NUTRICIA

KETOGENIC DIET GUIDELINES

for infants with refractory epilepsy

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"Generally, the ketogenic regimen is not helpful in very young children, particularly those under one year of age"
Samuel Livingston MD. Living with Epileptic Seizures, 1963.

"Children under the age of one year have trouble becoming ketotic and maintaining ketosis. They are also prone to hypoglycemia. Therefore, the diet is not normally advised for children under one year old."
John Freeman MD, et al. The Epilepsy Diet Treatment (1st edition), 1994.

"The ketogenic diet should be considered safe and effective treatment for infants with intractable seizures."
Doug Nordli, et al. Pediatrics, 2001

"The ketogenic diet is highly effective and well tolerated in infants with epilepsy. Seizure freedom is more often achieved and maintained in infants."
Anastasia Dressler MD, et al. Epilepsy Research, 2015.

We have come a long way. Paralleling the gradual acceptance and popularity of dietary therapies for epilepsy worldwide since the mid-1990s, the recognition that ketogenic diets can be successful in infancy is more striking and rapid. At Johns Hopkins Hospital, approximately 20 years ago, parents of infants with epilepsy were discouraged from using the ketogenic diet. Now nearly 1 in 3 started here on the ketogenic diet is under 1 year of age. What has led to this remarkable change in practice?

First, there has been a realization that not only can infants maintain ketosis, but they can do it better than their older counterparts. Hypoglycemia is real, but manageable. We no longer need to be afraid of complications and failure when using the diets in babies. Second, the widespread availability of ketogenic formulas has helped dietitians readily (and relatively easily) change infants' nutrition. In many ways, infants are now the most compliant population for dietary therapies. Lastly, exciting new research has shown that the ketogenic diet is highly successful for epilepsies specifically affecting infants: Dravet syndrome, infantile spasms, tuberous sclerosis complex, migrating focal seizures, and many more. Considering the relative lack of good medication options in this age group, the diet is an attractive therapy.

These well-written, thoughtful set of guidelines for infants with refractory epilepsy utilizing ketogenic diets continues to advance this field. It includes epilepsy indications for neurologists to consider diets, as well as nutritional recommendations for dietitians to follow. There are several very helpful tables to guide nutrition and laboratory monitoring in this at-risk young population. This should truly be a "go-to" guide for any ketogenic diet team considering the ketogenic diet for infants. I sincerely also hope it will be used to standardize care between ketogenic diet centers, especially in the design of prospective trials of dietary therapy for infants in the future. Congratulations to the authors on their fine work which will help improve the care of infants with epilepsy for years to come!

Eric Kossoff MD, Johns Hopkins Hospital, Baltimore, USA. – December 2015.

INTRODUCTION

The ketogenic diet is a high fat low carbohydrate diet designed to mimic the metabolic effects of starvation. It has been used in the treatment of therapy resistant epilepsy for almost one hundred years. There has only recently however been definitive class 1 evidence that it is effective for children 2-16 years of age. Case series suggest that the diet may be particularly useful in the infant population (< 2 years) but to date no RCT has been conducted. This aside there are few data on use of antiepileptic medication in this age group, particularly second or third line where first line has failed and this is where the ketogenic diet may be particularly helpful. Further there are certain metabolic disorders that may be diagnosed early in the first year of life where the ketogenic diet is the treatment of choice. Infants are a vulnerable population with specific nutritional requirements. It is therefore imperative that consensus is reached with regard to guidance on how the diet should be administered and in whom. This protocol aims to set out optimal practice that can be utilised and followed in the care of an infant being treated with a ketogenic diet.

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1 BACKGROUND INFORMATION

1. BACKGROUND INFORMATION.

The ketogenic diet (KD) is a non-pharmacologic treatment for children with drug resistant epilepsy. The efficacy of KD has been established by several multicentre studies and one randomized controlled trial. The randomized trial that further established the efficacy of KD has been conducted in children and adolescents aged 2 to 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) because this is such a crucial period in development and the risk of nutritional inadequacies was considered too great. This was based on the immaturity of lipase activity, liver function and lipid metabolism and the difficulty to achieve and maintain ketosis. Moreover, the possible long-term adverse effects are unknown. A KD infant formula is now available making the diet easier to administer in this group.

KD is usually used in infants with refractory epilepsy syndromes. Nordli et al. first reported their retrospective experience with treating 32 children under age 2 years with the KD. They concluded that the KD was efficacious in infantile refractory epilepsy as well as safe to use in infants [4]. The use of KD in infants has been increasingly reported in recent years allowing better appreciation of the efficacy and the safety of this non-pharmacological treatment in this age group. Particular attention should be given to growth parameters as well as the risk of kidney stones that might be higher than in older children [5]. There are several specific epilepsy syndromes in which the KD could be used earlier (Table 1). Some of them have already been reported in the previous consensus for the use of KD in children [2]. Among infant epilepsy syndromes, use of the KD is more established for infantile spasms (West syndrome) with more than 200 treated patients reported by open label studies. There are also other conditions for which the KD is the treatment of choice such as glucose transporter type 1 (GLUT-1) deficiency and pyruvate dehydrogenase complex (PDHC) deficiency syndromes.

A few years ago, the KD was reserved as a "last treatment option" for refractory epilepsy. Given the low level of chance for control to be gained by a new antiepileptic drug (AED) after more than three AEDs as well as the efficacy of KD, the KD was used earlier in the management of difficult-to-treat epilepsy [2].

Table 1: Epilepsy syndromes in infants.

(1) West Syndrome (Infantile spasms)
(2) Ohtahara syndrome
(3) Epilepsy of infancy with migrating focal seizures
(4) Refractory epilepsy with focal seizures
(5) Refractory unclassified epilepsy syndrome (after exclusion of contra-indication)

2 PRESENTATION

2.1. Infantile Spasms

2.2. Ohtahara Syndrome

2.3. Epilepsy with migrating focal seizures

2. PRESENTATION.

2.1. Infantile spasms or West syndrome.

West syndrome or infantile spasms (IS) is one of the most frequently encountered clinical presentations of epilepsy in the first year of life, although the overall incidence is relatively low (1 in 2,000). West syndrome is characterized by the association of epileptic spasms, psychomotor regression, and a specific electroencephalogram (EEG) pattern called hypsarrhythmia [6]. IS result from a whole range of causes comprising focal or multifocal, pre-, peri- or postnatal brain damage or malformation, genetic mutation, or an apparent lack of any underlying cause. This syndrome remains one of the most severe in infancy because of its association with profound developmental implications as well as high risk of later epilepsy. Children presenting with IS have a high risk of developing cognitive deterioration, which may be associated with a persistence of epilepsy in the majority of cases. Early and aggressive anticonvulsant treatment is warranted, since early control of the infantile spasms seems to be associated with a higher chance of better cognitive outcome. In this respect, both seizure control and long-term cognitive outcome should be considered as major outcome parameters in any study on IS.

There is no clear evidence for the best treatment. Hormonal therapies in the form of oral steroids or ACTH have been used as a standard treatment. High-dose vigabatrin seems to be more useful in IS associated with the tuberous sclerosis complex. Comparative studies show that spasms respond better and faster with hormonal treatment, although vigabatrin is better tolerated [7].

The effect of these therapies on long-term outcome is not clear. The KD has become a second line treatment [8-10]. It use as a first line treatment has been also reported [11].

2.2. Ohtahara syndrome.

This is one of the rare, but severe encephalopathic forms of epilepsy affecting neonates [12]. This syndrome is also called early infantile epileptic encephalopathy (EIEE) with suppression burst. The clinical distinctive feature of this syndrome is frequent tonic spasms that occur in isolation or clusters both in waking and sleeping states with onset in the first 3 months of life. Other seizure types can be also observed. The EEG pattern is distinctive, called suppression-burst, consisting of high-voltage bursts of multifocal spikes interspersed with prolonged periods of relative voltage attenuation. This EEG pattern is shared with another rare neonatal epilepsy syndrome: Early myoclonic encephalopathy (EME). EME seizure features consist of severe recurrent myoclonic seizures but focal seizures and even tonic spasms can be observed. EIEE is thought largely to be related to structural brain abnormalities while EME is associated with metabolic disorders (including nonketotic hyperglycinemia, propionic aciduria, methylmalonic acidemia, D-glyceric acidemia, sulphite and xanthine oxidase deficiency, Menkes disease, and Zellweger syndrome). Since these syndromes are usually highly pharmacoresistant, the use of KD can be considered but very few reports are available [13, 14].

2.3. Epilepsy of infancy with migrating seizures.

The seizure onset in this syndrome is usually observed in the first six months of life with the occurrence of almost continuous migrating polymorphous focal seizures, combined with multifocal ictal EEG discharges [15]. Unfortunately, the seizures are markedly drug-resistant. A progressive deterioration in psychomotor development is observed. Because of the epileptic and developmental outcome, the use of KD is naturally considered but only few reports are currently available [16].

3

CHOICE OF KETOGENIC DIET PROTOCOL IN INFANTS

3. CHOICE OF KETOGENIC DIET PROTOCOL IN INFANTS.

The KD is a high fat (71-90 % energy) and carbohydrate restricted (5-19 % energy) diet that contains adequate amount of protein to support growth.

There are two main versions of the traditional KD:

- **Classical KD:**

  Consists of 85-90 % energy from fat, mainly long chain triglycerides (LCT).

  Protein and carbohydrates combined provide a total of 10 %-15% of energy.

  The classical KD is implemented using a ratio system. Ratio means grams fat: grams (protein + carbohydrates). A ketogenic ratio of 3:1 or 4:1 is usually used in infants.

  This version of the KD is well tolerated by infants.

- **Ketogenic diet with medium chain triglycerides (MCT)**

  Consists of 71-75 % energy from fat, of which 50-60 % energy is from MCT and 11-25 % energy is from LCT. This version of the KD provides more protein (10 % energy) and carbohydrates (15-19 % energy). This version is not generally used in infants who have poor tolerance of high amounts of MCT.

More liberal versions of the traditional KD are the Modified Atkins diet, (10-30 grams of carbohydrates, free fat and protein intake) and the Low Glycemic Index Diet (60 % energy from fat, 30 % energy from protein and 40-60 grams of carbohydrates with a glycemic index of 50 or lower). These kinds of diets are not suitable for the infant based on the high amount of protein and need for strict control.

Based on evidence:

Prospective studies

1. Pires M, Auvin S. (2013): 17 infants , mean age 9.4 months used both 3:1 and 4:1 ratio KD. KD was well tolerated, all patients were hospitalized [9].
2. Kayyali H et al (2014): 20 infants, age range 0.3-2.9 years used 3-3.5: 1 ratio KD. Side effects were seen but no dietary adjustments were needed [10].
3. Hong A et al (2010): 104 infants, mean age 1.2 years used a 3-3.5: 1 ratio KD. Adverse effects were reported in 34 (33%) infants [11].

Retrospective studies

1. Eun SH et al (2006): 43 infants, age range 6-42 months used a 4:1 ratio KD (some were on a 3:1 to meet protein requirements). Most complications were transient and KD was well tolerated in most cases [8].
2. Dressler A et al (2015): 58 infants (< 18 months), age range 0.15-1.5 years (0.68 ± 0.45), (including 42 < 9 months) 3: 1 ratio modified on an individual basis to 2.5 (2.91 ± 0.38) when ketone bodies were high [18].

Based on best practice :

- Most centres use a classical 3:1 ratio diet in infants in order to meet protein requirements.
- Based on level of ketosis and/or tolerance the ratio may be increased up to 3.5 or 4:1 or decreased to 2.5 or 2:1.

RECOMMENDATION for the type of diet and ratio:

Most centres use the classical version of the KD with a 3:1 ratio in infants.

Based on level of ketosis and tolerance the diet can be adjusted to a lower ratio (2.5 or 2:1) or higher ratio (3.5 or 4:1). The KD formula Ketocal®3:1 is specially developed for infants and (young) children to meet the nutritional requirements. Ketocal 3:1® is based on the Classical KD and well tolerated by infants. If using breastmilk it is recommended to start combined use with Ketocal 3:1®. Using Ketocal 4:1® may not fully match with requirements and careful calculation on an individual basis is highly recommended. When calculated carefully the protein and vitamins/mineral requirement of the infant can be supplied.

4

PREPARING FOR DIETARY TREATMENT

4. PREPARING FOR TREATMENT.

Treatment with the KD is demanding on 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/paediatrician, epilepsy nurse, dietitian and close cooperation with pharmacy).
The aim of the treatment is to reduce epileptic seizures in refractory epilepsy.

Objectives of the dietary treatment:

- to achieve seizure reduction
- to prevent insufficient energy intake or deficiencies of macro- and micro nutrients with an optimally age-adjusted dietary prescription
- to achieve adequate growth based on an individual growth curve
- to limit/prevent adverse effects and complications due to the KD
- to achieve an age dependent feeding pattern and development

Before proceeding to dietary intervention, verification is needed as to the suitability of the KD as a treatment option for an individual patient. During an informative discussion, the dietitian provides the parents / caregivers with information about the dietary treatment, the possibilities and practicalities of the KD and risks of short and long term adverse effects. During the discussion, the dietitian reviews expectations of the dietary treatment, financial considerations, the dietary patterns, social circumstances and the practical and technical skills for applying the KD [19-21].

The treating physicians rule out medical disorders that are contraindicated with the diet. Based on these data, the multidisciplinary team assesses the suitability of the dietary treatment [2, 22].

Important issues in deciding on treatment with a KD:

- Proper medical indication (therapy-resistant epilepsy, GLUT-1 deficiency, PDHC deficiency)
- Absence of medical contra-indications
- Motivation of parent / caregivers
- Realistic picture of the treatment
    - expectations of effectiveness
    - the 'burdens' involved in the treatment, and limited flexibility of the diet
    - potential adverse effects of the diet
    - social implications of the treatment
    - follow-up with frequent contacts with the multidisciplinary team
- Age of the patient, developmental level
- Food patterns and possibility / acceptance of changing them
- Feeding method (oral or enteral feeding i.e by tube or PEG)

After a positive decision a tailor made KD will be designed.

If the patient is considered for treatment, the dietitian reviews the medical, nursing and psychosocial data during the diagnostic process.

4.1 Medical history

The (paediatric) neurologist determines the indication for the KD. This requires accurate information about the type of epileptic seizures, the seizure frequency and the syndrome classification. The paediatrician rules out, together with specialists if necessary, medical disorders that are contraindicated with the KD, which include several metabolic disorders, severe liver function disorders and certain cardiovascular diseases. This requires an accurate history, clinical study and additional blood and urine tests.

If there is a possibility of food allergy, the paediatrician will request additional tests. The following data are important:

- History:
  Information on history of epilepsy treatment.
- Epilepsy:
  ILAE classification of the epilepsy (syndrome and/or seizure types with or without aetiology) is required and an overview of all used AEDs including dosage and effect on seizure reduction and side effects.
- Metabolic screening:
  Verify if metabolic check up has been done (see table 2 contra indications).
- Physical examination.
- Growth:
  Evaluation of growth curves for weight for age, height for age and head circumference.
- Nutrition:
  Assess for presence of food allergies or feeding problems and consider how these can be overcome with KD using an exclusion diet, enteral feeding.
- Neurodevelopment:
  Evaluate level of development / PMR.
- Social data:
  - fully or partially institutionalised
  - home situation (family composition and social situation)
  - expected compliance (parental or caregiver)
  - educational level of parents / caregivers, language and mathematical skills
  - ability to work with a computer and/or availability of a computer at home
- Medical: *screening for presence of any deficiencies, family history of renal stones, prolonged QT-time or cardiomyopathy (see table 2 contra indications)*

Table 2: Indications/contra-indications for ketogenic diet in infants.

Indications for KD treatment

Epilepsy:

- Refractory epilepsy after use of 2 AEDs:
    - i.e. West syndrome
    - Ohtahara syndrome
- Adverse effects of AEDs
- Waiting for epilepsy surgery

Metabolic diseases:

- GLUT-1 deficiency
- PDHC deficiency
- optional: Mitochondrial diseases

Contra-indications for KD treatment

Absolute:

- 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

Relative

- Inability to maintain adequate nutrition
- Surgical focus identified by neuroimaging and video EEG monitoring
- Parent or caregiver noncompliance
- Growth retardation
- Severe gastrointestinal reflux

Table 3: Recommended baseline biochemical monitoring of infants on the ketogenic diet.

Investigation (baseline)	
Essential	**Recommended**
Blood: Full blood count	**Blood:** 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	

4.2. Epilepsy treatment.

The pediatric neurologist or epilepsy nurse collects detailled information on:

- AED use; current and past history of type, dosage, and side effects
- seizure type and frequency
- incidence of clustered seizures (and use of any emergency medication)
- compliance
- carbohydrate content of current AEDs and advice on ketoproof medication (in liaison with pharmacist)

4.3. Dietary information and nutritional status

Prior to the initiation of the KD, parents / caregivers are asked to keep a three-day food diary which is used to base calculations of average energy intake. The food diary / dietary history also provides information about the daily fluid intake, feeding method (oral or a enteral feeding tube), food consistency, food preferences and eating pattern. Food-related complaints (constipation, diarrhoea, vomiting), swallowing, chewing, and stomach emptying problems as well as the possibility of food allergy are also identified (information will be age dependent).

Nutritional status

The dietitian reaches a quantitative and qualitative assessment of the patient's nutritional status and the food patterns (for example, age-adjusted) based on:

- weight/age and/or weight/height. (Standard Deviation Score (SDS)).
- height/age (SDS).
- head circumference (SDS).
- information on growth in the preceding period (growth curves) in which a potential failure to thrive is established.
- history of fluid, energy and protein intakes.
- presence of food allergies.

5 THE KETOGENIC DIET PRESCRIPTION

5. THE KETOGENIC DIET PRESCRIPTION.

In order to achieve an adequate ketosis, an individual KD prescription is calculated, taking into account as much as possible the infants feeding pattern and preferences of parents / caregivers. This involves the practical implementation (orally or by enteral feeding tube) of the KD.

The nutritional composition of the KD differs substantially from a normal eating pattern. Examples of KD for infants are shown in appendices.

The Classical version of KD can be used for both bottle feeding and enteral feeding.

5.1 Energy.

The energy requirements of infants with epilepsy may vary greatly.

It is well known that in children with neurodevelopmental disability resting energy expenditure can be deviated due to deviant body composition [23].

There is no consensus in literature on how to calculate energy requirements in infants below age 6 months (see Table 4a). 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, 24]. Measurement of the assumed basic energy need (for example, using indirect calorimetry) has rarely been described in the application of the KD [25].

For infants with complex problems such as epilepsy possibly combined with psychomotor delay, a calculation of the expected energy requirement based only on the Schofield formula is not very accurate below 10 kg and/or age of 1 year.

The total energy requirement depends on the physical activity that may be influenced by epileptic seizures (and the AED used) and possibly the degree of spasticity or frequency of muscle spasm during epileptic seizures [23, 26].

The recommended daily intakes (RDA) are recommendations for groups of healthy children (see table 4a), making them less suitable for the individual with epilepsy.

Table 4a: Energy requirements in kcal/kg body weight according to various sources.

Age/months	USA[1]		UK [2]		Germany[3]		France[4]		The Netherlands[5]		Italy [6]	
	Mean weight/kg	Kcal/kg	Mean weight/kg	Kcal/kg	Mean weight/kg	Kcal/kg	Mean weight/kg	Kcal/kg	Mean weight/kg	Kcal/kg	Mean weight/kg	Kcal/kg
1.	♂ 6.0 ♀ 5.5	♂ 95 ♀ 95	♂ 5.9 ♀ 5.9	♂ 96- 120 ♀ 96- 120	♂ 4.5 ♀ 4.2	♂ 104 ♀ 100	♂ 3.8 ♀ 3.6	♂ 100 ♀ 98	♂ 4.5 ♀ 4.5	♂ 93 ♀ 93	♂ 4.0 ♀ 3.9	♂ ♀ 115
2.					♂ 5.6 ♀ 5.1	♂ 108 ♀ 104						
3.				♂ 96 ♀ 96	♂ 6.4 ♀ 5.8	♂ 94 ♀ 92	♂ 5.6 ♀ 5.1	♂ 97 ♀ 94	♂ 6.5 ♀ 6.5	♂ 83 ♀ 83	♂ 5.8 ♀ 5.4	♂ ♀ 100
4.	♂ 7.9 ♀ 7.2	♂ 82 ♀ 82	♂ 7.7 ♀ 7.7		♂ 7.0 ♀ 6.4	♂ 79 ♀ 80						
5.				♂ 72 ♀ 72	♂ 7.5 ♀ 6.9							
6.					♂ 7.9 ♀ 7.3	♂ 78 ♀ 79	♂ 7.5 ♀ 7.0	♂ 88 ♀ 89	♂ 8.5 ♀ 8.5	♂ 83 ♀ 83	♂ 7.9 ♀ 7.3	♂ 78 ♀ 79
7.	♂ 9.3 ♀ 8.5	♂ 80 ♀ 80	♂ 8.9 ♀ 8.9	♂ 72 ♀ 72	♂ 8.3 ♀ 7.6	♂ 77 ♀ 75					♂ 8.3 ♀ 7.6	♂ 77 ♀ 79
8.					♂ 8.6 ♀ 7.9	♂ 77 ♀ 76					♂ 8.6 ♀ 7.9	♂ 77 ♀ 76
9.					♂ 8.9 ♀ 8.2		♂ 8.8 ♀ 8.3	♂ 89 ♀ 89			♂ 8.9 ♀ 8.2	♂ 77 ♀ 76
10.	♂ 10.3 ♀ 9.5	♂ 82 ♀ 80	♂ 9.8 ♀ 9.8		♂ 9.2 ♀ 8.5	♂ 79 ♀ 77					♂ 9.2 ♀ 8.5	♂ 79 ♀ 77
11.					♂ 9.4 ♀ 8.7						♂ 9.4 ♀ 8.7	♂ 79 ♀ 77
12.					♂ 9.6 ♀ 8.9	♂ 79 ♀ 78	♂ 9.9 ♀ 9.4	♂ 97 ♀ 96			♂ 9.6 ♀ 9.9	♂ 79 ♀ 78

[1] National Academies Press, Dietary Refernce intakes for energy, carbohydrate, fiber, fat, fattyacids, cholesterol, protein and aminoacids, 2005.
[2] Clinical Paediatric dietetics 4th edition 2015, Vanessa Shaw.
[3] DACH (Deutschland-Osterreich-Schweiz) Referenzwerte für Nährstoffzufuhr, 2015.
[4] Encyclopedié Medicó Chirurgicale 10-308-A-10, C.Potier de Corcy et al. 2010.
[5] Health Councel of the Netherlands.Dietary Refernce intakes; energy, proteins, fats and digestible carbohydrates, 2001-19.
[6] Larn (Recommended daily allowances for Italian population), SINU, 2014.

In summary

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 adequate weight/age or weight/height to be used for adequate diet calculation.

In individual cases resting energy expenditure (REE) can be measured with a ventilated hood 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.

RECOMMENDATION for establishing energy requirements:

Table 4b: Energy requirements for an infant on the KD.

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

5.2 Fat.

The classical KD is based on LCT and works with different ratios. Most infants use the classical KD at a ratio of 3:1. This means that for every 3 grams of fat there is 1 gram of combined protein and carbohydrate. Based on individual tolerance and/or level of ketosis, a different ratio may be used (2:1 – 4:1). Use of MCT in infants will be limited, see section 6.4 on weaning.

5.3 Protein.

The protein requirements of infants with epilepsy are the same as in healthy infants (see table 5a). 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 gram 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 (see table 5a).

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, 27].

Table 5a: Protein requirements based on several sources.

Age/months	USA[1]		UK [2]		Germany[3]		France[4]		The Netherlands[5]		Italy [6]	
	Mean weight/ kg	Protein /g/kg/ day	Mean weight/ kg	Protein /g/kg/ day	Mean weight/ kg	Protein /g/kg/ day	Mean weight/ kg	Protein /g/kg/ day	Mean weight/ kg	Protein /g/kg/ day	Mean weight/ kg	Protein /g/kg/ day
1.	♂ 6.0 ♀ 5.5	♂ ♀ 1.52	♂ 5.9 ♀ 5.9	♂ ♀ 2.10	♂ 4.5 ♀ 4.2	♂ ♀ 2.70	♂ 3.8 ♀ 3.6	-	♂ 4.5 ♀ 4.5	♂ ♀ 1.80	♂ 4.0 ♀ 3.9	♂ ♀ 2.6
2.					♂ 5.6 ♀ 5.1	♂ ♀ 2.00						
3.					♂ 6.4 ♀ 5.8	♂ ♀ 1.50	♂ 5.6 ♀ 5.1	-	♂ 6.5 ♀ 6.5	♂ ♀ 1.40		
4.	♂ 7.9 ♀ 7.2		♂ 7.7 ♀ 7.7	♂ ♀ 1.60	♂ 7.0 ♀ 6.4	♂ ♀ 1.30					♂ 5.8 ♀ 5.4	♂ ♀ 1.7
5.					♂ 7.5 ♀ 6.9							
6.					♂ 7.9 ♀ 7.3	♂ ♀ 1.10	♂ 7.5 ♀ 7.0	♂ ♀ 1.25	♂ 8.5 ♀ 8.5	♂ ♀ 1.20	♂ 7.9 ♀ 7.3	♂ ♀ 1.4
7.	♂ 9.3 ♀ 8.5	♂ ♀ 1.00	♂ 8.9 ♀ 8.9	♂ ♀ 1.50	♂ 8.3 ♀ 7.6							
8.					♂ 8.6 ♀ 7.9							
9.					♂ 8.9 ♀ 8.2		♂ 8.8 ♀ 8.3				♂ 9.1 ♀ 8.4	♂ ♀ 2.09
10.	♂ 10.3 ♀ 9.5		♂ 9.8 ♀ 9.8		♂ 9.2 ♀ 8.5							
11.					♂ 9.4 ♀ 8.7							
12.					♂ 9.6 ♀ 8.9		♂ 9.9 ♀ 9.4				♂ 10 ♀ 9.4	♂ ♀ 1.87

[1] National Academies Press, Dietary Refernce intakes for energy, carbohydrate, fiber, fat, fattyacids, cholesterol, protein and aminoacids, 2005.
[2] Clinical Paediatric dietetics 4th edition 2015, Vanessa Shaw.
[3] DACH (Deutschland-Osterreich-Schweiz) Referenzwerte fr Nährstoffzufuhr. 2015.
[4] Encyclopedié Medicó Chirurgicale 10-308-A-10, C.Potier de Corcy et al, 2010.
[5] Health Councel of the Netherlands.Dietary Refernce intakes; energy, proteins,fats and digestible carbohydrates, 2001-19.
[6] Larn (Recommended daily allowances for Italian population), SINU, 2014.

RECOMMENDATION for establishing protein intake

For infants using the classical KD the protein intakes in Table 5b are advised.

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 adequate weight/age or weight/height to be used for adequate diet calculation.

Aim for the optimal amount of protein (see table 5b column 3).

Check if the amount of protein is above the minimal World Health Organisation (WHO) recommendation (see table 5b, see colum 4).

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

Table 5b: Recommended daily protein intake for an infant on the KD.

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

* Based on average RDA several countries : table 5A
** WHO 2007: safe level for growth +1.96 SD
*** FAO 2011

5.4 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 sweetners 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.

Specific variation lists are used for food containing carbohydrate. The variation lists are not needed when a computer program for the KD is used.

The potential presence of resorbable carbohydrate in medication and supplements should not be overlooked.

The treating physician consults the pharmacist for suitable medication [17, 28].

5.5 Fluid.

In the past, the KD was usually 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, no mechanism has been found that shows that overhydration has a negative effect on epileptic seizures [29]. Moreover, fluid restriction might add to the development of kidney stones so an adequate hydration is required.

Table 6a: Fluid requirements based on several sources.

Age/months	USA[1]		UK[2]		Germany[3]		France[4]		The Netherlands[5]		Italy[6]	
	Mean weight/ kg	Fluid ml/kg/ day	Mean weight/ kg	Fluid ml/kg/ day	Mean weight/ kg	Fluid ml/kg/ day	Mean weight/ kg	Fluid ml/kg/ day	Mean weight/ kg	Fluid ml/kg/ day	Mean weight/ kg	Fluid ml/kg/ day
1.	♂ 6.0 ♀ 5.5	♂ ♀ 700	♂ 5.9 ♀ 5.9	♂ ♀ 150	♂ 4.2 ♀ 4.0	♂ ♀ 130	♂ 3.8 ♀ 3.6	♂ ♀ 150	♂ 4.5 ♀ 4.5	♂ ♀ 150	♂ 4.0 ♀ 3.9	♂ ♀ 130-150
2.					♂ 5.2 ♀ 4.8			♂ ♀ 120				
3.					♂ 6.0 ♀ 5.4		♂ 5.6 ♀ 5.1		♂ 6.5 ♀ 6.5		♂ 5.8 ♀ 5.4	♂ ♀ 105-160
4.	♂ 7.9 ♀ 7.2		♂ 7.7 ♀ 7.7		♂ 6.0 ♀ 5.4	♂ ♀ 110				♂ ♀ 130		
5.					♂ 7.4 ♀ 6.8							
6.					♂ 8.0 ♀ 7.4		♂ 7.5 ♀ 7.0	♂ ♀ 100	♂ 8.5 ♀ 8.5		♂ ♀ 8.6	♂ ♀ 105-155
7.	♂ 9.3 ♀ 8.5	♂ ♀ 800	♂ 8.9 ♀ 8.9	♂ ♀ 120	♂ 8.4 ♀ 7.8					♂ ♀ 120		
8.					♂ 8.8 ♀ 8.2							
9.					♂ 9.2 ♀ 8.6		♂ 8.8 ♀ 8.3				♂ 9.1 ♀ 8.4	♂ ♀ 105-145
10.	♂ 10.3 ♀ 9.5		♂ 9.8 ♀ 9.8		♂ 9.5 ♀ 9.0					♂ ♀ 110		
11.					♂ 9.8 ♀ 9.2							
12.					♂ 10.0 ♀ 9.4		♂ 9.9 ♀ 9.4				♂ 10.0 ♀ 9.4	♂ ♀ 100-125

[1] National Academies Press, Dietary Refernce intakes for energy, carbohydrate, fiber, fat, fattyacids, cholesterol, protein and aminoacids, 2005.
[2] Clinical Paediatric dietetics 4th edition 2015, Vanessa Shaw.
[3] DACH (Deutschland-Osterreich-Schweiz) Referenzwerte für Nährstoffzufuhr, 2008.
[4] Encyclopedié Medicó Chirurgicale 10-308-A-10, C.Potier de Corcy et al, 2010.
[5] Health Councel of the Netherlands.Dietary Refernce intakes; energy, proteins,fats and digestible carbohydrates, 2001-19.
[6] Larn (Recommended daily allowances for Italian population), SINU, 2014.

RECOMMENDATION for establishing fluid intake.

An age and weight adequate fluid intake is advised, 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).

Table 6b. Recommended daily fluid intake for an infant on the KD

Age/months	Weight/kg	kcal/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

5.6 Vitamins, minerals and trace elements.

The classical KD contains insufficient micronutrients [30, 31] . Ketocal 3:1 is fully supplemented based on the infants requirements. Ketocal 4:1 may be used when calculated carefully on an individual level.

The potential presence of absorbable / resorb-able carbohydrate in vitamin/mineral supplements 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 [29].

RECOMMENDATION for establishing adequate vitamins, minerals and trace elements.

By means of adequate supplemention, 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 less than 80% of energy requirements).

6 TREATMENT PHASE

6. TREATMENT PHASE.

6.1.Diet initiation.

6.1.1 Methods.

The KD is usually initiated in infants during an admission of at least 3-5 days in an academic hospital or epilepsy centre. In older infants initiation at home may be possible with close communication and support of the KD team after thorough education of parents/caregivers. This includes teaching on how to monitor ketone and glucose levels at home.

The pediatric neurologist or epilepsy nurse informs the general practitioner and/or paediatrician that the patient has started KD.

There is no evidence that fasting is required at the onset of the KD. Studies have established that fasting prior to the diet intervention had no significant influence on the effectiveness of the KD [32-34]. Without a prior fasting period, short term KD complications such as dehydration and hypoglycaemia appear to occur less frequently [35].

Based on (inter)national guidelines:

In the international consensus statement [2] only diet initiation based on increased ratios from 1:1, 2:1, 3:1 and 4:1 is mentioned in general. No specific advice for infants is given.

The recent guideline by Kossoff et al 2015 [22] advises infants should be admitted to hospital for diet initiation.

Based on evidence:

Several studies mention efficacy and safety of KD treatment in infants but detailed information on diet initiation is scarce.

- In the study of Raju et al (2011): 38 children (age 6mnth-5y) were randomized into a group starting 4:1 KD and a group starting 2.5:1 KD by using a non-fasting gradual initiation protocol based on full calories. The KD was built up over a period of 3-4 days by increasing the ratio 1:1, 2:1 etc. [36].
- In the study of Pires et al (2013): 17 infants with IS started 3:1 (some 4:1) KD during hospital admission, by a non-fasting KD protocol based on increasing calorie amount in three days; day one 1/3, day two 2/3 and day three full calories [9].

Based on practice:

Table 7 shows different ways of diet initiation based on daily practice of several international teams.

Table 7: Options for diet initiation in infants *(based on personal communications from experts in different countries).*

	1	2	3	4	5	6	7	8
Steps	3:1 ratio 33 % 66 % 100% of kcal	1:1 ratio 2:1 ratio 3:1 ratio full kcal	1:1 ratio 2:1 ratio 3:1 ratio full kcal	start : 1.0-1.5:1 ratio steps: 0.5-1.0 ratio full kcal	1:1 ratio 2:1 ratio 3:1 ratio full kcal	1:1 ratio 2:1 ratio 3:1 ratio full kcal	1:1 ratio 2:1 ratio 3:1 ratio full kcal	25%-75% (0.4:1) 50%-50% (0.6:1) 70%-30% (0.9:1) 90%-10% (1.4:1) 100% (3.0:1) Mix of ketogenic formula/normal formula and kcal (based on 9.5% solution)
Frequency	daily	daily	daily	daily	Individually made	NICU: every 2 days. Non NICU: daily	individually made	daily
Admission	yes	yes	yes	yes	yes	yes	yes	yes
Diet ratio	3:1	3:1 (2.0-2.5:1 or 3.5-4:1 also)	3:1	3:1 (4:1 also)	3:1	3:1 (4:1 also)	3:1	3:1 (2-2.5:1 or 3.5-4:1 also)

1. France (Auvin), 2. USA (Dority), 3. Poland (Dudzinska), 4. Canada (Williams-Dyjur), 5. Austria (Dressler) 6. USA (Thompson), 7. UK (Neal), 8. Netherlands (Hurk/vdLouw).

RECOMMENDATION for diet initiation.

A young infant (<12 months) should be admitted to hospital for KD initiation. The KD is introduced by an individually designed step by step plan based on full energy intake and without initial fasting.

6.1.2 Monitoring during diet initiation.

Glucose.

There is a risk of hypoglycaemia during diet initiation although uncommon in the absence of a metabolic disease. During admission blood glucose should be checked twice daily (or more based on symptoms of hypoglycemia) and frequency must be adjusted based on tolerance. Glucose levels of 2-2.5 mmol/l (approximately 40mg/dl) should be treated immediately with 2-4 grams of carbohydrates by adding a small amount of breast milk or normal infant formula or glucose 10% solution (young infants < 4 months). Older infants (> 4 months) can be given other sources of rapidly absorbed carbohydrate such as a couple of tablespoons (30-60ml) of pure fruit juice. Infants with blood glucose > 3mmol/l but showing symptoms of hypoglycaemia (see Box 1) should also be treated in the same way. Blood glucose should be re-checked 15-20 minutes after treatment and if not improved, a further dose of breast milk or formula is given (or fruit juice if appropriate).

Box 1. Symptoms of hypoglycaemia in infants Jittery

Poor body tone, lethargy, pallor

Poor feeding

Low body temperature, cold and clammy

Cyanosis

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 Box 2). Ketones can be measured in blood or urine; these methods are compared in Table 8. 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.

Medical advice should always be sought for persistent hypoglycaemia or excess ketosis.

Box 2. Symptoms of hyperketosis in infants

Rapid breathing, increased heart rate Facial flushing

Irritability

Vomiting

Lethargy

Poor feeding

Table 8. Comparison of blood and urine ketone testing.

Monitoring method*	Ketone body measured	Ideal range on ketogenic diet	Limitations of method
Blood ketometer	Betahydroxybutyrate	2-5mmol/L	• Uncomfortable for child and parent • Testing strips expensive
Urine dipsticks	Acetoacetate	8-16mmol/L (3-4+)**	• Unpredictability of void times • Reflect past ketosis so not as accurate • Influence of urine dilution • Practical difficulties with nappies • Maximum 16mmol/L reading may limit detection of hyperketosis

* the testing method will differ between centres.** the range depends on the type of urine dipsticks.

Growth.

During diet initiation weight should be checked daily, with a baseline measure of height and head circumference. Longitudinal growth is not monitored at this stage, other than baseline measurement.

6.1.3 Adverse effects of the ketogenic diet in infants during diet initiation.

General.

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

Glucose/ketones.

There is a risk of hypoglycaemia, acidosis, dehydration and high levels of ketones on commencing a KD [35] with increased risk of excess ketosis and metabolic acidosis with concurrent use of carbonic anhydrase inhibitors (for example, topiramate or zonisamide) [37].

Gastro intestinal complaints.

Gastro-intestinal problems such as vomiting, nausea, diarrhea, and abdominal discomfort are common side effects of the KD [35, 38] however can usually be alleviated with dietary manipulation and by altering the step by step 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 intiation. Despite dietary changes to help lessen the problem many children need additional treatment with medication.

6.2 Feeding methods.

While on KD the infant can continue bottle feeding.

In daily practice the majority of infants with severe epilepsy have feeding difficulties and may need a 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 formula (Ketocal 3:1®). In case 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. (For examples see Appendices).

In some cases (i.e. the young infant) use of breastmilk may be possible, which highly depends on level of ketosis that is needed to achieve adequate seizure reduction. In this situation the use of Ketocal 3:1®is recommended. In some of these cases Ketocal 4:1® may be necessary, but use this only after careful calculation and monitoring. In some cases (i.e. the young infant) breastmilk on demand may be possible but this highly depends on level of ketosis that is needed to achieve adequate seizure reduction.

6.3. Fine-tuning the diet.

When the ketosis doesn't reach the adequate range (2-5mmol/l in blood) within 2 weeks after diet initiation and careful calculation, it is important to adjust the diet (ratio) to maximize efficacy of the diet on seizure reduction. It is also important to exclude medication, including IV, that contains glucose or similar substances.

Table 9: Fine tuning the diet.

Note:	Adjust the diet only once a week!
In general	• check for incompatible medication: (i.e carbohydrate-containing vitamin D supplement, multivitamin supplement, antibiotics) • check calculated recipes • check measuring scale is accurate

Ketosis too low (< 2.0 mmol/l)	• increase ratio:
	• stop adding breastmilk or infant formula: increase amount of ketocal formula used with same calories.
	• mix with ketocal 4:1®:
	  • 25%-75%
	  • 50%-50%
	  • switch to only ketocal 4:1® (check if all nutrients are covered!).
	  • increase amount of fat used in solid food: i.e butter, margarine, oil, cream, calogen®, mayonaise.
	• add 5% energy as MCT to the diet or increase the MCT used by 5%
	• decrease 5-10% of calories maintaining diet ratio. If this doesn't help measure resting energy expenditure.
	• start Carnitine supplementation (start with 10mg/kg , build up to maximum 50mg/kg based on tolerance).

Ketosis too high (> 5 mmol/l)	• decrease ratio: • add 1-2% protein (using standard infant formula or protein enriched powder) • add 1-2% carbohydrate (using carbohydrate polymer) or standard infant formula or increase amount of fruit, bread, potato, cereals) • decrease 5 % energy from MCT used and compensate calories from LCT by increasing amount of LCT emulsion (Calogen®, Carbzero®) cream, oil, margarine. • increase 5-10 % of calories, maintaining same diet ratio. • If this doesn't help, measure resting energy expenditure.

6.4. 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 due to developmental delay). Combination of 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.
(for examples see appendices).

At the age of 9-12 months when more carbohydrate containing foods are introduced (like 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. (for examples: see appendices).

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 .

RECOMMENDATION on using MCT.

In older infants only use MCT as emulsion (Liquigen® 50% MCT) mixed with (low fat) milk product (50-50) or a little amount of MCT emulsion drink (Betaquik ® 20% MCT).
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.

6.5. Follow up.

6.5.1 Monitoring during follow up.

Follow-up schedule.

- Post discharge from hospital phone or email contact by the dietitian or nurse ensures a high level of communication for first 2 weeks, then at least once (or twice) a week as needed. After the first 2-4 weeks on the diet the need for regular communication may diminish and will be determined according to age, dietary tolerance and/or side effects, family circumstances and speed with which the diet can be fine-tuned to provide the optimal prescription.
- Clinical reviews by the neurologist and diet team – 2 weeks post initiation for first review, then at 6 weeks and 3 months post initiation, then every 3 months until aged 2 years (more frequent visits are recommended if an infant has medical or nutritional needs that need review). After 2 years children can be seen every 6 months.

Home monitoring.

- Seizures: a seizure diary will enable parents and/or caregivers to record number, duration and types of seizures. Additional documentation about need for any emergency medications and other epilepsy-related events, for example emergency hospital admissions, will provide more information on dietary efficacy.
- Positive benefits or adverse effects: these should also be recorded, for example, changes in behaviour and cognition, changes in bowel function, sleep changes.
- Weight: an infant should be weighed weekly at home.
- Diet assessment: a food and feed diary should be completed by parents and/or caregivers every 3-6 months for assessment by the dietitian.
- Ketosis: an infant's ketones may be measured at home by the parent or caregiver, initially twice daily (morning and evening) for the first few weeks. Once established on the KD, this can be reduced to daily (preferably evening). After 3 months this can be reduced in frequency in discussion with the ketogenic team. A return to twice daily testing is advised during periods of dietary fine tuning and illness. Blood or urine ketones can be measured, aiming for an individual's ideal therapeutic range within the guidelines in Table 8. This will be established during dietary fine tuning.

The measurement of urine ketones in infants with nappies requires particular attention (see Box 3) and blood measures are recommended in infants where feasible.

Box 3. Urine ketones - technique for infants in nappies (diapers)

- Put cotton wool or gauze into a clean nappy.
- Squeeze the urine from the cotton wool into a receptacle or on to the dipstick (or place into a syringe and press the plunger).
- The colour will change and indicate the level of ketosis.
- Morning specimens – do not use the overnight nappy as the urine is contaminated with numerous urinations.
- Evening specimens - put on a clean nappy after the bath or evening meal and check the cotton wool before the infant goes to sleep.

Monitoring at clinical reviews.

- 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 10. 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.
- Due to the limited reference data for this young age group, routine monitoring with DEXA scans is not recommended in infants

Table 10: Recommendations for biochemical monitoring during follow up.

Investigation	Frequency of monitoring
Essential :	
Blood: Full blood count	• 6 weeks, 3 months, 6 months, then every 6 months
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: calcium: creatinine ratio, haematuria	• 6 weeks, 3 months, 6 months, then every 6 months
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

6.5.2 Adverse effects of the ketogenic diet during follow up.

Specific in infants.

Table 11 summaries the incidence of adverse events reported in the literature on KD use in infants. Most commonly seen 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 10. However Eun et al reported that 37% of their group of 43 infants discontinued the KD due to complications [8]. Most studies are based on retrospective data, which implies a lower quality assessment of side effects.

Gastro-intestinal.

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 6.1.2 [38, 39].

Growth.

There is evidence of impaired growth in children on the KD [25, 40]; younger children may be more at risk [27]. 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 [41]. 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 [42], a prescribed protein-to-energy ratio of at least 1.5g protein/100kcal has been suggested to help prevent growth faltering [43].

Nutritional deficiencies.

Children with drug resistant epilepsy are at risk of insufficient vitamin D status prior to starting a KD [44] 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 [45] despite reduction in anticonvulsant medication.

Selenium deficiency can occur in children on the KD [46] with the risk of impaired myocardial function [47].

Hypomagnesemia has also been seen [35], and may be a particular problem in children on the classical KD despite micronutrient supplementation [30].

Vitamin C deficiency has been reported in one child on the KD [48] but plasma levels of fat soluble vitamins A and E can often be raised as a consequence of a high fat intake [30]. 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 [49], although levels tended to normalise with time on diet therapy.

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 [50]. Although there is evidence of a trend back towards normal with time on the KD [51], this raises concern about long term adverse effects on vascular function. Studies suggest that while arterial stiffness may increase initially [52], the changes in arterial function observed within the first year of KD treatment are not significant after 24 months and appear to be reversible [53].

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 [54]. Uric acid, calcium oxalate, calcium phosphate or mixed composition stones have been reported in up to 7% of children on the KD [5, 54, 55]. Risk may be higher with long-term treatment [40] and concurrent use of carbonic anhydrase inhibitors [56]. 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 potasssium citrate supplement has suggested a preventive effect [57].

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 [35, 47, 58-60].

Table 11: Reported side effects of the ketogenic diet in infants.

Note:	Infant population	Adverse effects
Nordli et al, 2001 Retrospective review [4]	32 infants < 24 months Mean age KD initiation 14 months	**6/32 (19%):** Coma due to hypoglycaemia and acidosis post initiation−=1 Vomiting = 1, Renal stone = 1, Gastro-intestinal bleed (erosive oesophagitis from NG tube)=− 1-Hyperlipidemia − 1, Ulcerative colitis =1
Goyens et al, 2002 Single case report [61]	KD initiated at 13 days in GLUT1 DS neonate	Weight loss and malnutrition associated with low lipase activity, treated with pancreatic enzymes and use of MCT
Eun et al, 2006 Retrospective review [8]	43 infants aged 6-42 months with infantile spasms Mean age KD initiation 19 months	**24/43 (56%):** Gastrointestinal disturbances = 8 (1 within 4 weeks), Serious infectious disease = 4, Severe dehydration = 3 (2 within 4 weeks), Pneumonia = 3 (1 lipoid aspiration, 2 within 4 weeks), Renal stone = 2, Haematuria with hypercalcuria =1, Reflux oesophagitis = 1, Erosive gastritis = 1, Fatty liver = 1
Kossoff et al, 2008 Retrospective review [62]	13 infants <12 months treated with KD as first line for infantile spasms Median age of spasms onset − 5 months	**4/13 (31%):** Gastro oesophageal reflux =1, Constipation = 1, Poor tolerance of formula = 1, Weight loss =1
Hong et al, 2010 Prospective study [11]	104 infants with infantile spasms Mean age KD initiation 1.2 years	**34/104 (33%):** Dyslipidemia = 17, Constipation = 7, Gastro oesophageal reflux = 6, Behavioural problems =3, Haematuria = 3, Diarrhea = 3, Renal stone = 3, Acidosis = 3, Hair thinning = 2, Hypercalcaemia = 2, Dry skin = 1, Pica = 1
Numis et al, 2011 Retrospective review [63]	26 infants with infantile spasms Mean age KD initiation 19 months	**6/26 (23%):** Irritability, lethargy, decreased appetite, persistent hypoglycaemia, renal stone, vitamin D deficiency (numbers not specified)
Pires et al, 2013 Prospective study [9]	17 infants with infantile spasms, 16<12 months Mean age KD initiation 9 months	Weight loss and dyslipidaemia (raised triglycerides) in some infants
Kayyali et al, 2014 Prospective study [10]	20 infants with infantile spasms Mean age KD initiation 1.2 years (0.3-2.9 years)	**12/20 (60%):** Constipation = 7, Acidosis= 4, Minor dyslipidemia =3 Diarrhea = 1, Urinary sediment= 1
Dressler et al, 2015 Retrospective study [18]	58 infants < 18 months, (42 <9 months) Mean age KD initiation 0.68 years (0.15-1.5 years)	**29/58 (50%):** Carnitine deficiency =4, kidney stones = 3, Minor dyslipidemia =21 Weight gain=1, growth deficiency= 3, high cholesterol = 2

7 EMERGENCY SITUATIONS

7.1. Illness

7.2. Intensive care

7. EMERGENCY SITUATIONS.

7.1 Ketogenic diet during illness.

During illness, it is more important to treat the (acute) illness than to maintain optimal ketosis.

[64, 65]

Important

- In consultation with the parents, the paediatrician/physician determines when to be contacted in the event of illness.
- Each child receives a bespoke emergency plan in case of illness.
- Ketones should be monitored more frequently, in consultation with the physician.
- Measure the blood glucose in the event of paleness, clamminess and other signs that may indicate a hypoglycaemia.
- Maintain a fluid balance (check urine by weighing nappies)
- Do not insist on eating; accept a more limited food intake during days of illness.
- Each time there is vomiting / diarrhoea, compensate with 10 ml ORS* / kg body weight.

*** Use of Oral Rehydration Solution (ORS) :**

In calculating the allowed quantity of ORS / 24 hours, 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. A point to consider during illness is the increased risk of hyperketosis. 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 ORS, glucose solution) is then required.

**** Preparation and use:**

100 ml ORS, prepared according to the information on the package, contains 2.2 grams of carbohydrate.

With the classical KD, only a very limited quantity of ORS (standard solution) can be used, which is supplemented with water until the required quantity of fluid has been reached. It is important to emphasise this in the patient's individual emergency plan.

With the KD with MCT, more ORS (standard solution) can be used.

Illness, fever WITHOUT vomiting and/or diarrhoea

The treating paediatrician/physician should be contacted immediately

Phase 1:
1st 24 hours

Classical KD

- if the current feeding schedule (bottle feeding /breastmilk /solid food is not accepted; give numerous, smaller portions throughout the day. KD with small amount of MCT:
- divide the MCT emulsions over smaller portions throughout the day: It is important to give the MCT only if the child has eaten carbohydrate-containing foods. If the child eats 50% of their meal then only half of the MCT emulsion should be given.
- offer food limited in dietary fibre, also in small portions.

For enteral tube feeding:

- give numerous, smaller feeds throughout the day
- lower the pump position when using the feed pump or switch to continuous drip feeding.

Phase 2:

If the complaints subside, a switch can be made to the regular KD
(bottle feeding /breastmilk /solid food)
If the complaints do not subside, the advice mentioned under phase 1, 1st 24 hours can be continued for a maximum of 2 days.

Illness, fever WITH vomiting and/or diarrhoea

Always contact the treating paediatrician/physician about the dietary adjustments to be followed.

Phase 1:
1st 24 hours

Classical KD or KD with small amounts of MCT and enteral feeding:

- give 24 hour ORS according to the preceding guidelines. For fluid requirements see table 6a/b.
- compensate each episode of vomiting /diarrhoea with 10 ml ORS*/kg body weight. Use the ORS composition indicated in the individual emergency plan.

Phase 2:

Classical KD

- calculate the meals in a ratio 1.0 lower than the original diet. (i.e 2:1 if the original diet is 3:1)
- if the usual meals are not tolerated, give numerous, smaller portions throughout the day.

KD with small amounts of MCT:

- divide the MCT emulsions over smaller portions throughout the day: it is important to give the MCT only if the child has eaten carbohydrate containing foods. If the child eats 50% of their meal then only half of the MCT emulsion should be given.
- offer food limited in dietary fibre, also in small portions.

For enteral tube feeding:

- dilute the feed to ½ - ½ with water.
- give numerous, smaller portions throughout the day.
- lower the pump position when using the feed pump or switch to continuous drip feeding.

PLEASE NOTE:

- make sure that there is sufficient fluid intake, see table 6 a/b.
- compensate each episode of vomiting / diarrhoea with 10 ml ORS*/kg bodyweight. Use the composition indicated in the individual emergency plan.

Phase 3: If the complaints subside, a switch can be made to the usual KD.

7.2 Intensive Care.

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 Ringerslactate should be utilised. Blood sugars and ketone levels should be monitored 6 hourly. The NPO without glucose IV should be limited to max 6 hours. In case glucose levels drop < 2-2.5mmol/l (approximately 40mg/dl) this should be treated immediately by 2-4 gram carbohydrates glucose as a bolus. This can be done by adding 10% solution (young infants < 4 months) or glucose 5% solution (older infants) to reach glucose levels within normal range > 3 mmol/l or 50-60 mg/dl. Re-check glucose levels after 15-20 minutes.

If a child has a enteral feeding tube or PEG and is thought to be absorbing, then a liquid KD diet can be utilised as tolerated. In case glucose levels drop < 2-2.5mmol/l (approximately 40mg/dl) this should be treated immediately by 2-4 gram carbohydrates glucose as a bolus. This can be done by adding 30-60ml juice to reach glucose levels within normal range > 3mmol/l or 50-60 mg/dl.

Re-check glucose levels after 15-20 minutes.

Care needs to be given in the avoidance of aspiration. An enteral tube feed can also be utilised in status epilepticus that has failed first and second line therapy.

8 EVALUATION

8. EVALUATION.

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 IS varies according to the course of the disease. Infantile spasms are 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 child neurologist should then evaluate the patient to discuss the use of an AED in addition to KD (11). When the KD is used in refractory 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, 9, 11]. This outcome requires further evaluation in the future. The current data are limited by the small size of the groups in uncontrolled studies. The data 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.

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 [66]. This retrospective study evaluated the time to seizure reduction in 118 epilepsy patients who started on the KD. 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 [66].

Based on this study, we suggest that the KD should be maintained for 2-3 months to undoubtedly evaluate the efficacy of KD. 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.

9 DIET DISCONTINUATION

9. DIET 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 [67]. Children with GLUT 1 deficiency and PDHC deficiency do not usually discontinue the KD as this will be treating the underlying metabolic defect as well as any presenting seizures. However there is evidence that they may tolerate a reduced ratio in the 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 [68]. 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.

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KETOCAL 3:1 SPECIÁLIS GYÓGYÁSZATI CÉLRA SZÁNT ÉLELMISZER

Megújult összetétellel a csecsemőkori epilepszia diétás ellátására

3:1 arányú
Megbízható pontossággal kiszámított tápanyag és tápérték profil

Teljes értékű
Anyatej helyettesítésére is alkalmas

Életkornak megfelelő energia mennyiség
Megfelel az anyatejhelyettesítő tápszerek követelményeinek

Életkornak megfelelő fehérje mennyiség
Magas biológiai értékű fehérjetartalom

Tejalapú, tejcukor tartalmú
A laktóz hozzájárul a bifidobaktérium megfelelő működéséhez és szaporodásához[A]

Karnitin tartalmú
Támogatja a ß-oxidációt[B,C]

A **KetoCal 3:1** speciális élelmiszer gyorsan és kényelmesen elkészíthető, felhasználható italként és ételként egyaránt. Szondatáplálásra is javasolható.

Speciális gyógyászati célra szánt élelmiszer, csecsemőkori terápia-rezisztens epilepszia diétás ellátására. Kizárólag orvosi felügyelet mellett használható. A csecsemő számára a legjobb táplálék az anyagtej. A legegészségesebb táplálási mód a szoptatás. Amennyiben nem áll rendelkezésre elegendő anyatej vagy a szoptatásnak más akadálya van, a speciális élelmiszer kizárólag az orvos javaslatára, orvosi ellenőrzés mellett, használati utasítás szerint alkalmazható. Speciális gyógyászati célra szánt élelmiszer, enterális táplálásra. Kiegészítő és kizárólagos táplálásra egyaránt alkalmazható. Jelen kiadvány kizárólag egészségügyi szakemberek számára készült, a Numil Kft. nem vállal semmilyen felelősséget annak illetéktelen felhasználásáért. Jelen anyag elválaszthatatlan részét képezi a címkeszöveg.
*Bruttó fogyasztói ár: 10357 Ft; *Támogatási kategória: 100%; *Támogatási összeg: 10057 Ft; *Térítési díj: 300 Ft *Indikációs pont: EÜ 100/52.pont • *www.neak.gov.hu (2021.01.01.)

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KETOCAL 3:1 SPECIÁLIS GYÓGYÁSZATI CÉLRA SZÁNT ÉLELMISZER

Megújult összetétellel a csecsemőkori epilepszia diétás ellátására

Továbbfejlesztett lipid profil
Csökkentett telített zsírsav mennyiség

Hozzáadott hosszú láncú többszörösen telítetlen zsírsavakkal (LCP)
Esszenciálisak a csecsemők számára

Dokozahexaénsavval (DHA) és arachidonsavval (AA)
A kognitív és a vizuális fejlődés támogatására[A,B,C]

Vitaminokkal, ásványi anyagokkal
Minimalizálja az étrendkiegészítők használatát

Makro és mikrotápanyagok optimális egyensúlya
Szondatáplálás esetén is javasolható

A **KetoCal 3:1** speciális élelmiszer gyorsan és kényelmesen elkészíthető, felhasználható italként és ételként egyaránt. Szondatáplálásra is javasolható.

ELKÉSZÍTÉS

100 ml kész tápszer oldat
66 kcal 1,4 g fehérje

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