1. Introduction

Despite continued advancements in anticonvulsant development, approximately 30% of patients with epilepsy have refractory seizures [1], and so there remains a significant demand for additional options. Carbohydrate-restricted diets have become increasingly used as a treatment of chronic and acute epilepsy [2,3]. Evidence from randomized, controlled trials [2,4] and meta-analyses [5] has demonstrated that overall approximately 50% of children will respond to these diets with at least a 50% reduction in seizures. Ketogenic diets may be also effective for adult status epilepticus [6] and adult epilepsy [6,7], and as a first-line treatment of seizures associated with glucose transporter 1 deficiency [8]. These diets are being used worldwide in many new centers [9], and based on the approximately 200 centers today offering dietary treatment, an estimated 3000 children are likely actively receiving this treatment worldwide.

These children are also cared for by pediatricians, internists, emergency department physicians, intensivists, and house officers in academic and community hospitals when general pediatric illnesses arise. Similar to all children, they may become ill, require anesthesia for surgery, and receive oral medications. Therefore, there is a need for these general practitioners worldwide to recognize emergencies and complications requiring recognition and timely action. In addition, the ketogenic diet is a significant intervention requiring rigorous daily adherence; not every family is willing or able to make the necessary commitment to this therapy. We provide herein a survey of the most common situations faced in both the inpatient and outpatient settings, including a discussion of triage and management based on our center’s experience as well as the recent 2009 International Consensus Guideline.

As ketogenic diets become more frequently used as a standard treatment for epilepsy in children and adults, hospital and community neurologists, pediatricians, intensivists, general practitioners, and house officers will readily encounter patients who are receiving these dietary treatments. A growing body of evidence demonstrates that dietary therapies for epilepsy (classic ketogenic diet, medium-chain triglyceride diet, modified Atkins diet, and low-glycemic-index treatment) are highly effective, with approximately 30–60% of children overall having at least a 50% reduction in seizures after 6 months of treatment. However, as would be true of any other medical anticonvulsant therapy, these treatments have known side effects and complications requiring recognition and timely action. In addition, the ketogenic diet is a significant intervention requiring rigorous daily adherence; not every family is willing or able to make the necessary commitment to this therapy. We provide herein a survey of the most common situations faced in both the inpatient and outpatient settings, including a discussion of triage and management based on our center’s experience as well as the recent 2009 International Consensus Guideline.

2. Composition of dietary treatments

All dietary therapies used to treat epilepsy share the common characteristic of restricting carbohydrate intake to shift the predominant caloric source of the diet to fat [10]. Body tissues are thereby forced to catabolize fats as their primary source of energy, and the catabolism of fats results in ketones, hence the origin of the common descriptor for these therapies, “the ketogenic diet.” The precise mechanisms by which the ketogenic diet yields its anticonvulsant effect are not known, but appear unique from the mechanisms of action for other anticonvulsants [11].

2.1. The traditional ketogenic diet

The “classic” ketogenic diet has been in continuous use since 1921 and predates all other dietary treatments. It consists of primarily long-chain triglycerides and is a high-fat, moderate-protein, and low-carbohydrate diet. Patients are started on specific ratios (ratio of fat to carbohydrate and protein grams combined), with 4:1 most typical [10]. Diets with lower ratios of 3:1 or 2:1 can be used in instances where more protein is needed for growth, such as for young infants and adolescents [12] or during weaning of the diet from a higher ratio. Total calories and fluid intake volumes are calculated by a registered dietitian, and patients are provided meal plans, often created by computer. Calories may be restricted though this is no longer considered an essential component of the ketogenic diet [12].
2.2. The medium-chain triglyceride diet

Whereas the “classic” ketogenic diet relies on long-chain fatty acid oxidation, a variant ketogenic diet uses medium-chain fatty acids provided in oil form (MCT oil) as a dietary supplement. This diet provides an option for individuals with carnitine deficiency, as carnitine is required for processing long-chain but not medium-chain fatty acids [13]. This efficient processing means medium-chain fatty acids are more ketogenic than long-chain fatty acids and, therefore, allows for greater carbohydrate and protein intake than even a lower-ratio ketogenic diet [14]. Evidence would suggest the MCT diet can be as effective as the ketogenic diet and may have benefits with respect to dyslipidemia. Currently the MCT oil diet is used predominantly in Canada and the United Kingdom.

2.3. “Alternative” diets: Modified Atkins diet and low-glycemic-index treatment

In the past decade, there have emerged two new diets that primarily reduce carbohydrate intake without weighing or measuring calories, fluids, fat, or protein. These two diets are the modified Atkins diet [15] and the low-glycemic-index treatment [16]. These diets share the basic properties of ketogenic diets in that they eschew most carbohydrates while encouraging high fat intake, but they do not restrict protein or calories and are considerably less rigorous in their implementation than the aforementioned ketogenic diets. The modified Atkins diet limits carbohydrates to 10–20 g daily and is started as an outpatient without a fasting period [17]. Calories and fluid intake are ad libitum. The low-glycemic-index treatment derives its name from the glycemic index, which is a basis on the observation that ingestion of foods such as fruits, vegetables, nuts, and whole grains yields a slow, steady rise in serum glucose as compared with ingestion of refined grains and white potatoes, which yield large pulsatile spikes in serum glucose rapidly after intake [18]. The low-glycemic-index treatment recommends 40–60 g daily of carbohydrates with glycemic indices <50 and approximately 60% of dietary energy derived from fat and 20–30% from protein [18].

3. Pre-ketogenic diet preparations

As groups have gained experience with ketogenic diets, it has become obvious that some patients with certain epilepsy syndromes particularly benefit from this therapy, some are less likely to benefit but may merit a trial, and there are some for whom the diet is contraindicated. Appropriate screening and selection of eligible patients are imperative for best chance of success and more importantly for safety.

3.1. Indications and contraindications

For patients with GLUT-1 transport deficiency and for those with pyruvate dehydrogenase deficiency, the ketogenic diet is considered a first-line therapy and should be implemented as soon as the patient is identified [19]. In considering the epilepsy population as a whole, the International Consensus Statement for the Ketogenic Diet (2009) stated that “the [ketogenic diet] should be considered in a child who has failed two to three anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies.” [12]. As previously reported, seizures in approximately one-half of children will respond within 6 months [5]. Specifically, the ketogenic diet appears to be a particularly effective treatment for persons with Dravet [20] and Doose [21] syndromes, with a range of 18–58% seizure freedom in the latter [21]. It is also a particularly good option for the treatment of refractory infantile spasms [22], mitochondrial disorders [23], and tuberous sclerosis complex [24]. For infantile spasms specifically, the ketogenic diet is becoming a therapy of choice, with a single-center series of 104 infants reporting 64% with >50% spasm reduction after 6 months, of whom 37% had at least 6 months of spasm freedom [22]. Patients with focal, partial epilepsies appear to have a decreased relative chance of seizure freedom overall, especially if they have a readily localized lesion that makes them candidates for epilepsy surgery [25]. In one series, no child with a surgically approachable lesion became seizure free on the ketogenic diet [25].

There are conditions in which the ketogenic diet is contraindicated and these include primary carnitine deficiency, carnitine palmitol trans-ferase I or II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency, and porphyria [12]. It is important to screen for these deficiencies in all patients in whom there is clinical suspicion of an inborn error of metabolism as the initiation of the ketogenic diet and its reliance on mitochondrial fatty acid metabolism can precipitate a potentially fatal metabolic crisis in an affected individual.

3.2. Laboratory studies and counseling

There are certain studies and investigations summarized in Table 1 that should be completed prior to beginning any dietary therapy. Prior to diet initiation, serum lactate, ammonia, plasma amino acids, and urine organic acid levels should be obtained and reviewed. In addition to metabolic investigations, a prediet workup should include an EEG and MRI of the brain especially for patients with focal epilepsies, as a presurgical evaluation. Patients referred for progressive but idiopathic epilepsies should document a prior full evaluation including genetic, serum, urine, and possibly cerebrospinal fluid analyses to assess for etiology. In patients with personal or first-degree relatives with renal calculi, a renal ultrasound in advance of starting the diet could be considered.

The family should meet or discuss by phone in advance with a ketogenic diet team’s dietitian and neurologist to discuss specifics of the diet, expectations, and unique circumstances of their child that may impact therapy. The ketogenic diet is a significant intervention requiring rigorous daily adherence; not every family is willing or able to make the necessary commitment to this therapy. There are many resources in print and electronic media to aid parents’ decision making and education prior to starting the diet and beyond, but it is important parents and patients appreciate that dietary therapy represents a considerably more substantial investment of time and resources than a medication trial and with real risks. Families can make dietary changes in advance of ketogenic diet initiation to ease the transition, and dietitians can craft diet plans for children with food allergies. Appropriate foods should be stocked at home to continue the diet once initiated. Infants or individuals receiving total daily feeding via a gastrostomy tube will simply switch to one of several commercially available ketogenic diet formulas, but families should ensure procurement of the ketogenic formula in advance and resolve insurance reimbursement issues prior to starting the ketogenic diet.

4. Acute issues during initiation of the ketogenic diet

The practice at our institution and at the majority of institutions employing the ketogenic diet is that inpatient admission is helpful and important for close monitoring of children and the intense education of their parents. This short (3- to 4-day) admission is needed for patient safety should problems arise during diet initiation and as a means to ensure completion of parental education about the diet. In select circumstances, outpatient initiation has been reported as safe [26], but it should be considered only in situations where there are no clear metabolic contraindications, the patient remains within close proximity to a medical care facility, family attendance at education sessions is possible, and the risks of an inpatient admission such as contracting an illness for this patient would be unacceptable [12]. As stated previously, admission is not routine for the “alternative” diets.
may not be obligatory to achieve good long-term seizure control. These issues are listed in alphabetical order. Table 2.

Table 1

Investigations and planning required prior to initiating ketogenic diet therapy. Source. Modified and updated from the 2009 International Consensus Statement [10].

Counseling
Discuss seizure reduction, medication, and cognitive expectations. Identify potential psychosocial and financial barriers. Review anticonvulsants and other medications for carbohydrate content; make changes in dosage before diet initiation. Identify compounding pharmacy. Recommend family-read parent-oriented ketogenic diet information from Internet and books.

Plan ketogenic diet admission (or clinic visit for “alternative diet”) date.

Nutritional evaluation
Baseline weight, height, and ideal weight for stature
Body mass index (BMI) when appropriate (older children)
Nutrition intake history: 3-day food record, food preferences, allergies, aversions and intolerances, religious preferences, vegetarian?

Establish diet formulation: infant, oral, enteral, or a combination. Decision on which diet to begin (MCT, classic, modified Atkins, or low glycemic index)

Order ketogenic formula if applicable in advance.

Laboratory evaluation
Complete blood count
Electrolytes, including serum bicarbonate, total protein, calcium
Zinc, selenium, magnesium, phosphate
Electrolytes, liver, and kidney functions (including albumin, AST, ALT, blood urea nitrogen, creatinine, bicarbonate, total protein, calcium)
Fasting lipid profile (cholesterol, triglycerides, HDL, and LDL cholesterol)
Serum acylcarnitine profile
Anticonvulsant drug levels (if applicable)
Urine organic acids, serum amino acids, lactate, ammonia (if not previously obtained)

Ancillary testing (optional)
Renal ultrasound (if history of kidney stones)
EEG and MRI (to help establish diagnosis)
ECG (echocardiogram) if history of heart disease

During hospitalizations and as an outpatient, it is critical that all medications the patients take orally be carbohydrate free. Fully equipped inpatient pharmacies should be able to recommend or compound carbohydrate-free preparations of oral medications to render them carbohydrate free. As patients using the ketogenic diet are often on other anticonvulsants and may have other chronic medication needs, carbohydrate-free options should be chosen and be maintained during the ketogenic diet therapy. No anticonvulsants are contraindicated in conjunction with the ketogenic diet, though the usage of concurrent carbonyl anhydrate inhibitors (acetazolamide, topiramate, zonisamide) may require additional monitoring for metabolic acidosis as detailed above [12].

During initiation of the ketogenic diet, several commonly seen, often anticipated, issues emerge. As these issues usually occur during the inpatient admission, the patient’s guardians are able to witness these situations in a medically safe setting and these scenarios become a vital component of diet education. These issues are listed in Table 2.

Although many centers initiate the diet with 24–48 hours of fasting (clear fluids allowed) to achieve initial ketosis [27], fasting may not be obligatory to achieve good long-term seizure control [28,29]. Following whatever fasting period is chosen, the diet is implemented with increasing caloric content from fat or increasing ketogenic diet ratio, over 3–4 days, until the full ketogenic diet is tolerated and the child is discharged.

During fasting and diet initiation, patients require serial serum glucose monitoring for hypoglycemia. Generally, asymptomatic glucose levels >40 mg/dL are tolerated and will resolve during advancement of the ketogenic diet. Symptomatic hypoglycemia (diaphoresis, excessive fatigue, altered mental status, tachycardia, tachypnea) should always be treated, but usually can be ameliorated with 30–60 mL of orange juice or a similar carbohydrate-enriched beverage with a follow-up serum glucose check within 30 minutes. Rarely are intravenous or large oral boluses of glucose necessary to increase serum glucose levels, and the need for repeated aggressive measures to maintain euglycemia should prompt consideration for an unidentified congenital metabolic derangement that may contraindicate dietary therapy.

As ketone levels rise in serum, patients may have decreased activity and report gastrointestinal symptoms such as nausea and abdominal pain. These symptoms are often transient and can be monitored without interruption of the diet. If ketone levels rise too precipitously, or if the patient does not tolerate sustained high-concentration serum ketones, a temporary interruption of the diet with a carbohydrate-laden beverage as described above for symptomatic hypoglycemia is an option, and if the issue becomes chronic, then reducing the ketogenic ratio to produce a lower level of sustained ketosis may be warranted.

The ketogenic diet yields a metabolic acidosis that can be exacerbated by carbonic anhydrate-inhibiting anticonvulsants. There are suggestions that the acidosis is greatest at diet initiation [30], and it is recommended that serum bicarbonate levels be monitored in at-risk patients. Patients with clinically significant signs of acidosis (e.g., altered mental status, emesis) should receive bicarbonate supplementation acutely or on a long-term basis if needed.

Vomiting is among the most common occurrences during diet initiation and maintenance phases, with a study reporting vomiting in more than 50% of patients, regardless of whether the child was fasted [28,30]. Vomiting can be a sign of multiple issues, and those should be considered as well as the ketogenic diet, including gastroesophageal reflux or a coincidental gastrointestinal viral illness. Intravenous or rectal antiemetics (e.g., promethazine, metoclopramide) are also short-term options for control of emesis; however, they may reduce the seizure threshold. If emesis becomes prolonged (>24 hours) because of the diet, intravenous fluid administration either as a bolus or continuously may be helpful, and care should be taken to ensure the fluids used are carbohydrate free (e.g., 0.5 normal saline without dextrose).

Seizure frequency can increase during start of the ketogenic diet just as it can with initiation of any anticonvulsant treatment, although this is generally very infrequent. An appropriate initial evaluation would be to assess adequacy of ketosis to ensure that there are no “hidden” carbohydrate sources preventing achievement of adequate serum ketone levels. Obviously, the overall health of the patient should also be evaluated to ensure that elevated seizure frequency is not a symptom of a more global illness coincident in the patient. The ketogenic diet, like other anticonvulsants, has both acute and chronic effects on seizure frequency, and generally it is advised to allow at least 3 months of compliant treatment to fully evaluate the diet’s impact on an individual patient’s epilepsy before discontinuing it for inefficacy [27]. Obviously, a precipitous intractable increase in seizures after diet initiation may require a more immediate discontinuation.

5. Chronic issues with the ketogenic diet

Beyond the admission period, there are other adverse effects that may arise in children on dietary treatment (Table 3). The vast majority of inquiries and on-call issues with the ketogenic diet can be triaged
Long-term potential side effects of dietary treatments, listed in alphabetical order.

<table>
<thead>
<tr>
<th>Side Effect</th>
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<tbody>
<tr>
<td>Bone fractures</td>
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<tr>
<td>Decreased bone mineral density</td>
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<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Kidney stones</td>
</tr>
<tr>
<td>Poor linear growth</td>
</tr>
<tr>
<td>Secondary carnitine deficiency</td>
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<tr>
<td>Vitamin D deficiency</td>
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<tr>
<td>Weight loss (or insufficient weight gain)</td>
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and solved without an emergency room evaluation or hospital admission. Although issues with the ketogenic diet may seem at first glance more complicated than those of anticonvulsant medications, fielding a phone call or outpatient query about a possible diet-related side effect requires maintaining a wide differential diagnosis, as children on the diet are as prone to similar pediatric issues as children on anticonvulsants. For example, a nonverbal patient who suddenly refused to eat while on the ketogenic diet was found to have extensive dental abscesses requiring surgical debridement. In another instance, vomiting and abdominal discomfort were identified as acute appendicitis. All children are at risk for viral illnesses, which can lead to emesis, increased seizures, and food refusal as well. It is hoped these examples help demonstrate that attributing any symptom solely to the ketogenic diet is not a substitute for appropriate medical judgment.

6. Gastrointestinal complaints

The most common reported chronic complications of the ketogenic diet typically include gastrointestinal issues. Constipation is frequently associated with the ketogenic diet and can be managed by increasing dietary fiber intake, ensuring adequate carbohydrate-free fluid intake, or, if other measures fail, by prescribing carbohydrate-free laxatives such as polyethylene glycol. These children can present with abdominal distention, hematochezia (as a result of straining and rectal mucosal bleeding), and occasionally paradoxical diarrhea. Gastroesophageal reflux can also worsen with the ketogenic diet and occasionally begin during its use [31]. There are no data that empiric treatment for reflux with histamine receptor blockers or proton pump inhibitors prevents gastrointestinal complications associated with the ketogenic diet, but they may be warranted if clinically indicated [12]. Some patients may report increased hunger while on the ketogenic diet, and increasing intake of sugar-free snacks and decreasing the ketogenic ratio can be effective solutions.

More serious complications of the ketogenic diet can present as abdominal pain and need to be assessed. One such complication of the ketogenic diet includes the formation of renal calculi. Complaints of flank pain, dysuria, hematuria, or “gritty” or white “sand” in the urine in a patient on a ketogenic diet should prompt an evaluation for a renal calculus. Administering oral citrate preparations to patients is advised as a preventative measure [32], but kidney stones may still occur in approximately 1% of children even with their continued use. Conservative treatment with increased fluid intake and monitoring are typically all that is needed; lithotripsy is rarely required. Other reported complications include pancreatitis (likely more common in those treated with valproate [30,33]), hepatitis, and gallstones (possibly because of the high-cholesterol, low-fiber diet composition). Unexplained abdominal pain in a child on the ketogenic diet should lead to evaluation of amylase, lipase, alanine aminotransferase, and aspartate aminotransferase levels and abdominal and renal ultrasound.

6.1. Dyslipidemia

Regardless of which ketogenic diet is employed, elevated cholesterol and triglyceride levels are common laboratory findings, seen in approximately 60% of patients on the traditional ketogenic diet [34]. Parents of a child with very high cholesterol either at baseline or after 1–3 months on the diet should be screened for dyslipidemia themselves. If the lipid values are significantly abnormal (e.g., total cholesterol >300 mg/dL), it is advised to recheck a fasting specimen 2 weeks later. Should abnormalities persist, the ketogenic ratio could be lowered, MCT oil incorporated, polyunsaturated fats substituted for monounsaturated fats, or carnitine added [34]. We have not started a cholesterol-lowering agent (e.g., statin) on any child at our center to date. Although there is good evidence for the role of statins in preventing cardiovascular disease due to dyslipidemia in adults [35], it is less clear in children [36]. The role for statin drugs in children with dyslipidemia on the ketogenic diet has not been investigated to date. The ketogenic diet does not typically need to be discontinued because of elevated cholesterol in our opinion or that of the Consensus Statement [12].

6.2. Handling intercurrent illnesses and surgeries

Children on the ketogenic diet will have viral and bacterial illnesses, most of which can be managed effectively and safely without referral to an urgent care facility. During periods of illness, we advise unlimited intake of carbohydrate-free fluids as tolerated as a measure to prevent dehydration from high fever or diarrhea. In cases of protracted (>24 hours) vomiting, patients can drink half-strength oral rehydration solution (e.g., 1:1 Pedialyte with water or Powerade Zero) to maintain electrolyte levels. Illnesses can produce excessive ketosis in children on the ketogenic diet, which can be treated as previously discussed with small amounts of dextrose-containing drinks. The general principle for parents is to treat the illness first and to consult us to resume the diet when the child is improved. It is always important to remind parents and medical practitioners of the importance of dextrose-free intravenous solutions and carbohydrate-free prescriptions when they are needed. However, after 24–48 hours of continued dehydration with inability to tolerate oral intake, dextrose will need to be carefully introduced into intravenous fluids (or total parenteral nutrition) to prevent hypoglycemia and malnutrition.

Once the illness has resolved to a large degree, ketogenic foods should be reintroduced to the child. These foods can be started at one-third or one-half total daily calories for the first day, then gradually increased over 2–3 days, in a manner similar to when the ketogenic diet was first started. Parents of children on the ketogenic diet are counseled to always bring some nonperishable, quick ketogenic meals with them to emergency departments in case of an admission and delay in a hospital kitchen preparing appropriate foods. Should the kitchen be unable to calculate ketogenic diet meals, the parents are then advised to create meals from foods in the hospital cafeteria if possible.

Temporary cessation of a ketogenic diet for illness or to make a patient NPO for surgery is a common scenario and is easily handled as many medications can be administered intravenously and intravenous solutions can be administered free of dextrose. Temporary fasting can achieve higher serum ketone concentration and yield better short-term seizure management; in fact, patients with breakthrough seizures can benefit from an overnight fast to achieve previous seizure control, and this is an option worth considering for patients with an increase in seizures without other obvious pathological explanation. Patients who undergo surgery should have serum pH, glucose, and electrolytes monitored closely and the diet restarted as soon as possible postoperatively [37].

Children may require new medications while on dietary treatment to treat otitis media, streptococcal pharyngitis, or other pediatric conditions. When choosing medication preparations, as a general guideline, tablets are generally free of significant carbohydrate content, whereas many suspension preparations and chewable tablets are not. As the majority of preparations used for children are...
suspending because of pediatric patient preference, this may be a significant issue. Locating compounding pharmacies capable of making suspensions is one solution. Pharmacies can also advise families which tablet medications can be crushed and mixed into liquids. Any medical practitioners prescribing medications to a patient on a ketogenic diet must specify on the prescription “carbohydrate free” or consult with the prescribing pharmacy regarding low-carbohydrate options for the desired treatment. In years past, we would try and keep track of carbohydrate contents of common antibiotics and anticonvulsants. However, with the advent of many generic formulations today, this information may be misleading or even completely incorrect. We therefore advise parents to check all medications with the pharmacist rather than the neurologist or pediatrician.

It has been anecdotally reported that high doses of oral (not inhaled) corticosteroids can negate ketosis and lead to seizure exacerbations. Although this has never been formally studied, we would advise caution and use of lower doses of steroids when possible. In emergency situations such as an asthma exacerbation or allergic reaction, the use of high-dose steroids may require a temporary discontinuation of the ketogenic diet during steroid use.

7. Long-term issues with the ketogenic diet

Several issues require particular attention from those caring for patients on long-term use of the ketogenic diet. Typically the issues regarding hypoglycemia, constipation, acidosis, and hunger become less problematic over time. Exceptions may occur during intercurrent illnesses. In general, the long-term (over years) issues that a general practitioner needs to be aware of are related to 1) inadequate supplementation to prevent systemic deficiencies and 2) increasing risk of poor growth, bone fractures, and kidney stones.

7.1. Vitamin, mineral, and enzyme deficiencies

Although ketogenic diets are designed to provide relevant micro- and macronutrients, supplementation is essential to ensure adequate calcium and vitamin D, which are relatively reduced in ketogenic dietary foods [38]. There is some concern over other potential deficiencies, and therefore, it is recommended that all children be provided with multivitamin and mineral supplements [12]. Several of these vitamins are available in carbohydrate-free chewable preparations for pediatric use, so refusal of the child to take these supplements should not be an issue as an alternate vitamin can be prescribed.

Carnitine deficiency can cause serious cardiac and hepatic disease, but it is an exceedingly rare complication of the ketogenic diet. Serum carnitine levels should be checked routinely at diet-related follow-up visits and in patients with otherwise unexplained muscle weakness or excessive fatigue. Carnitine is important for long-chain triglyceride breakdown, it is not necessary for children on the MCT diet. Carnitine supplements can be expensive and are not universally recommended for patients on the ketogenic diet, but should be used if the patient is symptomatically deficient. Patients taking valproate may be at increased risk of hypocarnitremia [39].

Vitamin D deficiency occurs in many children on the ketogenic diet long term [40]. There are reports of bone mineralization loss and a higher risk of bone fractures in patients on the ketogenic diet, especially those who are less mobile [40,41]. Monitoring for bone changes via a dual-energy x-ray absorptiometry (DEXA) study is probably prudent in patients on the diet for 2 years or longer to identify children at risk for fractures [12]. Some children may require pamidronate injections if bone fractures persist despite vitamin D and calcium supplementation. Repeated bone fractures may eventually require discontinuation of the ketogenic diet.

Selenium deficiency has been reported as a cause of sudden death, prolonged QT intervals, and dilated cardiomyopathy [42–44]. In any child with cardiac abnormalities on the ketogenic diet, serum selenium levels should be checked immediately. The recommended daily allowance for young children is 20–30 μg/day, with 40–55 μg/day suggested for older children and adults. It is available in many nuts (brazil nuts and walnuts) and fish, but most supplements contain adequate selenium (55 μg), so the use of additional amounts is not recommended at this time.

7.2. Poor growth

Continued dietitian support throughout the duration of a ketogenic diet is needed to ensure that the diet’s constituents are optimized to ensure and maintain patient growth. Monitoring every 3 months is advised, with patients younger than 1 year requiring probably more frequent assessment [45]. Poor linear growth may require increased calories in the diet and, in the most extreme cases, reduction of the ketogenic ratio. However, overall it appears that patients on any properly monitored ketogenic diet have adequate growth [45,46]. Experienced dietitians can also provide dietary counseling for patients reporting “dietary fatigue” or boredom with a relatively limited selection of food by suggesting recipes or novel ingredients to prevent diet noncompliance. Significant weight loss is unusual and should prompt an evaluation for malabsorption, vomiting, or intercurrent illness. After 6–12 years, growth disturbance can become almost universal in children receiving the ketogenic diet [41].

7.3. Bone fractures and kidney stones

One study of children on the ketogenic diet longer than 6 years found an increased risk of bone fractures (20%) and kidney stones (25%) [41]. For these reasons, it is imperative that children receiving dietary treatment for these prolonged periods take vitamin D and oral citrates. Any concern for a bone fracture or kidney stone should lead to an immediate DEXA scan and renal ultrasound, respectively. Repeated difficulties with these problems may require strong consideration of discontinuing the ketogenic diet, and weighing of its relative benefits after prolonged use. Research investigating children who had discontinued the ketogenic diet years prior did not identify a higher risk of bone fractures or kidney stones [47].

7.4. Dyslipidemia

Dyslipidemia fortunately does not appear to be a long-term side effect of the ketogenic diet in studies to date [41]. The average total cholesterol for children on the diet over 6 years was 201 mg/dL in one study [41]. Similarly, children who had discontinued the diet years prior had a mean total cholesterol of 158 mg/dL [47]. The long-term effects of elevations in lipid profiles on coronary or carotid arteries, however, remain unknown at this time.

8. Rare reported adverse effects

Rare side effects have been described in case reports that have not been mentioned so far in this review (Table 4). These include basal ganglia changes, increased illnesses, bleeding, and other electrolyte and mineral deficiencies. The correlation between these adverse effects and the ketogenic diet has not been definitively demonstrated. However, as no centralized adverse effect registry exists for dietary treatment, as often occurs during the initial introduction of a new anticonvulsant drug by the pharmaceutical company and Food and Drug Administration (FDA), the practitioner treating a child on the ketogenic diet with a potential life-threatening illness needs to be aware of these single case reports. It is noteworthy that the consensus
Finally, adults who drink alcoholic beverages can be advised that low-carbohydrate diets such as scotch and scotch blends are low-carbohydrate as well. It is important to note that these restrictive diets; however, low-carbohydrate diets have been shown to be effective in reducing persistent elevations in an adult at risk may therefore require discontinued dietary therapy gradually with careful monitoring for worsening seizure activity. The modiﬁcation of the ketogenic diet ratio to increase carbohydrate intake and increased calories to restore a normal body mass index should restore hormonal cycling. Similarly, excessive and undesired weight loss in adult patients can be prevented or corrected with liberalization of the ketogenic diet ratio and increased calories. The ramiﬁcations for cardiovascular disease from dyslipidemia in adults may be higher than those for children; persistent elevations in an adult at risk may therefore require intervention. It is unknown if pregnancy is safe in humans while on these restrictive diets; however, low-carbohydrate diets have been used in many populations, and in animal studies chronic ketosis appears to be safe for the mother and newborn. In comparison to the known teratogenic effects of valproate and phenytoin, for example, dietary treatments may be a feasible alternative if successful. Finally, adults who drink alcoholic beverages can be advised that low-carbohydrate “light” and nonalcoholic beers are available; single malt scotch and scotch blends are low-carbohydrate as well.

9. Special issues for adults

As the number of adult patients trying ketogenic diets, especially the modiﬁed Atkins diet, for epilepsy has increased, issues unique to this population have become apparent. Caloric restriction in young women can cause loss of bone density and menstrual irregularities. This has been described before in women treated with the ketogenic diet for epilepsy. A reduction in ketogenic diet ratio to increase carbohydrate intake and increased calories to restore a normal body mass index should restore hormonal cycling. Similarly, excessive and undesired weight loss in adult patients can be prevented or corrected with liberalization of the ketogenic diet ratio and increased calories. The ramiﬁcations for cardiovascular disease from dyslipidemia in adults may be higher than those for children; persistent elevations in an adult at risk may therefore require intervention. It is unknown if pregnancy is safe in humans while on these restrictive diets; however, low-carbohydrate diets have been used in many populations, and in animal studies chronic ketosis appears to be safe for the mother and newborn. In comparison to the known teratogenic effects of valproate and phenytoin, for example, dietary treatments may be a feasible alternative if successful. Finally, adults who drink alcoholic beverages can be advised that low-carbohydrate “light” and nonalcoholic beers are available; single malt scotch and scotch blends are low-carbohydrate as well.

10. Discontinuing dietary therapy

Generally, for a patient whose response to the diet is a greater than 50% reduction in seizure frequency, the typical duration of ketogenic diet therapy is 2 years, though this time frame can be extended because of irreversibility of the underlying condition (i.e., GLUT-1 deﬁciency) or because of robust response without signiﬁcant side effects. After 2 years, it is advisable to weigh the relative beneﬁts with potential risks for any patients receiving dietary therapy, recognizing the adverse effects may be more prevalent. In most patients who have been treated for at least several months, abrupt discontinuation outside of an inpatient hospitalization is not usually advised because of the potential risk of seizure exacerbation. The ketogenic diet or modiﬁed Atkins diet should be gradually tapered over several weeks to months by decreasing the ketogenic ratio (or increasing carbohydrates gradually) with careful monitoring for worsening seizure frequency or severity. Should this occur, the neurologist can restart the diet at the previous ketogenic ratio or daily carbohydrate limit if the parent or patient is inclined.

opinion does not specify any scenario in which it is absolutely mandatory to discontinue the ketogenic diet.

9. Special issues for adults

As the number of adult patients trying ketogenic diets, especially the modified Atkins diet, for epilepsy has increased, issues unique to this population have become apparent. Caloric restriction in young women can cause loss of bone density and menstrual irregularities. This has been described before in women treated with the ketogenic diet for epilepsy. A reduction in ketogenic diet ratio to increase carbohydrate intake and increased calories to restore a normal body mass index should restore hormonal cycling. Similarly, excessive and undesired weight loss in adult patients can be prevented or corrected with liberalization of the ketogenic diet ratio and increased calories. The ramifications for cardiovascular disease from dyslipidemia in adults may be higher than those for children; persistent elevations in an adult at risk may therefore require intervention. It is unknown if pregnancy is safe in humans while on these restrictive diets; however, low-carbohydrate diets have been used in many populations, and in animal studies chronic ketosis appears to be safe for the mother and newborn. In comparison to the known teratogenic effects of valproate and phenytoin, for example, dietary treatments may be a feasible alternative if successful. Finally, adults who drink alcoholic beverages can be advised that low-carbohydrate “light” and nonalcoholic beers are available; single malt scotch and scotch blends are low-carbohydrate as well.

10. Discontinuing dietary therapy

Generally, for a patient whose response to the diet is a greater than 50% reduction in seizure frequency, the typical duration of ketogenic diet therapy is 2 years, though this time frame can be extended because of irreversibility of the underlying condition (i.e., GLUT-1 deficiency) or because of robust response without significant side effects. After 2 years, it is advisable to weigh the relative benefits with potential risks for any patients receiving dietary therapy, recognizing the adverse effects may be more prevalent. In most patients who have been treated for at least several months, abrupt discontinuation outside of an inpatient hospitalization is not usually advised because of the potential risk of seizure exacerbation. The ketogenic diet or modified Atkins diet should be gradually tapered over several weeks to months by decreasing the ketogenic ratio (or increasing carbohydrates gradually) with careful monitoring for worsening seizure frequency or severity. Should this occur, the neurologist can restart the diet at the previous ketogenic ratio or daily carbohydrate limit if the parent or patient is inclined.

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