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ORIGINAL RESEARCH

# Ketogenic Diet Therapy for Adult Febrile Infection-Related Epilepsy Syndrome (FIRES): A Case Series of Five Patients and Clinical Efficacy Analysis

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**Objective:** This study reports five clinical cases of adult Febrile Infection-Related Epilepsy Syndrome (FIRES) treated with a ketogenic diet (KD). The aim is to explore the clinical efficacy, safety, optimal initiation timing, and related efficacy factors of KD in adult FIRES through case analysis, and to provide reference for clinical decision-making.

**Methods:** We retrospectively reviewed the medical records of five FIRES patients treated with KD at Shanxi Bethune Hospital between October 2019 and January 2025.

**Results:** Among the five FIRES patients (2 males, 3 females), with a median age of 32 years [interquartile range (IQR) 25–34]. All patients presented with refractory status epilepticus following a febrile illness. EEG revealed slowed background activity with multifocal epileptiform discharges, and 60% (3/5) showed abnormal brain MRI findings. All patients received multidrug antiseizure therapy, anesthetics, and immunotherapy. KD was initiated at a median of 33 days (IQR 10–50) post-onset. Ketosis was achieved within a median of 2 days (IQR 2–3), followed by significant seizure reduction after a median of 3 days (IQR 3–4) of KD. At discharge, mRS scores were 2 (40%) or 4 (60%); by 3-month follow-up, all patients achieved an mRS score of 2. Common adverse effects included diarrhea (60%), hypoalbuminemia (100%), anemia (80%), fecal occult blood (60%), and hyperlipidemia (40%), all of which resolved with symptomatic management.

**Conclusion:** FIRES is a rare and devastating clinical syndrome with an unclear pathogenesis, high mortality, and poor prognosis, often accompanied by cognitive decline or severe neurological sequelae. KD appears effective in FIRES management; however, due to limited case data, further large-sample, prospective, or randomized controlled studies are needed to elucidate its short- and long-term efficacy in adult FIRES patients.

**Keywords:** febrile infection-related epilepsy syndrome, FIRES, ketogenic diet, new-onset refractory status epilepticus, NORSE, clinical efficacy, adverse effects

## Introduction

Febrile infection-related epilepsy syndrome (FIRES) is a rare and devastating condition. It is a clinical manifestation rather than a specific diagnosis, characterized by refractory status epilepticus (RSE) occurring in the absence of active epilepsy or other pre-existing relevant neurological disorders, and without clear acute or active structural, toxic, metabolic, or autoimmune causes. The diagnosis requires a febrile infection within 2 weeks to 24 hours before RSE onset, with the status epilepticus (SE) occurring with or without fever. FIRES carries a poor prognosis, often associated with high mortality, cognitive decline, or severe neurological sequelae.[1–3] FIRES was initially defined as a condition occurring exclusively in the pediatric population,[4] and it was not until recent international consensus that its diagnostic

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scope was expanded to include all age groups.[5] Due to this conceptual evolution, research data on adult FIRES remain substantially limited. In particular, whether there are fundamental differences between adults and children in terms of clinical characteristics, treatment response, and prognosis remains inconclusive. This knowledge gap urgently requires further research to address. Recent years have witnessed increasing research on the pathophysiology of FIRES. Elevated levels of cytokines/chemokines in patient serum and cerebrospinal fluid suggest it may be an inflammatory disorder.[6–10] The core pathological mechanism involves an infection-triggered vicious cycle: systemic infection initiates neuroinflammation, which then promotes epileptic activity, and the two processes mutually reinforce, ultimately leading to refractory seizures and neuronal damage.[11–13] During the acute phase of FIRES, better control of epileptic seizures may help protect the nervous system from damage. Currently, there is a lack of specific treatment for adult FIRES, and the efficacy of conventional antiepileptic drugs (ASM) and immunotherapy is limited. Although expert consensus in the literature generally recommends the use of ASMs or anesthetics, these medications prove ineffective in most FIRES cases.[14] In this context, the ketogenic diet (KD) is highlighted as an alternative treatment. It is a very low-carbohydrate, high-fat, and adequate/low-protein dietary regimen that exerts its effects by inducing ketosis. The classic KD typically consists of a 4:1 ratio of fat to (protein + carbohydrates).[15] In recent years, clinical studies have confirmed the safety and efficacy of KD in treating pediatric FIRES,[14,16] further underscoring its clinical value. However, current evidence regarding its application in adult FIRES is scarce and fragmented, with only isolated case reports available worldwide —such as the single case described by Obara et al in 2022[17]—and a lack of systematic case series analyses. Therefore, this study reports five cases of adult FIRES treated with KD, aiming to explore its clinical efficacy, safety, optimal initiation timing, and related efficacy factors, so as to provide a reference for clinical decision-making.

# Materials and Methods

## Study Participants

This single-center retrospective study was conducted in the Neurological Intensive Care Unit (NICU) of Shanxi Bethune Hospital using medical records from October 2019 to January 2025. Through systematic screening of electronic medical records, we identified patients meeting all inclusion criteria: (1) diagnosis conforming to the 2022 International Consensus Recommendations for Management of New-Onset Refractory Status Epilepticus (NORSE) including FIRES (1) characterized by RSE without pre-existing epilepsy or relevant neurological disorders, while excluding identifiable structural, toxic, metabolic or autoimmune causes, with documented febrile infection occurring 2 weeks to 24 hours prior to RSE onset; (2) age ≥18 years; (3) receipt of KD therapy; and (4) availability of complete medical records. The final analysis included five eligible adult FIRES cases that satisfied all selection criteria.

## Data Collection

In this retrospective study, the following data were systematically collected through medical record review: (1) Baseline characteristics including age, gender, prodromal symptoms, etiology, diagnosis, and medical history; (2) Clinical parameters encompassing brain Magnetic Resonance Imaging (MRI)/ Computed Tomography (CT) findings, electroencephalography (EEG) monitoring results (with clinical seizures determined by bedside video-EEG), and ASMs / anesthetic medication regimens prior to KD initiation; (3) Metabolic parameters comprising blood glucose and β-hydroxybutyrate levels; (4) Treatment-related indicators: KD prescription details, time to achieve ketosis, Time to onset of efficacy (for patients with seizures, defined as a ≥50% reduction in daily clinical seizure frequency detected via 24-hour bedside video-EEG monitoring, with seizure frequency calculated weekly; for patients with difficulty weaning off anesthetics, defined as successful completion of the anesthetic tapering protocol. The tapering protocol consisted of reducing the current dose by 20–50% every 3 hours under continuous EEG monitoring. If brief seizures progressed to status epilepticus during tapering, the reduction was immediately halted and the dose was restored to the prior effective level; another tapering attempt was made only after ensuring 24–48 hours of electrographic stability), and documentation of adverse effects; (5) Outcome measures including total hospital length of stay, NICU duration, and modified Rankin Scale (mRS) scores at admission, discharge, and 3-month follow-up. All data were independently extracted and cross-verified by two neurologists.

## KD Protocol

Table 1 shows the treatment parameters. After excluding contraindications, a 4:1 ketogenic liquid formula was initiated at 33% of the target volume via a nasoenteric tube and gradually increased to the full target volume (25–30 kcal/kg/day) over 72 hours. Blood glucose was monitored every 4 hours or as clinically indicated, and serum beta-hydroxybutyrate levels were recorded every 6 hours, with a target therapeutic range of 1.0–3.0 mmol/L. Dietary adherence was assessed through daily intake records and regular feedback from patients or caregivers. Ketone levels, therapeutic efficacy, and any adverse events were systematically documented. Adverse events were diagnosed using predefined laboratory criteria (eg, hypoalbuminemia: serum albumin < 35 g/L; anemia: hemoglobin < 120 g/L in males, < 110 g/L in females). Causality between adverse events and KD was assessed by actively ruling out other potential causes, such as active infection or underlying disease progression. When ketone levels fell below the target range, strategies such as supplementation with medium-chain triglyceride (MCT) oil or L-carnitine were employed to enhance ketogenesis.

## Statistical Analysis

Given the limited sample size (n=5), this study primarily employed descriptive statistics. For continuous variables, normality was assessed using both the Shapiro–Wilk test and Q-Q plots. Variables conforming to a normal distribution are presented as mean ± standard deviation, while non-normally distributed variables are expressed as median and interquartile range (IQR). Categorical variables are summarized as counts and percentages (n, %). Although there was an initial plan to explore potential associations between the timing of ketogenic diet initiation, ketone body levels, and treatment outcomes, the small sample size provided insufficient statistical power to conduct meaningful correlation analyses; therefore, these analyses were not performed.

# Results

## Clinical Characteristics

Between October 2019 and January 2025, five FIRES patients were treated in the Neurology Intensive Care Unit at Shanxi Bethune Hospital. The study cohort included 2 male and 3 female patients, with a median age of 32 years (IQR 25–34). At admission, all patients showed significant neurological impairment with mRS scores of 4. The median duration of hospitalization was 135 days (IQR 98–158). All patients had a history of fever prior to the first epileptic seizure, with other prodromal symptoms including headache, gastrointestinal symptoms, and behavioral changes. For the five enrolled patients, the median duration of fever was 6 days (IQR: 6–7.5). The median interval from fever onset to seizure occurrence was 5 days (IQR: 3.5–6.5), with all individual values falling within the 24-hour to 2-week range specified by the FIRES diagnostic criteria. All patients exhibited generalized tonic-clonic seizures. After onset, the seizures rapidly worsened in a short time, with gradually increasing frequency (dozens to hundreds of times per day), and developed into RSE, without consciousness recovery between seizures. Notably, comprehensive medical histories revealed no preexisting neurological conditions, family history of neurological disorders, or prior epileptic events in any of the patients (Table 1).

## Serological and CSF Examinations

All patients underwent standard serological testing, with no significant abnormalities detected in serum metabolic parameters or etiological findings. The cerebrospinal fluid analysis results and intracranial pressure measurements for the five patients upon admission are presented in Table 2. CSF routine and biochemical analyses were within normal ranges. Results were negative for serum AQP4 antibody and NMO antibody, and oligoclonal bands. CSF metagenomic next-generation sequencing (mNGS) and oligoclonal band testing yielded negative results. Comprehensive autoimmune encephalitis antibody panels in both serum and CSF were negative, including antibodies against: MOG, NMDAR, AMPAR1, AMPAR2, LGI1, CASPR2, GABABRα1, GABAARβ3, GABAAR, DPPX, IgLON5, GlyR1, D2R, GAD65, mGluR5, mGluR1, and Neurexin3α.

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**Table 1** Baseline Characteristics of FIRES Patients Receiving KD Therapy

| Patients | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Age (years)/gender | 39/male | 32/male | 18/female | 25/female | 34/female |
| Prodromal symptoms | Fever | FeverHeadachebehavioral changes | FeverHeadachegastrointestinal symptoms | FeverNausea and vomitinggastrointestinal symptoms | Fever |
| Past medical history | No | No | No | Hypothyroidism | No |
| Seizure Types | GTCS | GTCS | GTCS | GTCS | GTCS |
| MRI/CT | Normal | Normal | Diffuse abnormal signals in the cerebral cortex | Abnormal signals in bilateral frontal lobes, basal ganglia, and left insular cortex | Bilateral Symmetric Abnormal Signals in Putamen |
| EEG | Sharp wave discharges in the left frontotemporal region | Paroxysmal sharp waves | Generalized diffuse slowing with increased epileptiform discharges | Generalized slowing with predominant theta waves and poorly modulated amplitude | Moderate-to-high amplitude slow waves with sharp components, mixed with EMG artifacts. |
| Maintenance KD ratio | 4:1 | 4:1 | 4:1 | 4:1 | 4:1 |
| Pre-KD MV | Yes | Yes | Yes | Yes | Yes |
| Pre-KD ASMs (oral) | LEV, VPA, OXC, CZP | LEV, VPA, OXC, CZP | LEV, OXC, CZP, PER | LEV, OXC, TPM | LEV, OXC, CZP, PER, LCM |
| Pre-KD ASMs (IV) | PB, VPA | PB, VPA | PB, VPA, DZP | PB, VPA, DZP | PB, VPA, DZP |
| Pre-KD Anesthetic agents | MDZ, PFP, DEX, REM | MDZ, PFP | MDZ, PFP, DEX, RBR | MDZ, PFP, ESK | MDZ, PFP, REM |
| Pre-KD other therapy | MP, IVIG | MP, IVIG | MP, IVIG | MP, IVIG | MP, IVIG, Tocilizumab |
| Pre-KD Antiviral therapy | Yes | Yes | Yes | Yes | Yes |

**Abbreviations**: GTCS, Generalized Tonic-Clonic Seizures; MRI, magnetic resonance imaging; CT, Computed Tomography; EEG, electroencephalogram; EMG, Electromyography; KD, ketogenic diet; MV, mechanical ventilation; ASMs, antiseizure medications; LEV, Levetiracetam; VPA, Valproic acid; OXC, Oxcarbazepine; CZP, Clonazepam; PER, Perampanel; TPM, Topiramate; LCM, Lacosamide; PB, Phenobarbital; DZP, Diazepam; MDZ, Midazolam; PFP, Propofol; DEX, Dexmedetomidine; REM, Remifentanil; RBR, Rocuronium Bromide; ESK, Esketamine; IV, intravenous; MP, methylprednisolone; IVIG, intravenous immunoglobulin.

**Table 2** Cerebrospinal Fluid and Intracranial Pressure Findings in Five Patients at Admission

| Patients | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Intracranial Pressure | 120mm$H_2O$ | 150mm$H_2O$ | 110mm$H_2O$ | 130mm$H_2O$ | 125mm$H_2O$ |
| White Blood Cell Count | 5*$10^6$/L | 2*$10^6$/L | 3*$10^6$/L | 0*$10^6$/L | 1*$10^6$/L |
| Red Blood Cell Count | 0*$10^6$/L | 5*$10^6$/L | 0*$10^6$/L | 8*$10^6$/L | 2*$10^6$/L |
| Glucose | 4.20mmol/L | 2.95mmol/L | 3.63mmol/L | 3.73 mmol/L | 3.60mmol/L |
| Chloride | 116.2 mmol/L | 112.6 mmol/L | 125.0 mmol/L | 125.5 mmol/L | 121.3mmol/L |
| Protein | 0.384g/L | 0.282g/L | 0.271g/L | 0.239 g/L | 0.437g/L |

## Neuroimaging

Neuroimaging studies revealed normal head CT/MRI findings in 2 patients (40%). The remaining 3 patients (60%) demonstrated abnormal MRI signals localized to multiple regions including the cortex, bilateral frontal lobes, basal ganglia, left insular lobe, and bilateral putamen (Table 1 and Figure 1).

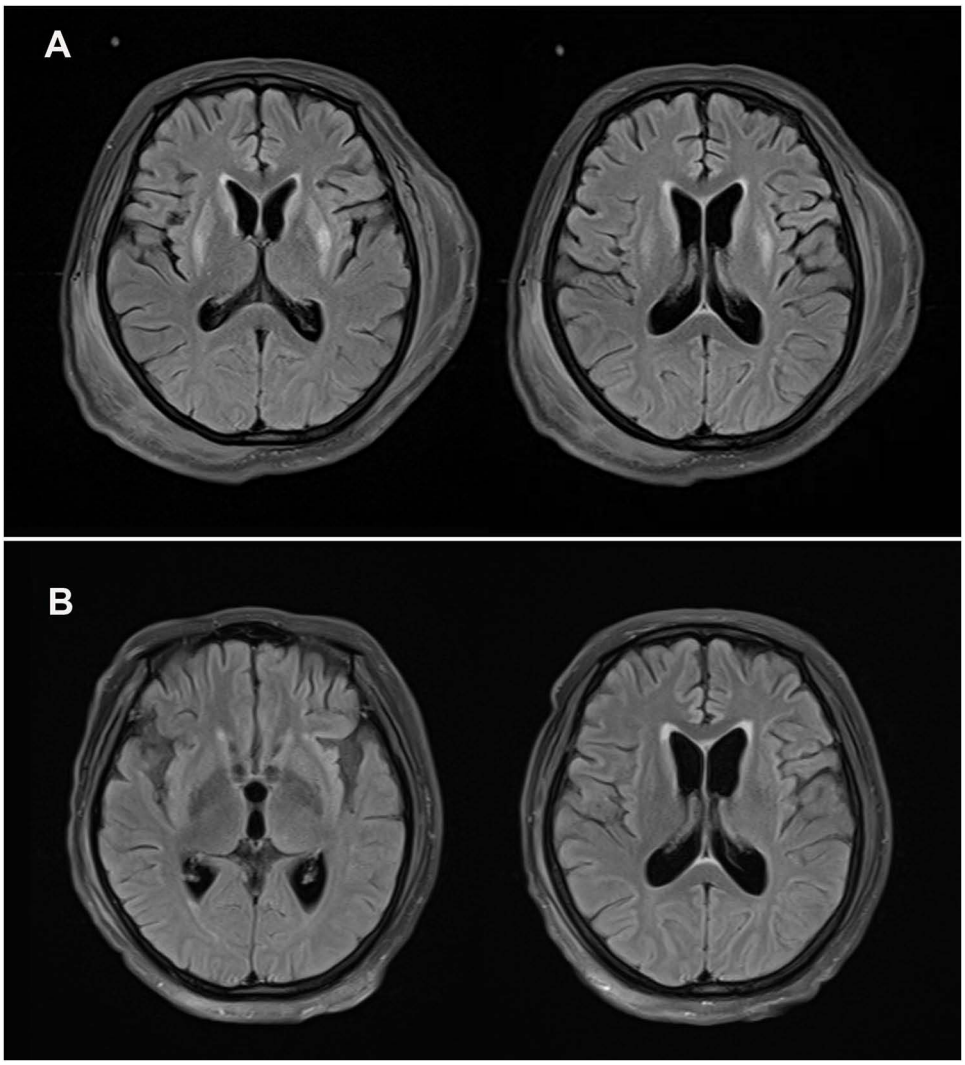


**Figure 1** Brain MRI findings in Case 5. (**A**) FLAIR sequence at 1 month after onset: symmetric hyperintensity is observed in the bilateral putamen. (**B**) FLAIR sequence at 3 months after onset: the extent of the symmetric hyperintensity in the bilateral putamen is significantly reduced compared to previous findings.


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## Eeg

All patients exhibited background slowing on EEG. As the disease progressed, frequent multifocal epileptiform discharges were observed in all cases (Table 1 and Figure 2).

## Treatment

All patients received combination therapy with multiple (5–8 types) ASMs. All patients were administered anesthetic medications. All patients received antiviral therapy for a median duration of 30 days (IQR 18–46) following hospitalization due to clinically suspected viral encephalitis. All patients underwent immunotherapy, including corticosteroids (100%), intravenous immunoglobulin (IVIG) (100%), and tocilizumab (20%). The median initiation time for corticosteroid pulse therapy was day 2 of disease course (IQR 2–6), while for IVIG therapy it was day 3 (IQR 2–4). Following the aforementioned treatments, four patients (80%) remained in RSE with severe consciousness impairment; the remaining one patient (20%) achieved seizure cessation but without consciousness recovery, additionally demonstrating medication tapering difficulty during treatment. This particular patient received adjunctive tocilizumab 97 days after KD initiation, which enabled successful anesthetic reduction without seizure recurrence on the following day of administration. All patients (100%) initiated ketogenic diet therapy at a median of 33 days (IQR 10–51) into their disease course. All patients (100%) achieved ketosis, and serum beta-hydroxybutyrate levels in all patients (100%) generally fluctuated within the range of 1.0–3.0 mmol/L. Ketosis was achieved within a median of 2 days (IQR 2–3), the monitoring results of blood β-hydroxybutyrate and glucose levels in patients are shown in Figures 3 and 4, with clinical response observed after a median of 3 days (IQR 3–4) of KD therapy. Four patients (80%) achieved a ≥50% reduction in seizure frequency, while one patient (20%) remained seizure-free during gradual anesthetic tapering. The median duration of KD therapy was 123 days (IQR 30–141). All patients successfully transitioned to regular diet before discontinuing the ketogenic regimen, with no treatment interruptions due to adverse effects. All mechanically ventilated patients were successfully weaned from ventilation after KD initiation. By discharge, all patients had discontinued intravenous anesthetics and ASMs, requiring only oral ASMs for seizure prophylaxis. The medication timeline and key efficacy outcomes in FIRES patients are detailed in Figure 5.

## Adverse Effects

Among the five patients receiving KD therapy in this study, the incidence and timing of adverse effects were as follows: hypoalbuminemia (100%, median onset time 9 days [IQR 5–13]), anemia (80%, 20.5 days [IQR 16.5–28.5]), diarrhea (60%, 5 days [IQR 3–7]), occult blood in stool (60%, 18 days [IQR 11–34]), and hyperlipidemia (40%, 6.5 days [IQR 6–7])(see Table 3 for details). All adverse events were mild in severity and were effectively controlled within one week

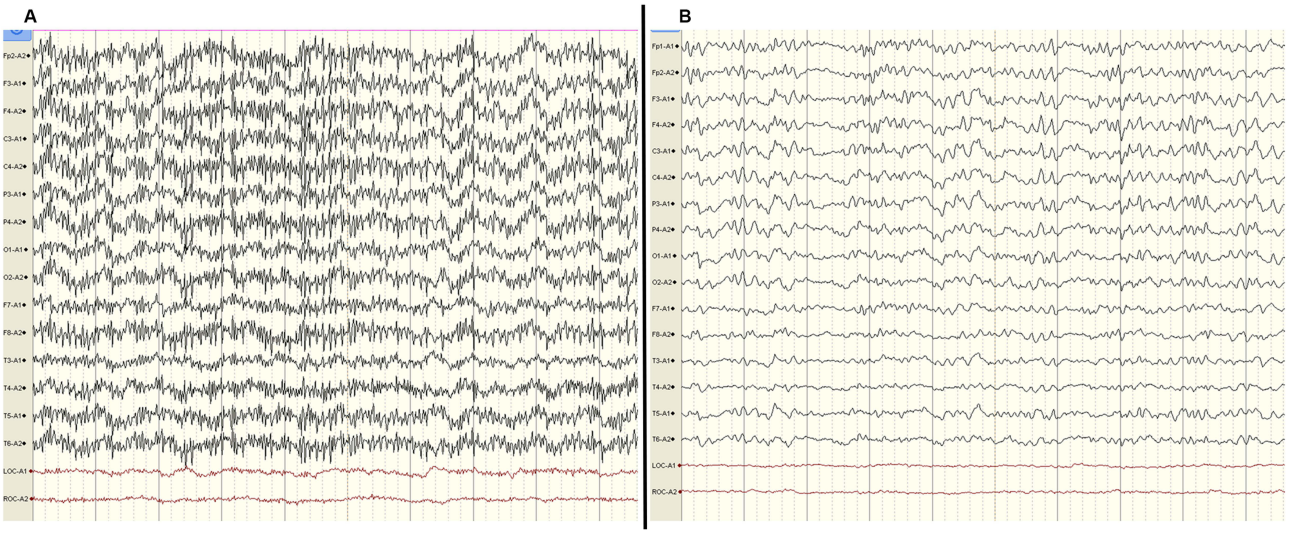


**Figure 2** EEG findings in Case 1. (**A**) EEG before Ketogenic Diet initiation. (**B**) EEG on day 3 after Ketogenic Diet initiation.

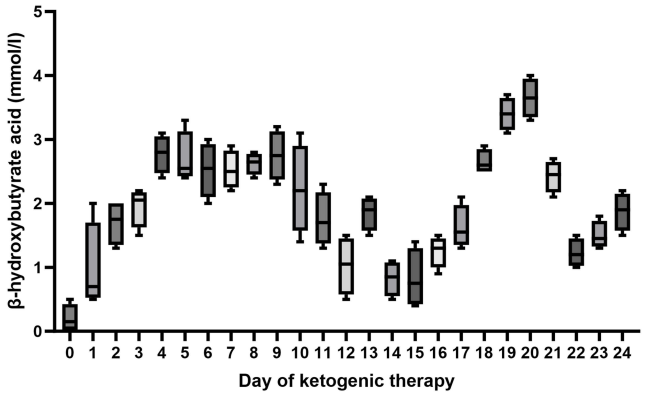


**Figure 3** Blood β-hydroxybutyrate acid Levels After Initiation of Ketogenic Diet in Case 1. The box plots represent median values with interquartile ranges (IQR, box boundaries) and whiskers showing data range, derived from four daily blood β-hydroxybutyrate acid measurements (collected every 6 hours).

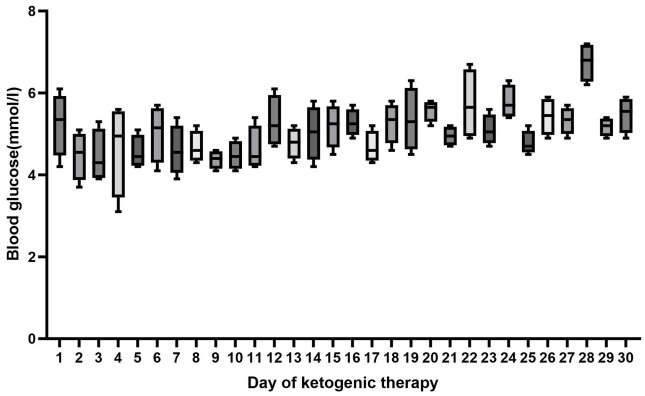


**Figure 4** Blood Glucose Levels After Initiation of Ketogenic Diet in Case 1. The box plots represent median values with interquartile ranges (IQR, box boundaries) and whiskers showing data range, derived from four daily blood glucose measurements (collected every 6 hours).

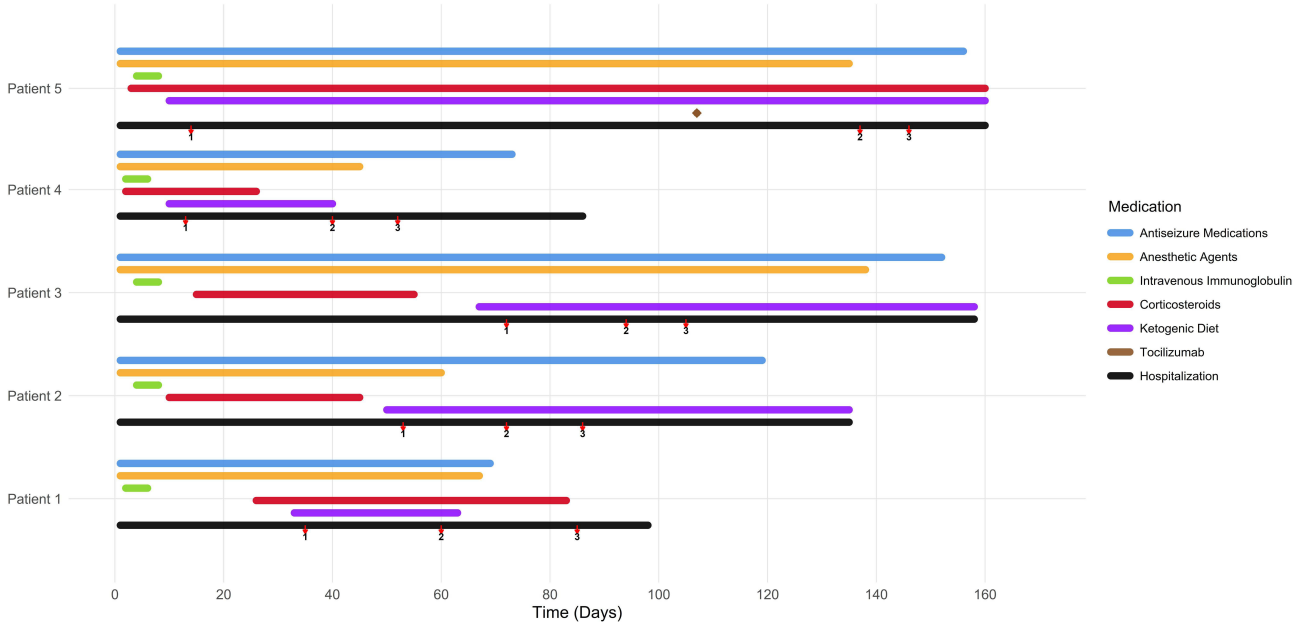


**Figure 5** Medication timeline and key efficacy outcomes in FIRES patients. The horizontal colored bands represent the duration of different medication treatments, arranged from top to bottom as follows: antiseizure medications, anesthetic agents, intravenous immunoglobulin, corticosteroids, ketogenic diet (KD), tocilizumab, and total hospitalization duration. Red arrows indicate important clinical milestones after KD initiation: Arrow 1, time to onset of efficacy; Arrow 2, time to consciousness recovery; Arrow 3, time to mechanical ventilation withdrawal. The diamond marker indicates the single administration time point of tocilizumab.


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**Table 3** Treatment Parameters and Outcomes of KD Therapy

| Patients | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Time to KD initiation (days) | Day 33 post-onset | Day 50 post-onset | Day 67 post-onset | Day 10 post-onset | Day 10 post-onset |
| Time to achieve ketosis (days) | 1 | 2 | 2 | 3 | 28 |
| Time to onset of efficacy (days) | 2 | 3 | 5 | 3 | 4 |
| Days from KD initiation toregain consciousness(days) | 27 | 22 | 27 | 30 | 127 |
| Time to anesthetic cessation after KD initiation(days) | 34 | 10 | 71 | 35 | 125 |
| Time to IV ASMs withdrawal after KD initiation(days) | 36 | 69 | 85 | 63 | 146 |
| Time to MV withdrawal after KD initiation(days) | 52 | 36 | 38 | 42 | 136 |
| Adverse events | DiarrheaAnemiaFecal occult bloodHypoalbuminemia | AnemiaFecal occult bloodHypoalbuminemia | DiarrheaAnemiaFecal occult bloodHypoalbuminemia | Hypoalbuminemia Hyperlipidemia | DiarrheaAnemia HypoalbuminemiaHyperlipidemia |
| The duration of KD therapy (days) | 30 | 123 | 132 | 30 | 150 |
| Length of hospital stay (days) | 98 | 135 | 158 | 86 | 160 |
| NICU length of stay (days) | 71 | 91 | 109 | 60 | 160 |
| mRS score at admission | 4 | 4 | 4 | 4 | 4 |
| mRS score at discharge | 2 | 4 | 4 | 2 | 4 |
| mRS score at 3-month post-discharge | 2 | 2 | 2 | 2 | 2 |

**Abbreviations**: KD, ketogenic diet; IV, intravenous; ASMs, antiseizure medications; MV, mechanical ventilation; NICU, Neurological Intensive Care Unit; mRS, modified Rankin Scale.

following appropriate symptomatic management, including albumin supplementation, blood component transfusion, antidiarrheal medications, and lipid-lowering therapy.

## Follow-up and Prognosis

All patients achieved seizure cessation at discharge. The mRS scores at discharge ranged from 2 to 4 points. At the 3-month post-discharge follow-up, all patients remained seizure-free with an mRS score of 2 (see Table 3).

# Discussion

FIRES represents a rare yet devastating clinical syndrome characterized by RSE, with diagnostic criteria requiring a febrile infection occurring between 2 weeks and 24 hours prior to RSE onset, regardless of fever presence during the actual SE episode.[5] This condition carries a particularly poor prognosis, typically associated with high mortality rates and significant neurological sequel including cognitive decline.[1,2] Our case series describes five patients (2 males, 3 females; median age 32 years, IQR 25–34) who presented with RSE following febrile prodromal symptoms, all meeting diagnostic criteria for FIRES.

The pathogenesis of FIRES remains incompletely understood. Although inflammatory or autoimmune mechanisms represent the predominant hypotheses for this condition, clinical observations have revealed that FIRES patients consistently test negative for various antibodies and respond poorly to immunotherapy, thus lacking direct evidence to support an autoimmune mechanism.[11] An alternative proposed mechanism involves an explosive aberrant inflammatory response within the central nervous system. Following systemic infection, the release of inflammatory molecules may

trigger a proinflammatory cascade. The progressive accumulation of these inflammatory mediators ultimately lowers the seizure threshold and induces recurrent epileptic episodes. Importantly, SE itself can further amplify proinflammatory responses, establishing a vicious "inflammation-seizure-reinflammation" cycle.[18,19]

FIRES demonstrates variable and nonspecific abnormal imaging findings.[20] During the early disease stage, 41%-55% of patients may present with normal initial MRI findings,[2] while positive cases predominantly involve neocortical regions (temporal, frontal, parietal, and occipital lobes) and deep structures (basal ganglia, insula, and thalamus). As the disease progresses, characteristic chronic-phase manifestations develop, featuring generalized cerebral atrophy accompanied by medial temporal lobe sclerosis.[12,21] Notably, recent studies have identified bilateral claustrum lesions on brain MRI as a potential key diagnostic marker for FIRES.[22] This study analyzed neuroimaging characteristics in five FIRES patients, with three cases (60%) demonstrating abnormal MRI signals predominantly involving the cortex, bilateral frontal lobes, basal ganglia, left insula, and bilateral putamen. This distribution pattern aligns with previously reported FIRES imaging manifestations. The observed MRI abnormalities are more likely to represent consequences of persistent epileptic activity rather than direct sequelae of underlying pathogenic mechanisms.[23] It is particularly noteworthy that neuroimaging alterations in FIRES patients typically demonstrate dynamic evolutionary characteristics. Initial imaging studies may appear normal, yet progressive structural changes emerge with disease progression. This pattern suggests persistent neuroinflammatory processes and ongoing neuronal injury extending beyond the acute phase.[24] Among the five FIRES patients observed in this study, two critically ill cases could not complete early MRI examinations due to disease severity. Their first delayed scans at 1-month post-onset revealed diffuse abnormal signals in the bilateral putamen and cortex respectively. Three-month follow-up scans showed significant lesion reduction in one case (Figure 1) and complete resolution in the other. Another patient demonstrated dynamic radiological evolution: initial MRI at admission was normal, but 1-month follow-up revealed mild cerebral atrophy predominantly featuring sylvian fissure enlargement. One patient exhibited abnormal signals in bilateral frontal lobes, basal ganglia, and left insula as early as day 2 of onset but lacked follow-up scans. The remaining patient showed consistently normal findings on both admission and 3-month MRI. Although these imaging observations generally align with existing literature, the lack of systematic standardized follow-up examinations necessitates verification through larger-scale prospective studies.

Current clinical guidelines have established recommended treatment protocols for FIRES patients.[1] However, regarding the use of ASMs and anesthetic agents, these recommendations still adhere to conventional SE treatment paradigms, without yet developing FIRES-specific therapeutic standards. Phenobarbital remains one of the therapeutic options for SE.[25–27] While high-dose intravenous phenobarbital can effectively control SE by inducing burst-suppression coma,[11,28] all five patients in our cohort experienced seizure recurrence during medication tapering after achieving initial burst-suppression. Early initiation of immunotherapy may help mitigate or interrupt the cerebral inflammatory cascade, thereby reducing irreversible neurological damage.[29,30] The 2022 International Consensus on NORSE (including FIRES) management[1] recommends that during acute phase treatment, in addition to ASMs, anesthetics, and potential infection management, first-line immunotherapy (corticosteroids or IVIG) should be initiated within 72 hours. IVIG may be used concurrently with corticosteroids or serve as an alternative first-line immunotherapy.[31] For patients who do not respond to first-line immunomodulatory therapy, cytokine antagonists are considered potential second- or third-line treatment options, including rituximab, anakinra, tocilizumab, and tofacitinib. In this study, all five patients received high-dose corticosteroid pulse therapy and IVIG treatment prior to KD initiation. The median initiation time for corticosteroid pulse therapy was day 2 of disease course (IQR 2–6), while for IVIG therapy it was day 3 (IQR 2–4). No significant improvement in seizure control was observed following these treatments. One patient demonstrated treatment response by day 4 of KD initiation, but subsequently developed medication tapering difficulty. Tocilizumab was therefore added on day 97 of KD therapy, with successful anesthetic reduction achieved without seizure recurrence by the second day post-administration. This clinical course, combined with previous case evidence, suggests a potential therapeutic role of tocilizumab in this context.[32] However, the extent of its specific contribution—whether it acts independently, synergizes with KD, or is primarily attributable to the cumulative effects of KD manifesting at this point—cannot be definitively distinguished due to the observational design of this study.

Current research increasingly demonstrates that the KD is both safe and effective for treating FIRES.[14,16,17] Li et al[14] reported a case of a 3-year-old male FIRES patient who was admitted to the pediatric intensive care unit. Despite

treatment with intravenous anesthetics and multiple ASMs, the patient remained in super-refractory status epilepticus (SRSE). KD therapy was initiated on day 14 of the disease course, resulting in significant clinical improvement. The patient ultimately achieved complete neurological recovery and successful weaning from mechanical ventilation. Follow-up demonstrated sustained seizure control after discharge. Kessi et al[33] conducted a systematic review of PubMed and Embase databases up to May 2019 to analyze the efficacy of different treatment regimens during acute and chronic phases in FIRES patients. The study included 45 eligible articles encompassing 229 cases. The mean age of onset was 8.26±4.406 years (median 8 years, range 0–30). Multivariate regression analysis demonstrated a significant association between favorable prognosis and KD implementation during the acute phase ($P<0.05$). However, the aforementioned studies have primarily focused on evaluating the efficacy and safety of KD in pediatric FIRES patients, while clinical research on adult FIRES remains relatively scarce, with only isolated case reports available globally. For instance, Obara et al[17] described a 21-year-old adult FIRES patient in whom KD initiation during the chronic phase—as late as 27 months after disease onset—still led to a rapid reduction in seizure frequency and gradual improvement in cognitive function. Furthermore, a systematic review focusing on super-refractory status epilepticus (SRSE) has corroborated that KD is broadly effective across the NORSE spectrum, including FIRES, with most NORSE patients deriving benefit ($p < 0.004$).[16] Nonetheless, key aspects such as efficacy metrics, safety profile, and long-term outcomes of KD in adult patients still require further validation through large-sample, multicenter, prospective studies. The 2022 International Consensus on NORSE (including FIRES) management[1] recommended that KD therapy should be initiated within 7 days of disease onset. When enteral administration is not feasible, parenteral delivery should be considered. However, the precise mechanisms underlying KD's antiepileptic effects remain incompletely understood. The KD serves as a biochemical model of fasting, utilizing ketone bodies to replace glucose as the brain's primary energy source. Current research suggests that ketone bodies and polyunsaturated fatty acids may play a pivotal role in mediating the anticonvulsant effects of the KD.[34] The mechanisms by which ketone bodies exert their antiepileptic effects primarily involve four key aspects: neurotransmitter modulation, cerebral energy metabolism, oxidative stress regulation, and ion channel function.[34–36] Notably, the ketogenic diet is closely related to energy metabolism and the aging process.[37,38] Ketone bodies exhibit neuroprotective effects, potentially by optimizing cellular energy metabolism and reducing oxidative stress, which can modulate neuronal excitability and enhance mitochondrial function. These mechanisms may elevate the seizure threshold and reduce seizure frequency in some patients with epilepsy.[39] From the perspective of the link between aging and epilepsy, the aging process is accompanied by blood-brain barrier disruption, abnormal protein deposition (eg, Aβ/tau), and glial cell dysfunction, collectively triggering persistent neuroinflammation and oxidative stress. These pathological changes further lead to mitochondrial dysfunction, an imbalance between neuronal excitation and inhibition, and cumulative DNA damage, ultimately resulting in hyperexcitability of neural networks and a significantly increased susceptibility to epilepsy.[40,41] In contrast, the ketogenic diet may improve energy metabolism and synaptic function in the aging brain by elevating circulating ketone levels and activating the PKA-BDNF signaling axis. This, in turn, suppresses neuroinflammation and stabilizes neural network activity, thereby reducing susceptibility to epilepsy.[42,43] The KD also increases plasma decanoic acid concentrations. This fatty acid directly inhibits AMPA receptors, thereby exerting anticonvulsant effects.[44] Additionally, studies have proposed that the KD may exert its antiepileptic effects through potential mechanisms including modulation of central and peripheral inflammatory responses and influence on gut microbiota composition. However, the precise underlying mechanisms require further validation.[45,46]

In this study, all five patients (100%) receiving KD therapy achieved ketosis. The median time to KD initiation was 33 days (IQR 10–50), with median time to ketosis attainment being 2 days (IQR 2–3) and median time to observable therapeutic effect being 3 days (IQR 3–4), the median duration of KD therapy was 123 days (IQR 30–141). The results demonstrate a complex relationship between KD initiation time and treatment duration: Although Cases 4 and 5 both started KD at the earliest time point (10 days after onset), Case 5 had longer KD duration than other cases, which may be related to its more severe baseline condition. It is noteworthy that Patient 5 achieved ketosis 28 days after KD initiation, yet their clinical symptoms began to improve as early as 4 days after starting KD. A similar phenomenon was also observed in the study by Ren et al,[47] suggesting that reaching an optimal level of ketosis may not be a prerequisite for KD to exert its therapeutic effects. All patients remained in refractory status epilepticus despite having received

corticosteroids and intravenous immunoglobulin prior to KD initiation. The rapid onset of KD efficacy within a median of 3 days strongly suggests an independent antiseizure effect. It should be specifically noted that Patients 1 and 4 still required continuous intravenous medication for several days after KD discontinuation. The clinical course of Patient 4 was particularly complex and provided crucial insights into efficacy attribution: initial improvement occurred as early as day 4 after KD initiation, but difficulty in medication tapering emerged later. It was not until tocilizumab was added on day 97 of KD treatment that successful anesthetic reduction was achieved on the second day after its administration. This pattern suggests that tocilizumab may have addressed the later "therapeutic bottleneck" by interrupting persistent immunopathological processes, whereas the early efficacy observed prior to tocilizumab use was primarily attributable to KD. The two interventions likely functioned sequentially through distinct mechanisms. In conclusion, KD should be regarded as an indispensable core component of comprehensive treatment strategies for such complex cases. Prospective studies are needed to further confirm the independent efficacy of KD and elucidate its interactive mechanisms with immunotherapy.

In patients with drug-resistant epilepsy treated with a ketogenic diet, the spectrum of adverse effects is generally similar between adults and children. Gastrointestinal symptoms (such as constipation, diarrhea, and vomiting) and metabolic disturbances (such as hypoglycemia, acidosis, and hyperlipidemia) are the most common adverse reactions in both groups.[15,16,48] However, when focusing on the specific critically ill patient population of adult FIRES, the observed manifestations differ from those in general adult drug-resistant epilepsy. In the five patients included in this study, the observed adverse effects and their onset times were as follows: hypoalbuminemia (100%, median time 9 days [IQR 5–13]), anemia (80%, median time 20.5 days [IQR 16.5–28.5]), diarrhea (60%, median time 5 days [IQR 3–7]), occult blood in stool (60%, median time 18 days [IQR 11–34]), and hyperlipidemia (40%, median time 6.5 days [IQR 6–7]). All adverse effects improved after symptomatic treatment (Table 2). Among the adverse reactions reported in this study, the incidence of hypoalbuminemia was 100%, whereas hypoalbuminemia has rarely been reported in pediatric FIRES patients in the literature, indicating a notable discrepancy. This difference may be related to the metabolic characteristics of adults: compared to children, adults have relatively stable but higher absolute protein requirements per unit body weight, and muscle mass, serving as a protein reserve, is more rapidly depleted during critical illness. When high-fat intake predominates while protein intake is restricted due to dietary limitations, loss of appetite, or increased disease-related consumption, adult patients may find it more challenging to maintain a positive nitrogen balance, thereby increasing the risk of hypoalbuminemia. Additionally, diarrhea, hyperlipidemia, and hypoglycemia have also been observed in pediatric FIRES patients treated with a ketogenic diet.[16,49,50] It should be noted that, due to the small sample size of this study (n=5), the reported incidences of adverse effects are merely descriptive and require validation through larger prospective studies in the future. Currently, studies specifically reporting the timing of adverse effects associated with ketogenic diet therapy remain limited. These effects may be confounded by FIRES-induced catabolic states or ICU-acquired weakness,[47] thus necessitating further validation to establish their causal relationship with KD therapy. The primary reasons for discontinuing KD therapy typically include poor patient compliance, nutritional imbalance risks, early-phase adverse effects (hypoglycemia, gastrointestinal symptoms, excessive ketosis), metabolic disturbances, and urological complications.[51] In contrast, all patients in the current study successfully transitioned to regular diets without treatment interruption due to adverse effects.

FIRES is a rare and catastrophic clinical syndrome. Patients typically require prolonged hospitalization and face poor prognoses, often developing residual cognitive impairments, progressing to refractory epilepsy, and in severe cases, resulting in mortality.[19] Among the five adult FIRES patients in this study, all presented with refractory epileptic seizures upon hospital admission and had poor baseline functional status (mRS score of 4). Each patient required mechanical ventilation during the disease course, with prolonged length of stay in the NICU - findings that corroborate the conclusions mentioned above. The mRS is a routine assessment tool in the diagnosis and treatment of neurological disorders. In our study, it was used as a practical indicator for evaluating long-term prognosis based on the existing theoretical framework.[52–54] Its 0–6 grading scale can effectively differentiate outcomes in FIRES patients, ranging from completely asymptomatic (0 points) to death (6 points). It is suitable for assessing key prognostic indicators focused on in this study, including motor function, independence in daily living, and care dependency levels. However, this scale has notable limitations, including inadequate sensitivity for non-motor symptoms (eg, cognitive impairment and

neuropsychiatric abnormalities) and relatively poor discriminative validity within the moderate disability range (scores 3–4). These constraints require special consideration when evaluating diseases like FIRES that often involve significant cognitive sequelae. This limitation suggests that mRS may need to be combined with specialized neuropsychological assessments (such as Mini-Mental State Examination or Montreal Cognitive Assessment) to comprehensively evaluate functional outcomes in FIRES patients. Future studies should focus on developing or validating multidimensional evaluation systems better suited to the clinical characteristics of FIRES. Finally, this study has several limitations. First, as a single-center retrospective study, it may be subject to individualized variations in treatment protocols and subjective assessment biases. Additionally, this design prevented us from obtaining crucial cognitive function data (such as MMSE scores), as patients in the acute phase were often unable to cooperate due to sedation, and no systematic follow-up assessments were arranged during the stable phase. Second, the 3-month follow-up period was relatively short, which is insufficient to comprehensively evaluate the long-term efficacy of the ketogenic diet (KD) and its potential adverse effects (such as osteoporosis and vitamin deficiencies). Future studies with longer follow-up durations are needed to verify its sustained effectiveness and safety.

## Conclusion

FIRES is a rare and devastating clinical syndrome with an unclear pathogenesis, high mortality, and poor prognosis, often leading to cognitive decline or severe neurological sequelae. Although the KD demonstrates therapeutic potential for FIRES patients, the currently limited case data necessitate further validation through large-scale prospective studies to confirm its short- and long-term efficacy.

## Ethics Statement

The studies involving humans were approved by the Medical Ethics Committee of Shanxi Academy of Medical Sciences/ Shanxi Bethune Hospital (Approval No: YXLL-2025-131). This approval represents a retroactive ethical review and confirmation for this retrospective case series study, which analyzed data from patients treated between 2019 and 2025. The study was conducted in compliance with local regulations and institutional requirements. For hospitalized patients, written informed consent was obtained through face-to-face communication with patients or their legal guardians, followed by signing of hardcopy consent forms. For discharged patients, initial consent was obtained via telephone or WeChat communication, with subsequent confirmation and signing of hardcopy consent forms during outpatient follow-up visits. All patient data were anonymized and strict confidentiality measures were maintained throughout the study in accordance with the ethical principles of the Declaration of Helsinki. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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