosure

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Conflict of interest statement

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Appendix I

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejpn.2016.07.009.

REFERENCES

1. Neal EG, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol* 2008;**7**(6):500–6.
2. Kossoff EH, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia* 2009;**50**(2):304–17.
3. Wilmshurst JM, et al. Treatment of infants with epilepsy: common practices around the world. *Epilepsia* 2015;**56**(7):1033–46.
4. Nordli Jr DR, et al. Experience with the ketogenic diet in infants. *Pediatrics* 2001;**108**(1):129–33.
5. Dressler A, et al. The ketogenic diet in infants – advantages of early use. *Epilepsy Res* 2015;**116**:53–8.
6. Eun SH, et al. Ketogenic diet for treatment of infantile spasms. *Brain Dev* 2006;**28**(9):566–71.
7. Pires ME, et al. Ketogenic diet for infantile spasms refractory to first-line treatments: an open prospective study. *Epilepsy Res* 2013;**105**(1–2):189–94.
8. Kayyali HR, et al. Ketogenic diet efficacy in the treatment of intractable epileptic spasms. *Pediatr Neurol* 2014;**50**(3):224–7.
9. Hong AM, et al. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. *Epilepsia* 2010;**51**(8):1403–7.
10. Ishii M, et al. The ketogenic diet as an effective treatment for Ohtahara syndrome. *No To Hattatsu* 2011;**43**(1):47–50.
11. Sivaraju A, et al. Substantial and sustained seizure reduction with ketogenic diet in a patient with Ohtahara syndrome. *Epilepsy Behav Case Rep* 2015;**3**:43–5.
12. Caraballo R, Noli D, Cachia P. Epilepsy of infancy with migrating focal seizures: three patients treated with the ketogenic diet. *Epileptic Disord* 2015;**17**(2):194–7.
13. Klepper J. GLUT1 deficiency syndrome in clinical practice. *Epilepsy Res* 2012;**100**(3):272–7.
14. Prasad C, Rupar T, Prasad AN. Pyruvate dehydrogenase deficiency and epilepsy. *Brain Dev* 2011;**33**(10):856–65.
15. Raju KN, et al. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. *Epilepsy Res* 2011;**96**(1–2):96–100.
16. Peterson SJ, et al. Changes in growth and seizure reduction in children on the ketogenic diet as a treatment for intractable epilepsy. *J Am Diet Assoc* 2005;**105**(5):718–25.
17. Bertoli S, et al. Evaluation of nutritional status in children with refractory epilepsy. *Nutr J* 2006;**5**:14.
18. Vining EP, et al. Growth of children on the ketogenic diet. *Dev Med Child Neurol* 2002;**44**(12):796–802.
19. WHO. *Protein and amino acid requirements in human nutrition.* Geneva Switzerland: World Health Organization; 2007. p. 235.
20. *Dietary protein quality evaluation in human nutrition, in Food and Nutrition Papers.* Rome Italia: FAO; 2013. p. 66.
21. Homer C. Nutrition management of seizure disorders. In: Nevin- Folino NL, editor. *Pediatric manual of clinical dietetics.* Chicago: American Dietetic Association; 2003. p. 423–49.
22. Christodoulides SS, et al. The effect of the classical and medium chain triglyceride ketogenic diet on vitamin and mineral levels. *J Hum Nutr Diet* 2012;**25**(1):16–26.
23. Papandreou D, et al. The ketogenic diet in children with epilepsy. *Br J Nutr* 2006;**95**(1):5–13.
24. Kang HC, et al. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia* 2004;**45**(9):1116–23.
25. Takeoka M, et al. Concomitant treatment with topiramate and ketogenic diet in pediatric epilepsy. *Epilepsia* 2002;**43**(9):1072–5.
26. Schwartz RM, Boyes S, Aynsley-Green A. Metabolic effects of three ketogenic diets in the treatment of severe epilepsy. *Dev Med Child Neurol* 1989;**31**(2):152–60.
27. Kang HC, Kim HD, Kim DW. Short-term trial of a liquid ketogenic milk to infants with West syndrome. *Brain Dev* 2006;**28**(1):67.
28. Groesbeck DK, Bluml RM, Kossoff EH. Long-term use of the ketogenic diet in the treatment of epilepsy. *Dev Med Child Neurol* 2006;**48**(12):978–81.
29. Groleau V, et al. Long-term impact of the ketogenic diet on growth and resting energy expenditure in children with intractable epilepsy. *Dev Med Child Neurol* 2014;**56**(9):898–904.
30. Patel A, et al. Long-term outcomes of children treated with the ketogenic diet in the past. *Epilepsia* 2010;**51**(7):1277–82.

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31. Neal EG, et al. Growth of children on classical and medium-chain triglyceride ketogenic diets. *Pediatrics* 2008;**122**(2):e334–40.
32. Nation J, et al. Linear growth of children on a ketogenic diet: does the protein-to-energy ratio matter? *J Child Neurol* 2014;**29**(11):1496–501.
33. Bergqvist AG, Schall JI, Stallings VA. Vitamin D status in children with intractable epilepsy, and impact of the ketogenic diet. *Epilepsia* 2007;**48**(1):66–71.
34. Bergqvist AG, et al. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. *Am J Clin Nutr* 2008;**88**(6):1678–84.
35. Bergqvist AG, et al. Selenium deficiency associated with cardiomyopathy: a complication of the ketogenic diet. *Epilepsia* 2003;**44**(4):618–20.
36. Bank IM, et al. Sudden cardiac death in association with the ketogenic diet. *Pediatr Neurol* 2008;**39**(6):429–31.
37. Willmott NS, Bryan RA. Case report: scurvy in an epileptic child on a ketogenic diet with oral complications. *Eur Arch Paediatr Dent* 2008;**9**(3):148–52.
38. Berry-Kravis E, et al. Carnitine levels and the ketogenic diet. *Epilepsia* 2001;**42**(11):1445–51.
39. Kwiterovich Jr PO, et al. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. *JAMA* 2003;**290**(7):912–20.
40. Nizamuddin J, et al. Management and risk factors for dyslipidemia with the ketogenic diet. *J Child Neurol* 2008;**23**(7):758–61.
41. Coppola G, et al. The impact of the ketogenic diet on arterial morphology and endothelial function in children and young adults with epilepsy: a case-control study. *Seizure* 2014;**23**(4):260–5.
42. Kapetanakis M, et al. Effects of ketogenic diet on vascular function. *Eur J Paediatr Neurol* 2014;**18**(4):489–94.
43. Furth SL, et al. Risk factors for urolithiasis in children on the ketogenic diet. *Pediatr Nephrol* 2000;**15**(1–2):125–8.
44. Kielb S, et al. Nephrolithiasis associated with the ketogenic diet. *J Urol* 2000;**164**(2):464–6.
45. Herzberg GZ, et al. Urolithiasis associated with the ketogenic diet. *J Pediatr* 1990;**117**(5):743–5.
46. Paul E, et al. Urolithiasis on the ketogenic diet with concurrent topiramate or zonisamide therapy. *Epilepsy Res* 2010;**90**(1–2):151–6.
47. McNally MA, et al. Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. *Pediatrics* 2009;**124**(2):e300–4.
48. Berry-Kravis E, et al. Bruising and the ketogenic diet: evidence for diet-induced changes in platelet function. *Ann Neurol* 2001;**49**(1):98–103.
49. Best TH, et al. Cardiac complications in pediatric patients on the ketogenic diet. *Neurology* 2000;**54**(12):2328–30.
50. Stewart WA, Gordon K, Camfield P. Acute pancreatitis causing death in a child on the ketogenic diet. *J Child Neurol* 2001;**16**(9):682.
51. Goyens P, et al. Pitfalls of ketogenic diet in a neonate. *Pediatrics* 2002;**109**(6):1185–6. author reply 1185-6.
52. Kossoff EH, et al. A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. *Epilepsia* 2008;**49**(9):1504–9.
53. Numis AL, et al. The relationship of ketosis and growth to the efficacy of the ketogenic diet in infantile spasms. *Epilepsy Res* 2011;**96**(1–2):172–5.
54. Kossoff EH, Nabbout R. Use of dietary therapy for status epilepticus. *J Child Neurol* 2013;**28**(8):1049–51.
55. Kossoff EH, et al. When do seizures usually improve with the ketogenic diet? *Epilepsia* 2008;**49**(2):329–33.
56. Martinez CC, Pyzik PL, Kossoff EH. Discontinuing the ketogenic diet in seizure-free children: recurrence and risk factors. *Epilepsia* 2007;**48**(1):187–90.
57. Kang HC, et al. Comparison of short- versus long-term ketogenic diet for intractable infantile spasms. *Epilepsia* 2011;**52**(4):781–7.

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