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# Chinese expert recommendations on ketogenic diet therapy for super-refractory status epilepticus

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## Abstract

Super-refractory status epilepticus (SRSE) is a serious and life-threatening neurological condition. Ketogenic diet (KD) is a diet characterized by high fat, low carbohydrate, and moderate protein. As KD shows effectiveness in controlling seizures in more than half of SRSE patients, it can be a treatment option for SRSE. Currently, KD treatment for SRSE is based on personal experience and observational evidence has been published. In the context of a lack of a validated guideline, we convened a multicenter expert panel within the China Association Against Epilepsy (CAAE) Ketogenic Diet Commission to work out the Chinese expert recommendations on KD for SRSE. We summarize and discuss the latest clinical practice of KD for SRSE in critical care settings. Recommendations are given on patient selection, the timing of KD, diet implementation, and follow-up. More research data are needed in this area to support better clinical practice.

**Keywords:** Super-refractory status epilepticus, Ketogenic diet, Intensive care units, Consensus, China

## Introduction

According to the International League Against Epilepsy (ILAE) definition, status epilepticus (SE) is either the failure of the mechanism responsible for seizure termination or the initiation of a mechanism leading to abnormally prolonged seizures, which can have long-term consequences [1]. Refractory SE (RSE) is defined as SE resistant to an adequate dose of an initial benzodiazepine and acceptable second-line antiseizure medication. Super-refractory SE (SRSE) is defined as RSE that persists after 24 h of appropriate anesthetic therapy or recurs upon reduction or withdrawal of anesthetics [2, 3]. SRSE is a serious and life-threatening neurological condition, resulting in a mortality rate of 30% to 50% as reported by different studies and significant neurological deficits and functional impairments [4–7]. Therefore, determining the optimal management for SRSE is critical. However, there are currently no clear protocols to treat SRSE. Apart from the antiseizure agents and anesthetics, other alternative options for SRSE treatment include ketogenic diet (KD), neuromodulation devices, emergent resective surgery, pyridoxine infusion, cerebrospinal fluid drainage, and magnesium infusion [8]. However, when continuous infusion as first- or second-line treatment fails to achieve satisfactory therapeutic endpoints, we are frustrated with the limited guidelines for treatment options due to the lack of robust data.

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KD is a high-fat, low-carbohydrate, and moderate-protein diet that can alter the primary cerebral energy metabolism from glucose to ketone bodies and involves multiple mechanisms of antiepileptic action and antiepileptogenic properties [9–11]. Although KD is typically suggested for chronic intractable epilepsy, recent studies have illustrated the safety and reasonable efficacy of KD in treating SRSE in both adults and children [12–15]. Treatment for SRSE is difficult due to the failure of first- and second-line therapies. Despite the insufficient evidence for KD use as an established treatment for SRSE, previous studies have repeatedly demonstrated the essential role of KD in cutting off continuous infusion of anesthetic agents, weaning from mechanical ventilation, or controlling seizures in more than half of patients [12, 13, 15–21]. As recommended by the International Ketogenic Diet Study Group, KD is "particularly useful" for SRSE, with greater benefits (>70%) than the average KD response (defined as >50% seizure reduction) [9]. In addition, KD is relatively easy to implement in critical care settings without hemodynamic instability and respiratory depression seen in anesthesia [13, 15, 17]. However, since no controlled or randomized studies are available on this issue, further management of SRSE using approaches other than anesthetics and antiseizure agents is based on personal experience and published evidence is from observational studies. In the context of a lack of validated guideline, we convened a multicenter expert panel within the China Association Against Epilepsy (CAAE) Ketogenic Diet Commission [22], to work out the Chinese expert recommendations on KD for SRSE treatment.

## Patient selection

### Indications

Up to now, all available data on KD for RSE/SRSE treatment are from clinical retrospective studies or case reports, except for two prospective studies [14, 23]. Previous studies, although including highly heterogeneous patients, have collectively demonstrated feasibility and safety of the use of KD for RSE/SRSE treatment.

Schoeler et al. have systematically reviewed reports on the use of KD in children with SRSE [21]. They identified 31 articles including 147 children with SRSE. In 25 studies with information on sex, 60 of 114 (53%) children were boys. In 26 studies with clear information given, 30 out of 108 (28%) children had epilepsy prior to SRSE. The most common diagnosis/etiology of SRSE was febrile infection-related epilepsy syndrome (FIRES), reported in 72/126 (57%) children with known etiology [21]. Autoimmune encephalitis and viral encephalitis are also common etiologies in children [12]. Among the 147 children, 141 (96%) achieved ketosis, and 85 of the 141 (60%) children achieved resolution of SRSE after a mean of 6.3 ± 4.4 days of KD [21]. For adults, another systematic review summarized 17 articles, which contained 55 adults (22 males, 40%) with RSE/SRSE receiving adjunctive KD [24]. The reported common etiologies in the adults included new-onset RSE, viral or autoimmune encephalitis, brain ischemic or hemorrhagic disease, and traumatic brain injury. KD successfully achieved cessation of SE in 45 out of the 55 (82%) patients [24]. Types of SE reported included generalized, focal motor, myoclonic, and nonconvulsive in both children and adults [12, 16]. Taken together, in these studies involving patients with different sex, ages, seizure types and diagnosis/etiology, most patients achieved cessation of SE after KD initiation.

KD can effectively treat epilepsy in individuals from infancy to adulthood [9]. Many studies have indicated that KD is safe, tolerable, and possibly more advantageous for infants with drug-resistant epilepsy, including those aged around 1 month [25–28]. Nevertheless, few reports have focused on the use of KD in very young infants (<3 months) with RES/SRSE in intensive care units (ICUs). According to the age information given in 27 studies in the systemic review [21], SRSE children treated with KD had a mean age of 4.2 years. The youngest SRSE patients who received KD safely were 0.1 year old (two cases) [13, 21]. Based on the available data and our experience, we consider that KD is basically safe and feasible for the treatment of SRSE in patients older than 1 month, even though further research on the safety and efficacy of KD in very young infants with SRSE is still needed. Meanwhile, since young infants are more vulnerable to adverse events such as hypoglycemia and acidosis, they should be more closely monitored when receiving KD.

SE can have different presentations, such as convulsive, nonconvulsive, focal motor, focal sensory, focal impairment of function. It has been observed that patients with some types of SE respond well to KD. Caraballo summarized 3 major SE types that are most likely to respond to KD: focal and less frequently generalized SE (primarily in focal epilepsies of diverse etiologies), pure form of myoclonic SE, and nonconvulsive and/or electrical SE (in the framework of epileptic encephalopathies) [16, 29]. A large number of studies on the use of KD have been conducted in children and adults with motor, focal nonconvulsive, myoclonic, and generalized RSE/SRSE, and good responses have been shown in these SE types [13, 16, 18, 23, 30–38]. In children, many epileptic encephalopathies are associated with nonconvulsive and electrical SE, including electrical SE during sleep and hypsarrhythmia. KD has also shown efficacy in these conditions [16, 39, 40].

In addition, KD works particularly well in certain epilepsy syndromes and etiologies. It is well known that KD is the first choice for glucose transporter protein 1 deficiency syndrome and pyruvate dehydrogenase deficiency. In both disorders, ketones provided by KD can bypass the metabolic defect and serve as an alternative fuel to the brain [9, 41]. Apart from them, FIRES, infantile spasms, tuberous sclerosis complex, Dravet syndrome, Angelman syndrome, complex I mitochondrial disorders, Ohtahara syndrome, and myoclonic-astatic epilepsy (Doose syndrome) as well as SRSE can benefit more from KD as studies have consistently shown an at least 20% improvement in efficacy above the average 50% KD response [9, 29, 42]. Therefore, these disorders are classified as "indications" of KD by the latest international consensus guideline [9]. It is particularly noteworthy that FIRES is the most common etiology of childhood SRSE [21], and SRSE caused by FIRES is suggested to respond well to KD, especially with early initiation [13, 18]. KD is also demonstrated to be effective in the control or prevention of SE in patients with Dravet syndrome [43, 44]. However, many of these "indications" of KD are rarely reported in RSE/SRSE patients receiving KD treatment, due in part to the etiological feature of RSE/SRSE itself, or the small sample size in related studies.

#### *Recommendations*

KD can be considered for patients of either sex at any age with a diagnosis of SRSE and with no contraindications to KD. At present, there are very few reports of KD application in very young infants with SRSE. However, more KD applications in young infants with drug-resistant epilepsy have shown its safety. Based on the available data so far, the expert panel considers that it is basically safe and feasible to use KD in patients with SRSE older than 1 month. But it needs to be emphasized that the young infants should be monitored closely. In addition, KD can be indicated for SRSE with diverse seizure types and etiologies. For certain epilepsy syndromes and etiologies, such as FIRES and Dravet syndrome, it is reasonable to give priority consideration for KD and/or start KD earlier due to the high response rate.

### Contraindications

As KD induces a shift from carbohydrates to lipids as the primary energy source, patients with a disorder of fat metabolism might develop severe catabolic deterioration in the setting of fasting or a KD. Therefore, KD is absolutely contraindicated in metabolic disorders involving fatty acid transport and oxidation, including primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, β-oxidation defects, long- or medium- or short-chain acyl dehydrogenase deficiency, long- or medium-chain 3-hydroxyacyl-CoA deficiency, and pyruvate carboxylase deficiency. And as the lack of carbohydrates is a precipitating factor for relapse of porphyria, patients with this condition should avoid KD [9, 15, 45]. Before initiation of KD, patients should be screened for the above disorders especially in the pediatric population. These rare metabolic disorders are typically diagnosed in early childhood, and thus are typically not a major consideration in adults presenting with new-onset epilepsy or SE.

Propofol is often used for the treatment of RSE. In both children and adults, long-term infusion of propofol may cause a rare but potentially fatal complication – the propofol infusion syndrome (PRIS). PRIS is characterized by metabolic acidosis, rhabdomyolysis, or electrocardiogram (ECG) changes, with or without acute kidney injury, hyperkalaemia, lipidaemia, cardiac failure, fever, elevated liver enzymes, or raised lactate. The mechanism underlying the development of PRIS is still unclear. Previous studies have suggested impaired fatty acid oxidation and lipid microembolization as potential mechanisms [46, 47]. Although evidence for possible interactions between propofol and KD-induced metabolic changes is insufficient, there can be an increased risk of developing PRIS when these two therapies are combined. A case of fatal PRIS associated with the initiation of KD has been reported [47]. For this reason, the use of propofol within 24 h is listed as a relative contraindication to KD.

For KD application in SRSE, conditions specific to critically ill patients may complicate the treatment. Dysfunctions of certain organs or systems may cause failure to support the change of energy source, or the latter may worsen the already unstable internal environment. Therefore, severe complications and unstable vital signs and/or internal environment can be considered as relative contraindications to KD in SRSE. Such conditions include unstable metabolic (including blood glucose, sodium, calcium and pH), hemodynamic or cardiopulmonary conditions, severe infection, severe malnutrition, acute pancreatitis, liver and renal failure, coagulopathy, etc.[14–16, 32, 45, 48]. Liver or kidney damage that has not reached the terminal stage would not be a contraindication to KD [45]. As hyperlipidemia is a common adverse effect of KD and can occur early after KD initiation [9], KD therapy should be applied with caution in patients with total cholesterol > 300 mg/dL. Lastly, as the safety of KD during pregnancy has not been established yet, pregnancy should also be listed as a relative contraindication.

#### *Recommendations*

Known fatty acid transport and oxidation disorders, pyruvate carboxylase deficiency and porphyria are absolute contraindications to KD. Exposure to propofol within 24 h before KD initiation, total cholesterol > 300 mg/dL, pregnancy, severe complications and unstable vital signs and/or internal environment (metabolic, hemodynamic, or cardiopulmonary instability, severe infection, severe malnutrition, acute pancreatitis, liver and renal failure, coagulopathy, etc.) are relative contraindications to KD in SRES.

## Timing of KD

When SE is refractory to general anesthesia for more than 24 h, alternative anesthetics like ketamine, second- and third-line anticonvulsants, combination of multiple anticonvulsants, or maximizing doses of anticonvulsants are usually tried. Other therapies including KD could also be considered [8, 49].

In clinical practice, questions regarding the proper timing of KD arise frequently. However, the optimal timing for KD initiation in the treatment of SRSE has not been successfully determined yet. In the past, KD was usually initiated late in the course of SRSE. In previous reports, the interval between the onset of SE and initiation of KD varied widely from 1 to 420 days, with a mean interval of 24 days [12, 13, 16, 18]. Risks may arise from the long lag from SE onset to KD initiation, as unremitting seizures, prolonged coma therapy, ventilatory support, and use of a number of anticonvulsants during this period may increase the risk of serious infection, critical multiorgan dysfunction, and irreversible brain damage.

It has been revealed that KD plays an essential role in cutting off continuous infusion of anesthetic agents or controlling seizures in more than half of patients. KD is also helpful for weaning from mechanical ventilation [12, 13, 15–21]. Based on its known antiepileptogenic effects, theoretical neuroprotective properties, and low adverse effect profile, in recent studies there is a growing trend towards earlier consideration of KD in the treatment algorithm for RSE/SRSE [13, 16, 19, 34, 50]. Lin et al. summarized 8 large serial studies published in recent years, and in most of the studies, more than half of the patients started KD within 2 weeks after SE onset [50]. Farias-Moeller et al. have reported that the initiation of KD was becoming earlier in recent years, from 28 days during 2005–2010 to 14.8 days during 2011–2016 [19]. Although a causal effect is difficult to determine, the timing of KD initiation may be crucial for its efficacy. By reviewing 31 articles, Schoeler et al. found that KD is more likely to induce a response when initiated earlier in the course of SRSE ($P = 0.03$) [21]. Considering that the mechanisms by which KD suppresses seizures are different from those of antiseizure medication, Park et al. suggested an early consideration of KD when seizures persist after 48 h of continuous anesthetic agents or recur upon tapering continuous anesthetics [13]. Furthermore, KD has shown to work particularly well in certain conditions as we discussed above. It can be hypothesized that in RSE/SRSE with certain etiologies, early initiation of KD would be more beneficial. Taking FIRES as an example, Peng et al. observed a better outcome (lower modified Rankin Scale score) in SRSE patients of FIRES etiology when KD was started within 15 days after SE onset [18]. Taken together, most experts believe that KD is a prioritized option when we start to consider other options apart from antiseizure medication and anesthetics (i.e., when SE persisted more than 24 h after appropriately chosen and dosed continuous anesthetics), rather than a last-choice after all other attempts have failed.

In addition, three important points should be noted. First, the SRSE must be real SRSE, not iatrogenic SRSE. For the latter, stopping the inappropriate interventions is the key. Second, etiological evaluations (including neuroimaging, genetics, cerebrospinal fluid pathogen and immunological analysis) are critical throughout the whole process of SE management. Once the etiology is identified, priority should be given to etiological treatment. Third, immunotherapy may be prioritized ahead of KD in many cases, especially for new-onset RSE/SRSE. Inflammatory or autoimmune encephalitis is one of the main etiologies of SE, and it is not always identifiable. We should keep in mind the possibility of inflammatory or autoimmune etiology in conditions such as subacute onset of seizures with possible neuropsychiatric symptoms, high seizure frequency, multifocal localization, and history of cancer or autoimmune disease. Even in new-onset RSE/SRSE with unclear etiology, immunotherapy might be efficacious [2, 51–53]. Although evidence-based immunotherapy guideline is currently lacking, based on our experience, immunotherapy can be given when the etiology of SRSE is not clear or there is a suspicion of immunological etiology. Before starting KD, it is better to try at least one immunotherapy such as high-dose corticosteroids, intravenous immunoglobulin, and plasmapheresis, most of which are easy to implement.

#### Recommendation

KD can be considered as early as 24 h after continuous anesthetics infusion if seizures persist or recur upon tapering the anesthetics. And it is better to try at least one immunotherapy (corticosteroids, intravenous immunoglobulin, or plasmapheresis) before starting KD for SRSE with immunological or unclear etiology. The early use initiative is particularly relevant in certain epilepsy syndromes and etiologies in which KD has been shown

to be "good early", for which FIRES is the most obvious example.

## Diet implementation

Initiation of KD in SRSE in critical care settings is often associated with significant challenges including multiple intravenous infusions, difficulty in eliminating all sources of carbohydrates, use of corticosteroids which can inhibit the establishment of ketosis, inability to provide enteral nutrition, and lack of a skilled team with expertise in KD formulation and implementation. As these challenges involve multidisciplinary issues, a trained collaborative team composed of neurologists/epileptologists, intensivists, dietitians, pharmacists, and nurses is important and should be involved throughout the course of KD implementation in critical care settings [13, 15, 19, 34].

At present, despite the lack of validated guidelines, considerable experience in practice has been accumulated. The International Ketogenic Diet Study Group has given detailed recommendations on various aspects of KD use in the treatment of epilepsy in children. Most of them are also applicable in KD treatment for SRSE [9]. Some clinical studies have reported practical approaches which seem to work well in their respective centers [13, 14, 19, 35, 48, 54]. Here, we propose a protocol to implement KD for SRSE in ICUs based on the current reviews and clinical practice (Fig. 1).

### Pre-diet evaluation

After ruling out contraindications, a pre-diet evaluation is recommended before KD initiation. By measuring the height and weight, the basic nutritional status is evaluated and the required calories and fluid are estimated. To help evaluate the seizure type, nutritional status and complications, we recommend the following laboratory and ancillary examinations, by combining the experience of other centers [9, 13, 14, 19, 35, 48, 54]: complete blood count, fasting lipid profile, electrolyte and trace elements (including calcium, phosphorus, iron, magnesium, zinc, selenium), serum liver and kidney tests, blood gas analysis (including serum bicarbonate), serum acylcarnitine profile, vitamin D level, urinalysis (including urine ketones), and electroencephalogram (EEG). If applicable and conditions permit, continuous EEG monitoring, abdominal and urinary ultrasound, ECG and echocardiography (strongly needed in the presence of a history of heart disease), bone age (for children) and bone mineral density, amylase and lipase (for parenteral KD) test are advised.

#### *Recommendations*

The recommended pre-diet evaluation includes baseline weight and height; complete blood count, fasting lipid profile, electrolyte and trace elements, serum liver and kidney tests, blood gas analysis, serum acylcarnitine profile, vitamin D level, urinalysis, and EEG. Optional examinations include continuous EEG monitoring, abdominal and urinary ultrasound, ECG and echocardiography, bone age and bone mineral density, amylase and lipase test.

### Diet initiation and maintenance

#### *Feeding methods*

Due to the anesthetic-induced coma therapy, most of the patients with SRSE are enterally fed via a gastrostomy or a nasogastric tube. In this condition, KD may be provided as an all-liquid, formula-based diet. Liquid diets may be appropriate as enteral delivery has good patient compliance and high efficacy [55, 56]. There is a variety of commercial formula products available. Although all products are fortified with vitamins and minerals, the diet therapy should be supplemented to meet the Dietary Reference Intakes (DRIs) [57, 58].

In ICUs, because of the critical status of the patients who are often in a coma or unable to tolerate enteral feeds (due to, e.g., ileus and intestinal failure), sometimes KD therapy needs to be started through parenteral administration, which usually acts as a temporary bridge towards enteral KD [59].

The preparation of parenteral KD could be feasible with commercially available, standard intravenous fat and amino acid solutions [60, 61]. For example, a parenteral KD preparation can contain commercially available fat emulsion with medium-chain triglycerides (20% lipid emulsion), fat emulsion with long-chain triglyceride (20% lipid emulsion), and amino acid hyperalimentation (6.67% or 10% concentration). Glucose-free solutions such as saline can also be contained as required. Ketogenic parenteral nutrition can be prepared by properly combining these solutions. The Ketogenic parenteral nutrition is mixed in a laminar air flow under sterile conditions and administered to the patient via a central or a peripheral line [62]. It can be infused continuously over 16 h and stopped for 8 h at nighttime.

Intravenous KD may increase the risk of transient elevation of liver enzymes, lipid profiles, and pancreatic enzyme concentrations. Additionally, patients with SRSE are often receiving multiple medications that are metabolized in the liver. Intravenous KD may enhance cholestasis and hepatotoxicity [33, 60]. Farias-Moeller et al. once reported a 5-year-old child who experienced severe pancreatitis while being on the combinational treatment of valproic acid and intravenous KD [19]. Therefore, enteral KD is preferred if the patient condition permits, and rigorous monitoring of lipids and pancreatic enzymes in patients receiving parenteral KD is required. As soon as

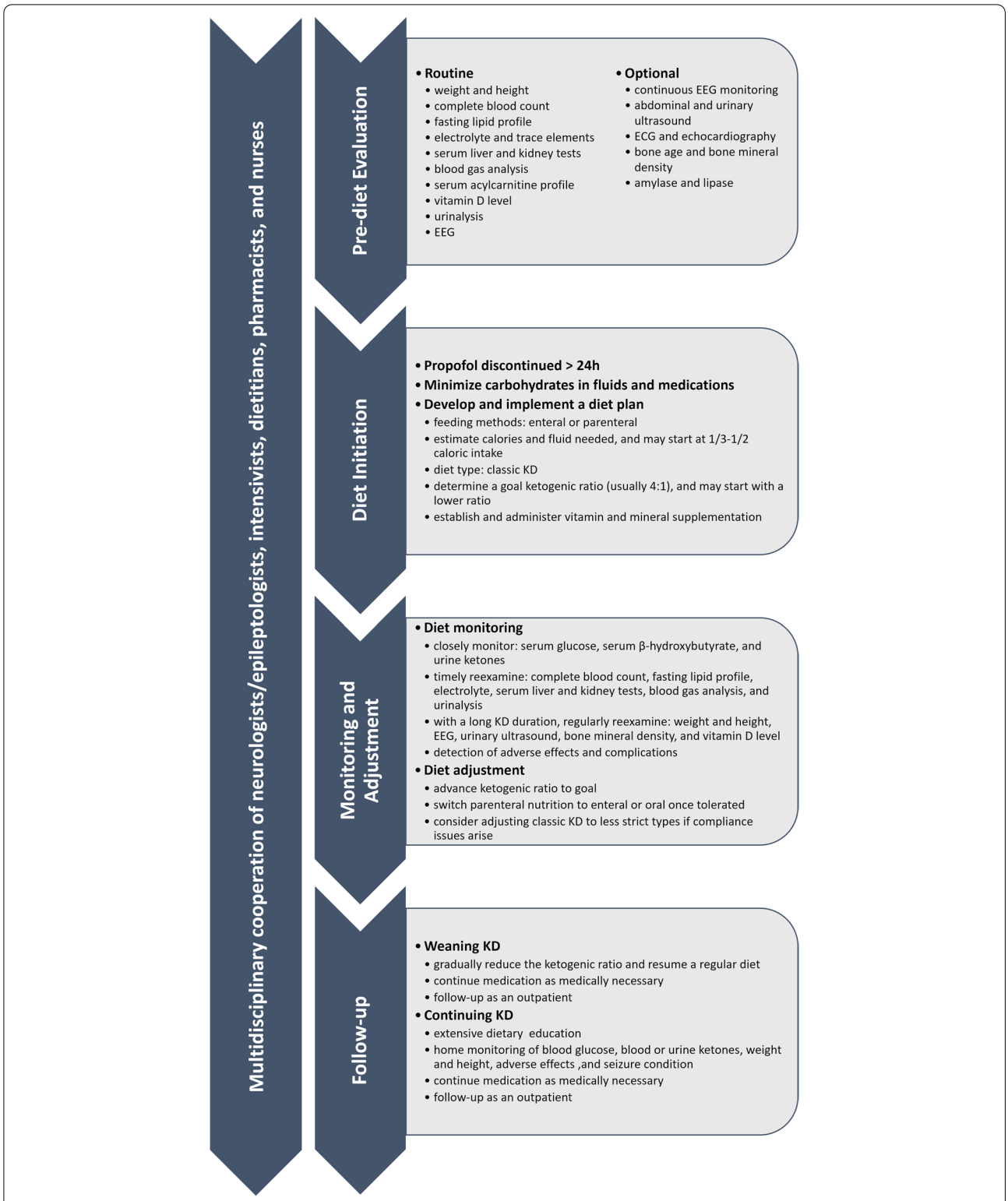


**Fig. 1** The recommended implementation protocol of ketogenic diet for super-refractory status epilepticus

the patient can absorb nutrients through the digestive tract, intravenous KD should be switched to enteral or oral administration.

#### *Recommendations*

Enteral KD is preferred if the patient condition permits. Parenteral KD may benefit patients with enteral feeding intolerance. Ketogenic parenteral nutrition can be prepared with commercially available fat and amino acid solutions. Intravenous administration of KD should be switched to enteral or oral approach once the patient can absorb nutrients through the digestive tract.

#### *Classic KD*

The determination of diet regimen requires professional help from dietitians. According to the available reports, the majority of patients with RSE/SRSE follow the classic KD. Almost all adults and 83% (74/89) of children are given a target ketogenic ratio (fat to protein plus carbohydrates) of 4:1 [12, 21, 24]. Till now, the efficacy of different ketogenic ratios for SRSE has not been specially compared because of the rarity of the disease. As patient compliance to KD is usually not an issue in patients with RSE/SRSE due to their critical condition, KD can be started or rapidly escalated to the 4:1 ratio [12, 23]. This aggressive administration helps to produce ketosis quickly and effectively. On the other hand, some studies have reported the use of a stepwise approach, which initiates KD at a low ratio and then gradually advances to the ratio of 3–4:1. This approach shows comparable efficacy in suppressing SE, but may lead to delayed ketosis [18, 35, 63].

As ketone bodies are considered to have an antiepileptogenic effect, one of the goals of KD therapy is to achieve ketosis [10]. Successful KD initiation marked by achievement of ketosis is feasible in the ICUs, and in literature, 96% of children could achieve ketosis [21]. Regarding the optional levels of ketosis, current data from literature are insufficient. In addition, a consistent ketosis level may not be easy to maintain in the ICUs partly due to the complicated concomitant medications such as corticosteroids, barbiturates, anesthetics, and carbohydrate-containing medications. The common presence of carbohydrates in medications and intravenous fluids can interfere with the production of ketone bodies. Minimizing carbohydrates in medications and fluids is therefore essential for the onset and maintenance of ketosis. The limitation of carbohydrates of medical origin should be assisted by pharmacists, and a well-designed treatment protocol can help achieve ketosis more efficiently. In two studies with standardized KD treatment protocols, ketosis was achieved in 25 out of 26 (96%) adult patients with RSE/SRSE, and the median time to achieve ketosis was 1–2 days. In contrast, in earlier case reports, the time to achieve ketosis was at least 3.5 days in adults with RSE/SRSE [24].

The traditional method of initiating KD involves a period of fasting (12–24 h), with no carbohydrate-containing fluids provided. Fasting may lead to a quicker ketosis and seizure reduction, and therefore is advantageous for SRSE where a more immediate response is desired [64, 65]. However, fasting is by no means mandatory. Since it may lead to additional adverse events such as hypoglycemia and acidosis, fasting should be considered on an individual basis. If fasting is applied, glycemia and serum bicarbonate should be monitored frequently [9, 66]. Yet in the current literature, a compromised approach has been successfully applied in SRSE patients in some centers, which includes a 1/3 or 1/2 cal for the first 24 h, followed by advancement in every 1–3 days by 1/3 or 1/2 caloric intervals until full calories [13, 14, 18, 50]. This approach seems to offer a good balance between efficacy and side effects. For infants, it is more appropriate to initiate KD with a low ketogenic ratio (e.g., 1:1 or 2:1) and then gradually advance and titrate the ratio [50, 67, 68].

#### *Recommendations*

Classic KD with a 4:1 ratio is recommended. If there is no patient compliance issue, KD initiation with this high ratio directly is usually feasible and effective. And the ratio can also be individualized on a case-by-case basis and adjusted as needed. For example, it is suggested that KD start with a lower ketogenic ratio and/or a lower portion of energy needs, and then advance it to the goal ratio and/or full calories. Fasting is optional when a more rapid KD benefit is desired.

#### *Alternative KD types*

Less restrictive types of KD, such as the modified Atkins diet (MAD) and the low glycemic index treatment (LGIT), have also been successfully used to treat patients with nonconvulsive SE [30, 69]. Numerous studies on intractable epilepsy have shown that compared with the classic KD, MAD and LGIT have advantage of better tolerability [70]. However, clinical experience on these KD variants for SRSE treatment is too little to make a conclusion. For patients with SRSE, compliance problems rarely occur in the acute phase; instead, they may arise when patients begin to eat orally. In this case, a switch from classic KD to MAD or LGIT can be considered, especially for adolescents and adults.

#### *Recommendations*

When compliance issues arise from the start of oral feeding or when patients intend to continue KD in the long

term, alternative KD such as MAD and LGIT can be considered, especially for teenagers and adults.

#### *Supplementation*

For non-full nutritional formula, carbohydrate-free multivitamin, minerals, vitamin D and calcium should be supplied to meet the recommended daily nutritional requirements. Although commercial formula-based KD products are usually fortified with vitamins and minerals, supplementations are sometimes still needed according to DRIs. And age-appropriate requirements should be considered [9, 71, 72]. Oral citrates can reduce the risk of metabolic acidosis and kidney stones in children treated with KD [9, 73]. They can be supplemented in patients receiving enteral or oral nutrition. Carnitine supplementation has been a controversial issue. Empiric carnitine supplementation can be expensive and adds an additional medication to patients. Most ketogenic centers recommend carnitine supplementation if it is at a low level or when patients become symptomatic [9, 74].

#### *Recommendations*

Multivitamin, minerals, vitamin D, calcium, citrates, and carnitine can be supplemented according to patients' condition.

#### *Monitoring and adverse events*

First, monitoring of vital signs, including continuous ECG, is required. This is usually the default setting in ICUs. Second, once KD is initiated, serum glucose (e.g., q4h, and then q8h after ketosis), serum β-hydroxybutyrate (e.g., q24h) and urine ketones (e.g., q12h-q24h) should be monitored to assess the ketosis status[9, 13, 14, 19, 34]. Ketosis can be defined as > 3 mmol/L serum β-hydroxybutyrate, or > 3 + urine ketones [13, 21]. The serum ketosis is more accurate, but it is more expensive and requires finger sticks. We recommend that both indicators be monitored during KD implementation [75]. Third, assessments including complete blood count, fasting lipid profile, electrolyte, serum liver and kidney tests, blood gas analysis, and urinalysis should be appropriately re-examined to detect adverse events and complications. The adverse events/complications requiring interventions include metabolic acidosis defined as serum $CO_2$ < 16 mmol/L and hypoglycemia defined as serum glucose < 2.2 mmol/L, for which interventions include bicarbonate and sugar supplementation, respectively. Fourth, EEG should be re-examined in a timely manner to assess the epileptic electrical activity. In institutions where conditions permit, continuous EEG monitoring is strongly recommended. Lastly, during a long KD therapy, weight and height should be measured weekly and urinary ultrasound, bone mineral density, and vitamin D level should be re-examined regularly to reassess the nutritional status and detect long-term adverse events/complications [9].

KD is generally safe in RSE/SRSE cohorts. Adverse events have been reported in about 1/3–1/2 of the patients with RSE/SRSE [12, 21]. Commonly reported adverse events are similar in children and adults, including gastrointestinal disturbance (e.g., regurgitation, vomiting, constipation, diarrhea, abdominal distention, and gastrointestinal paresis), hyperlipidemia, acidosis, and hypoglycemia. Other less common side effects include elevated liver enzymes, hypokalemia, hyponatremia, hypoproteinemia, weight loss, kidney stones, pancreatitis, and arrhythmia. KD should be stopped when serious adverse events occur, such as fatal arrhythmia (ventricular fibrillation) and pancreatitis [12, 21, 76]. Some serious complications such as sepsis and aspiration pneumonia have also been reported, which, however, are not necessarily attributable to KD. The majority of the adverse events could be successfully managed with symptomatic and supportive treatment and do not necessitate KD discontinuation [12, 15, 21]. Still, close monitoring and preventive management of potential adverse events are important for successful KD treatment.

#### *Recommendations*

After KD initiation, it is recommended to closely monitor serum glucose, serum β-hydroxybutyrate and urine ketones, and timely re-examine the complete blood count, fasting lipid profile, electrolyte, serum liver and kidney tests, blood gas analysis, and urinalysis. Regular EEG or continuous EEG monitoring is key to the evaluation of therapeutic effect. During a long KD therapy, weekly measurement of weight and height and regular examination of urinary ultrasound, bone mineral density, and vitamin D level are recommended. The most common adverse events are gastrointestinal symptoms, hyperlipidemia, acidosis, and hypoglycemia. Most of the patients can well tolerate the diet without serious adverse events. Close monitoring and preventive management of potential adverse events are important.

## Follow-up

The optimal duration of KD after SE remission is uncertain. In the literature, many SRSE patients with good response to KD would continue the diet for weeks to months [77]. Decision on whether to continue or wean KD should be made based on the individual's condition, with comprehensive considerations of seizure control, EEG, cognitive function, tolerability, compliance, and socio-economic situation, etc. We do not have enough evidence at this stage to give a suggestion on the time and the criteria for KD termination. Neither does the

expert panel have a consensus on this issue. Meanwhile, some experts suggest that patients with immune-related etiologies (including FIRES) or unknown causes should adhere to KD for at least 3–6 months after SE remission, and patients with a clear acute cause, such as intracranial hemorrhage, can wean KD after 2 weeks of seizure control. For patients with a previous history of epilepsy, or who have developed chronic epilepsy, KD can also be continued as part of the long-term epilepsy management.

To transition off KD, the ketogenic ratio can be decreased by 0.5:1 every week until negative urine ketones, and then a regular diet is started [19]. If KD is continued, there is a need for extensive dietary education on practical issues, such as KD prescription, meal planning and preparation, monitoring indicators and methods, and supplements. It is also important to help patients and their families understand and accept the limitations and difficulties of long-term KD treatment. Classic KD can be changed to other types such as MAD and LGIT if necessary. Home monitoring of blood glucose, blood or urine ketones, weight and height, adverse events, and seizure condition is necessary during continuation of KD. Lastly, whether or not to continue KD, medication should be continued as medically necessary, and regular follow-up is required [9, 14, 19, 34].

### Recommendations

After the acute phase of SE, whether to continue KD should be judged according to the individual's condition. Discontinuation of KD, if necessary, should be implemented gradually. If KD is to be continued, patients and families should receive relevant dietary education and adhere to the monitoring and follow-up examinations during treatment.

## Conclusion

This recommendatory statement represents multicenter efforts in China to optimize the clinical use of KD for the treatment of SRSE. KD is a valuable adjunctive treatment in the management of SRSE and can be indicated for patients from infancy to adulthood and with diverse seizure types and etiologies. Early use of KD may be advantageous, especially in certain epilepsy syndromes and etiologies like FIRES. Implementation of KD for SRSE in the ICUs requires multidisciplinary cooperation, careful evaluation, and close monitoring. Classic KD with a 4:1 ratio is recommended in the acute phase, and can be initiated directly, or by a step-by-step approach, or through a fasting period. Adjustment and discontinuation of KD should be considered based on individual's condition. Overall, there is currently a lack of robust research data in this area, and our recommendations are based on limited clinical observation and expert experience. Further studies, especially prospective studies with controlled design, are needed.

#### Abbreviations

CAAE: China Association Against Epilepsy; DRI: Dietary Reference Intake; ECG: Electrocardiogram; EEG: Electroencephalogram; FIRES: Febrile infection-related epilepsy syndrome; ICUs: Intensive care units; ILAE: International League Against Epilepsy; KD: Ketogenic diet; LGIT: Low glycemic index treatment; MAD: Modified Atkins diet; PRIS: Propofol infusion syndrome; RSE: Refractory status epilepticus; SE: Status epilepticus; SRSE: Super-refractory status epilepticus.

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#### Authors' contributions

This work was completed under the framework of the CAAE Ketogenic Diet Commission. Jianxiang Liao, Rong Luo, and Jiong Qin initiated, organized, and structured this expert recommendation. Rong Luo, Xin Tong, and Qianyun Cai completed the writing and revision of the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

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### Declarations

#### Ethical approval and consent to participate.

Not applicable

#### Consent for publication

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#### Competing interests

Jiong Qin and Qun Wang are the members of the Editorial Board for Acta Epileptologica, who was not involved in the journal's review of, or decisions related to this manuscript. Other authors declare no conflicts of interest.

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## References


1. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015;56(10):1515–23.
2. Gofton TE, Gaspard N, Hocker SE, Loddenkemper T, Hirsch LJ. New onset refractory status epilepticus research: What is on the horizon? Neurology. 2019;92(17):802–10.
3. Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia. 2018;59(4):739–44.
4. Barberio M, Reiter PD, Kaufman J, Knupp K, Dobyns EL. Continuous infusion pentobarbital for refractory status epilepticus in children. J Child Neurol. 2012;27(6):721–6.
5. Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia. 2001;42(11):1461–7.
6. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain. 2011;134(10):2802–18.
7. Hocker S, Tatum WO, LaRoche S, Freeman WD. Refractory and Super-Refractory Status Epilepticus—an Update. Current Neurology and Neuroscience Reports. 2014;14(6):452.
8. Kirmani BF, Au K, Ayari L, John M, Shetty P, Delorenzo RJ. Super-Refractory Status Epilepticus: Prognosis and Recent Advances in Management. Aging Dis. 2021;12(4):1097–119.
9. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3(2):175–92.
10. Zhang Y, Xu J, Zhang K, Yang W, Li B. The Anticonvulsant Effects of Ketogenic Diet on Epileptic Seizures and Potential Mechanisms. Curr Neuropharmacol. 2018;16(1):66–70.
11. Chen F, He X, Luan G, Li T. Role of DNA Methylation and Adenosine in Ketogenic Diet for Pharmacoresistant Epilepsy: Focus on Epileptogenesis and Associated Comorbidities. Front Neurol. 2019;10:119.
12. Sandu C. MAGUREANU SA, Iliescu C, Pomeran C, and Craiu DC, Ketogenic Diet Treatment for Status Epilepticus. Farmacia. 2019;67(2):218–25.
13. Park EG, Lee J, Lee J. The ketogenic diet for super-refractory status epilepticus patients in intensive care units. Brain Dev. 2019;41(5):420–7.
14. Cervenka MC, Hocker S, Koenig M, Bar B, Henry-Barron B, Kossoff EH, et al. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. Neurology. 2017;88(10):938–43.
15. McDonald TJW, Cervenka MC. Ketogenic Diet Therapies for Seizures and Status Epilepticus. Semin Neurol. 2020;40(6):719–29.
16. Caraballo RH. Ketogenic Diet for Refractory Status Epilepticus in Children. Curr Treat Options Peds. 2019;5:417–30.
17. Williams TJ, Cervenka MC. The role for ketogenic diets in epilepsy and status epilepticus in adults. Clin Neurophysiol Pract. 2017;2:154–60.
18. Peng P, Peng J, Yin F, Deng X, Chen C, He F, et al. Ketogenic Diet as a Treatment for Super-Refractory Status Epilepticus in Febrile Infection-Related Epilepsy Syndrome. Front Neurol. 2019;10:423.
19. Farias-Moeller R, Bartolini L, Pasupuleti A, Brittany Cines RD, Kao A, Carpenter JL. A Practical Approach to Ketogenic Diet in the Pediatric Intensive Care Unit for Super-Refractory Status Epilepticus. Neurocrit Care. 2017;26(2):267–72.
20. Dozières-Puyravel B, Höhn S, and Auvin S, Considering safety and patient tolerance in the use of ketogenic diet in the management of refractory and super-refractory status epilepticus: a systematic review. Expert Review of Neurotherapeutics, 2021: p. 1–6.
21. Schoeler NE, Simpson Z, Zhou R, Pujar S, Eltze C, Cross JH. Dietary Management of Children With Super-Refractory Status Epilepticus: A Systematic Review and Experience in a Single UK Tertiary Centre. Frontiers in Neurology. 2021;12:643105.
22. China Association Against Epilepsy (CAAE) Ketogenic Diet Commission. Available from: http://caae.org.cn/aboutxh/index/id/60.
23. Arya R, Peariso K, Gaínza-Lein M, Harvey J, Bergin A, Brenton JN, et al. Efficacy and safety of ketogenic diet for treatment of pediatric convulsive refractory status epilepticus. Epilepsy Res. 2018;144:1–6.
24. Mahmoud SH, Ho-Huang E, Buhler J. Systematic review of ketogenic diet use in adult patients with status epilepticus. Epilepsia Open. 2020;5(1):10–21.
25. Lyons L, Schoeler NE, Langan D, Cross JH. Use of ketogenic diet therapy in infants with epilepsy: A systematic review and meta-analysis. Epilepsia. 2020;61(6):1261–81.
26. Dressler A, Trimmel-Schwahofer P, Reithofer E, Gröppel G, Mühlebner A, Samueli S, et al. The ketogenic diet in infants – Advantages of early use. Epilepsy Res. 2015;116:53–8.
27. Kim JA, Yoon J-R, Lee EJ, Lee JS, Kim JT, Kim HD, et al. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. Epilepsia. 2016;57(1):51–8.
28. Dressler A, Trimmel-Schwahofer P. The ketogenic diet for infants: How long can you go? Epilepsy Res. 2020;164:106339.
29. Armeno M, Caraballo R. The evolving indications of KD therapy. Epilepsy Research. 2020;163:106340.
30. Kumada T, Miyajima T, Kimura N, Saito K, Shimomura H, Oda N, et al. Modified Atkins Diet for the Treatment of Nonconvulsive Status Epilepticus in Children. J Child Neurol. 2009;25(4):485–9.
31. Villeneuve N, Pinton F, Bahi-Buisson N, Dulac O, Chiron C, Nabbout R. The ketogenic diet improves recently worsened focal epilepsy. Dev Med Child Neurol. 2009;51(4):276–81.
32. Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia. 2010;51(10):2033–7.
33. Caraballo RH, Flesler S, Armeno M, Fortini S, Agustinho A, Mestre G, et al. Ketogenic diet in pediatric patients with refractory focal status epilepticus. Epilepsy Res. 2014;108(10):1912–6.
34. O'Connor SE, Ream MA, Richardson C, Mikati MA, Trescher WH, Byler DL, et al. The ketogenic diet for the treatment of pediatric status epilepticus. Pediatr Neurol. 2014;50(1):101–3.
35. Cobo NH, Sankar R, Murata KK, Sewak SL, Kezele MA, Matsumoto JH. The Ketogenic Diet as Broad-Spectrum Treatment for Super-Refractory Pediatric Status Epilepticus. J Child Neurol. 2014;30(2):259–66.
36. Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. Seizure. 2016;41:62–5.
37. Caraballo RH, Valenzuela GR, Armeno M, Fortini S, Mestre G, Cresta A. The ketogenic diet in two paediatric patients with refractory myoclonic status epilepticus. Epileptic Disord. 2015;17(4):491–5.
38. Caraballo R, Darra F, Reyes G, Armeno M, Cresta A, Mestre G, et al. The ketogenic diet in patients with myoclonic status in non-progressive encephalopathy. Seizure. 2017;51:1–5.
39. Reyes G, Flesler S, Armeno M, Fortini S, Ariela A, Cresta A, et al. Ketogenic diet in patients with epileptic encephalopathy with electrical status epilepticus during slow sleep. Epilepsy Res. 2015;113:126–31.
40. Pasca L, Caraballo RH, De Giorgis V, Reyes JG, Macasaet JA, Masnada S, et al. Ketogenic diet use in children with intractable epilepsy secondary to malformations of cortical development: A two- centre experience. Seizure. 2018;57:34–7.
41. Scholl-Bürgi S, Höller A, Pichler K, Michel M, Haberlandt E, Karall D. Ketogenic diets in patients with inherited metabolic disorders. J Inherit Metab Dis. 2015;38(4):765–73.
42. Nangia S, Caraballo RH, Kang H-C, Nordli DR, Scheffer IE. Is the ketogenic diet effective in specific epilepsy syndromes? Epilepsy Res. 2012;100(3):252–7.
43. Dressler A, Trimmel-Schwahofer P, Reithofer E, Muhlebner A, Groppel G, Reiter-Fink E, et al. Efficacy and tolerability of the ketogenic diet in Dravet syndrome - Comparison with various standard antiepileptic drug regimen. Epilepsy Res. 2015;109:81–9.
44. Tian X, Chen J, Zhang J, Yang X, Ji T, Zhang Y, et al. The Efficacy of Ketogenic Diet in 60 Chinese Patients With Dravet Syndrome. Front Neurol. 2019;10:625.
45. Watanabe M, Tuccinardi D, Ernesti I, Basciani S, Mariani S, Genco A, et al. Scientific evidence underlying contraindications to the ketogenic diet: An update. Obes Rev. 2020;21(10):e13053.

46. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. Br J Anaesth. 2019;122(4):448–59.
47. Baumeister FA, Oberhoffer R, Liebhaber GM, Kunkel J, Eberhardt J, Holthausen H, et al. Fatal propofol infusion syndrome in association with ketogenic diet. Neuropediatrics. 2004;35(4):250–2.
48. Thakur KT, Probasco JC, Hocker SE, Roehl K, Henry B, Kossoff EH, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology. 2014;82(8):665–70.
49. Lee SK. Diagnosis and Treatment of Status Epilepticus. J Epilepsy Res. 2020;10(2):45–54.
50. Lin K-L, Lin J-J, Wang H-S. Application of ketogenic diets for pediatric neurocritical care. Biomedical Journal. 2020;43(3):218–25.
51. Abboud H, Probasco JC, Irani S, Ances B, Benavides DR, Bradshaw M, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosurg Psychiatry. 2021;92(7):757–68.
52. Rai S, Drislane FW. Treatment of Refractory and Super-refractory Status Epilepticus. Neurotherapeutics. 2018;15(3):697–712.
53. Alolayan YS, Mckinley K, Bhatia R, Alkhachroum A. Review and Updates on the Treatment of Refractory and Super Refractory Status Epilepticus. J Clin Med. 2021;10(14):3028.
54. Francis BA, Fillenworth J, Gorelick P, Karanec K, Tanner A. The Feasibility, Safety and Effectiveness of a Ketogenic Diet for Refractory Status Epilepticus in Adults in the Intensive Care Unit. Neurocrit Care. 2019;30(3):652–7.
55. Hosain SA, La Vega-Talbott M, Solomon GE. Ketogenic diet in pediatric epilepsy patients with gastrostomy feeding. Pediatr Neurol. 2005;32(2):81–3.
56. Kossoff EH, McGrogan JR, Freeman JM. Benefits of an all-liquid ketogenic diet. Epilepsia. 2004;45(9):1163.
57. Chinese Nutrition Society. The Chinese Dietary Guidelines. Available from: http://dg.cnsoc.org/.
58. United States Department of Agriculture. Dietary Guideline for Americans. Available from: https://dietaryguidelines.gov/.
59. Chiusolo F, Diamanti A, Bianchi R, Fusco L, Elia M, Capriati T, et al. From intravenous to enteral ketogenic diet in PICU: A potential treatment strategy for refractory status epilepticus. Eur J Paediatr Neurol. 2016;20(6):843–7.
60. Lin JJ, Lin KL, Chan OW, Hsia SH, Wang HS, Group CS. Intravenous ketogenic diet therapy for treatment of the acute stage of super-refractory status epilepticus in a pediatric patient. Pediatr Neurol. 2015;52(4):442–5.
61. Strzelczyk A, Reif PS, Bauer S, Belke M, Oertel WH, Knake S, et al. Intravenous initiation and maintenance of ketogenic diet: proof of concept in super-refractory status epilepticus. Seizure. 2013;22(7):581–3.
62. Dressler A, Haiden N, Trimmel-Schwahofer P, Benninger F, Samueli S, Groppel G, et al. Ketogenic parenteral nutrition in 17 pediatric patients with epilepsy. Epilepsia Open. 2018;3(1):30–9.
63. Worden LT, Abend NS, Bergqvist AGC. Ketogenic diet treatment of children in the intensive care unit: Safety, tolerability, and effectiveness. Seizure. 2020;80:242–8.
64. Freeman JM, Vining EP. Seizures decrease rapidly after fasting: preliminary studies of the ketogenic diet. Arch Pediatr Adolesc Med. 1999;153(9):946–9.
65. Kossoff EH, Laux LC, Blackford R, Morrison PF, Pyzik PL, Hamdy RM, et al. When do seizures usually improve with the ketogenic diet? Epilepsia. 2008;49(2):329–33.
66. Bergqvist AG, Schall JI, Gallagher PR, Cnaan A, Stallings VA. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. Epilepsia. 2005;46(11):1810–9.
67. Thompson L, Fecske E, Salim M, Hall A. Use of the ketogenic diet in the neonatal intensive care unit-Safety and tolerability. Epilepsia. 2017;58(2):e36–9.
68. van der Louw E, van den Hurk D, Neal E, Leiendecker B, Fitzsimmon G, Dority L, et al. Ketogenic diet guidelines for infants with refractory epilepsy. Eur J Paediatr Neurol. 2016;20(6):798–809.
69. Martikainen MH, Päivärinta M, Jääskeläinen S, Majamaa K. Successful treatment of POLG-related mitochondrial epilepsy with antiepileptic drugs and low glycaemic index diet. Epileptic Disord. 2012;14(4):438–41.
70. Zarnowska IM. Therapeutic Use of the Ketogenic Diet in Refractory Epilepsy: What We Know and What Still Needs to Be Learned. Nutrients. 2020;12(9):2616.
71. Vestergaard P. Effects of Antiepileptic Drugs on Bone Health and Growth Potential in Children with Epilepsy. Pediatr Drugs. 2015;17(2):141–50.
72. Bergqvist AGC, Schall JI, Stallings VA. Vitamin D Status in Children with Intractable Epilepsy, and Impact of the Ketogenic Diet. Epilepsia. 2007;48(1):66–71.
73. Bjurulf B, Magnus P, Hallbook T, Stromme P. Potassium citrate and metabolic acidosis in children with epilepsy on the ketogenic diet: a prospective controlled study. Dev Med Child Neurol. 2020;62(1):57–61.
74. Berry-Kravis E, Booth G, Sanchez AC, Woodbury-Kolb J. Carnitine levels and the ketogenic diet. Epilepsia. 2001;42(11):1445–51.
75. Carmant L. Assessing ketosis: approaches and pitfalls. Epilepsia. 2008;49(Suppl 8):20–2.
76. Wang X, Gao X, Lu G, Lu Z, Zhou S, Wang Y, et al. The ketogenic diet for paediatric patients with super-refractory status epilepticus in febrile infection-related epilepsy syndrome. Acta Epileptologica. 2020;2(1):4.
77. Fung EL, Chang SK, Yam KK, Yau PY. Ketogenic Diet as a Therapeutic Option in Super-refractory Status Epilepticus. Pediatr Neonatol. 2015;56(6):429–31.