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Case Study

FATAL SUPER-REFRACTORY STATUS EPILEPTICUS IN ADULT-ONSET FEBRILE INFECTION-RELATED EPILEPSY SYNDROME (FIRES): A CASE REPORT OF PHARMACOKINETIC CHALLENGES AND EARLY IMMUNOMODULATION

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ABSTRACT

Febrile infection-related epilepsy syndrome (FIRES), a subcategory of New-Onset Refractory Status Epilepticus (NORSE), is a catastrophic epileptic encephalopathy that is rarely described in adults. This report describes a fatal case of a 25 y old woman who developed explosive-onset generalized seizures following a mild febrile prodrome. She rapidly progressed to refractory status epilepticus and met criteria for adult-onset FIRES after exclusion of infectious, structural, toxic, and antibody-mediated autoimmune etiologies. Despite aggressive escalation to super-refractory status epilepticus (SRSE) management with quadruple continuous intravenous anesthetics (propofol, midazolam, ketamine, thiopentone) and multiple antiseizure medications, seizure control remained unstable. The clinical course was critically destabilized by a preventable pharmacokinetic interaction: the initiation of meropenem for multidrug-resistant sepsis in a patient receiving valproic acid resulted in a rapid decline in serum valproate exposure and breakthrough seizures. Advanced immunomodulatory strategies including plasmapheresis, rituximab, and interleukin-6 (IL-6) receptor blockade with tocilizumab were instituted. Tocilizumab achieved transient seizure cessation (48 h) and permitted partial anesthetic weaning but was followed by profound neutropenia and worsening septic shock. The patient ultimately succumbed to multidrug-resistant sepsis and multiple organ dysfunction syndrome (MODS) on day 39. This case highlights the high mortality of adult FIRES, the absolute contraindication of concurrent carbapenem–valproate therapy, and the potential value of earlier cytokine-targeted immunotherapy.

Keywords: Febrile infection-related epilepsy syndrome, New-onset refractory status epilepticus, Super-refractory status epilepticus, Carbapenem–valproate interaction, Tocilizumab, Multidrug-resistant sepsis

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INTRODUCTION

Status epilepticus (SE) is a neurological emergency with substantial morbidity and mortality, defined as a prolonged seizure or a series of seizures without return to baseline consciousness. Refractory status epilepticus (RSE) is diagnosed when seizures persist despite adequate doses of a benzodiazepine and at least one appropriately selected second-line antiseizure medication (ASM). Super-refractory status epilepticus (SRSE) refers to SE continuing or recurring 24 h or more after anesthetic therapy initiation, including cases where seizures recur upon reduction of anesthetic infusions; reported adult mortality rates range from 30–50% [1-3].

New-Onset Refractory Status Epilepticus (NORSE) describes RSE in previously healthy individuals without clear acute structural, toxic, or known pre-existing epileptic cause. Febrile Infection-Related Epilepsy Syndrome (FIRES), a NORSE subtype, manifests as new-onset RSE or SRSE following non-specific febrile illness (typically 24 h to 2 w prior) without active central nervous system (CNS) infection or structural etiology [4-6]. Although historically paediatric, adult FIRES cases are increasingly recognized, mediated predominantly by innate immune dysregulation and CNS cytokine storm rather than classical antibody-mediated autoimmunity [7-9].

Standard SE algorithms prioritize sequential benzodiazepines, second-line ASMs, and escalation to continuous intravenous anesthetics (CIVAs) such as midazolam, propofol, ketamine, and barbiturates for SRSE.[1–3] Adult FIRES demonstrates marked pharmaco-resistance, creating a therapeutic ceiling requiring progressively higher anesthetics doses to suppress cortical excitability, at the cost of profound systemic toxicity. This “treatment trap” can culminate in sepsis, cardiovascular collapse, ileus, and multi-organ dysfunction that may drive mortality more than the seizures themselves [2, 3].

This case report describes fatal adult-onset FIRES presenting as fatal SRSE, emphasizing two critical and potentially modifiable care aspects. First, it illustrates a preventable pharmacokinetic failure: the interaction between carbapenem antibiotics and valproic acid causing precipitous loss of valproate exposure and seizure breakthrough. Second, it underscores the need for early cytokine-targeted immunotherapy (e. g. interleukin-1 or interleukin-6 blockade) in NORSE/FIRES when first-line immunomodulatory strategies fail, rather than prolonged reliance on escalating anesthetic coma.

CASE REPORT

Patient profile and initial presentation

A 25 y old woman presented to the emergency department with generalized tonic–clonic seizures (GTCS) and altered sensorium. Her history included remote eclampsia eight years prior, but no chronic epilepsy. Two to three days before admission, she developed a non-specific febrile illness characterized by low-grade fever and malaise without focal infectious symptoms. There was no documented meningism, rash, or respiratory or gastrointestinal focus. Seizures began abruptly as recurrent GTCS at home and rapidly evolved into established SE. At a referring facility, she required intubation for airway protection and was loaded with benzodiazepines and intravenous ASMs but remained in convulsive and electrographic SE. She was transferred to the tertiary centre on day 1 of illness for advanced neurocritical care.

Phase 1: Diagnostic evaluation and initial seizure suppression (Days 1–14)

On arrival, the patient was comatose, mechanically ventilated, and in ongoing refractory seizures despite initial sedation. Continuous EEG (cEEG) confirmed generalized ictal discharges evolving into burst–suppression with interburst intervals of 2-5 seconds only with high-dose anesthetics. Magnetic resonance imaging (MRI) of the brain demonstrated symmetric T2-weighted and FLAIR hyperintensities involving the bilateral basal ganglia without diffusion restriction or contrast enhancement. This pattern, in the appropriate clinical context, was considered compatible with cytotoxic and excitotoxic injury described in FIRES/NORSE [4-6].

Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis with mildly elevated protein and normal glucose. CSF Gram stain, culture, and multiplex PCR panels were negative for common viral, bacterial, and fungal pathogens, including herpes simplex virus, varicella zoster virus, enteroviruses, and Mycobacterium tuberculosis. Serum and CSF autoimmune encephalitis panels (including NMDA-R, LGI1, CASPR2, GABAB, AMPAR, and GAD65 antibodies) were negative. Metabolic, toxicology, vasculitic, and connective tissue disease screens were unrevealing.

Based on (i) explosive onset of RSE following a short febrile prodrome, (ii) absence of identifiable infectious, structural, metabolic, or toxic etiology, and (iii) negative neuronal autoantibody panels, a working diagnosis of cryptogenic NORSE consistent with adult-onset FIRES was made in accordance with recent international consensus criteria [4, 5].

Aggressive seizure suppression was pursued using a "maximum dose" CIVA strategy under cEEG guidance (fig. 1). The regimen included:

- Propofol infusion escalated up to 2 mg/kg/h.
- Midazolam infusion escalated to a maximum of 180 mg/h.
- Ketamine infusion up to 10 mg/kg/hour for NMDA receptor antagonism.
- Thiopentone intermittently as a barbiturate coma agent, reaching up to 15 mg/kg/h.

Multiple ASMs were optimized concomitantly. The extensive polytherapy regimen included intravenous levetiracetam (1 g every 8 hourly), sodium valproate (500 mg every 8 hourly), lacosamide (200 mg every 12 hourly), fosphenytoin (400 mg every 12 hourly), and phenobarbitone (1200 mg stat followed by 600 mg every 12 hourly). Enteral agents administered via nasogastric tube included perampanel (10 mg every 24 hourly), clobazam (10 mg every 8 hourly), carbamazepine (600 mg every 8 hourly), and cannabidiol syrup (150 mg every 8 hourly). Despite intermittent periods of electrographic quiescence, attempts at gradual weaning of anesthetics during the first two weeks consistently precipitated seizure recurrence, fulfilling criteria for SRSE.

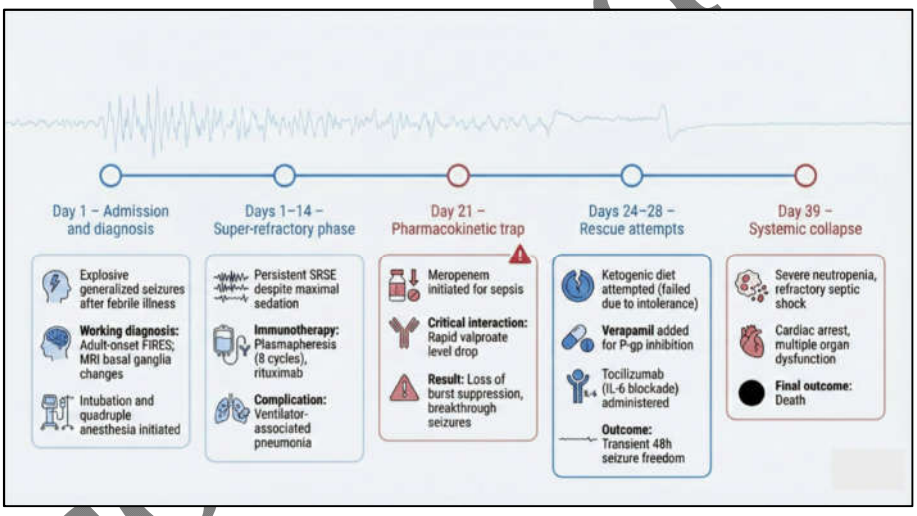

Fig. 1: Clinical Journey Map. A timeline of the patient's intensive care course in adult-onset FIRES with super-refractory status epilepticus. The graphic depicts five key phases: (1) Day 1 - explosive onset of generalized seizures following fever and working diagnosis of FIRES; (2) Days 1–14 - persistent super-refractory status epilepticus with early immunotherapy (plasmapheresis/rituximab) and ventilator-associated pneumonia; (3) Day 21 - the "pharmacokinetic trap" of meropenem-valproate coadministration leading to loss of burst suppression; (4) Days 24–28 - rescue attempts including ketogenic diet, adjunct verapamil, and tocilizumab (IL-6 blockade) yielding transient seizure freedom; and (5) Day 39 - systemic collapse characterized by severe neutropenia, refractory shock, cardiac arrest, and death

Phase 2: Nosocomial complications and pharmacokinetic interaction (Days 15–30)

During prolonged mechanical ventilation and deep sedation, the patient developed ventilator-associated pneumonia (VAP) with cultures growing multidrug-resistant (MDR) Klebsiella pneumoniae and Acinetobacter baumannii. On day 21, therapy was escalated to intravenous meropenem 1 g every 8 h for presumed MDR Gram-negative sepsis. The patient was maintained on sodium valproate as a key ASM. Within 24 h of meropenem initiation, cEEG revealed loss of burst–suppression and re-emergence of frequent electrographic seizures. This abrupt deterioration was attributed to the carbapenem antibiotics and valproic acid interaction: carbapenems inhibit acylpeptide hydrolase–mediated deconjugation of valproate–glucuronide, causing accelerated clearance and a 60–100% reduction in circulating active valproate within 1–2 days [10, 11]. In this patient, while specific serum levels of meropenem and valproate were not routinely checked, the interaction was clinically confirmed by the immediate recurrence of breakthrough seizures and loss of burst-suppression despite maximal anesthetic therapy [10, 11].

Recognizing this pharmacokinetic "trap," meropenem was discontinued and replaced with a combination of ceftazidime–avibactam and aztreonam guided by microbiological susceptibility. Valproate was effectively considered non-therapeutic for the subsequent period, and other ASMs were aggressively optimized. However, the transient destabilization significantly prolonged the duration and depth of anesthetic coma required.

Adjunctive therapies during this phase included an attempt at a ketogenic diet, which was hindered by feeding intolerance and recurrent hypoglycaemia. Verapamil 40 mg every 8 h was introduced as an adjunct to inhibit P-glycoprotein efflux transporters at the blood–brain barrier, with the aim of enhancing central penetration of ASMs, as described in case reports and small series of refractory epilepsy and status epilepticus [12].

Given the presumed immune-mediated basis of FIRES, immunotherapy was escalated (table 1). The patient underwent eight cycles of plasmapheresis and received rituximab; however, no consistent seizure reduction or anesthetic-sparing effect was observed. On day 28, tocilizumab (4 mg/kg IV, planned once a week for two doses), an interleukin-6 (IL-6) receptor antagonist, was administered as rescue cytokine-targeted therapy, guided by emerging evidence implicating IL-6 and IL-1β in FIRES pathophysiology and by expert consensus recommending consideration of cytokine blockade when first-line immunotherapy fails. Following tocilizumab, the patient achieved approximately 48 h of electroclinical seizure freedom, enabling partial tapering of propofol and other anesthetics. EEG at this stage showed burst suppression with interburst intervals of 5‑12 seconds. This improvement, however, coincided with the development of severe neutropenia, raising concern for tocilizumab-related immunosuppression amidst persistent MDR sepsis [5, 13, 14].

Table 1: Summary of immunotherapy agents

Agent	Mechanism	Timing	Observed effect	Adverse events
Plasmapheresis	Removal of circulating antibodies/cytokines	Phase 1 (8 cycles total)	No consistent seizure reduction	Coagulopathy risk; hypotension
Rituximab	B-cell depletion (anti-CD20)	Day 10 (1st Dose)	No response (consistent with non-antibody etiology)	Long-term immunosuppression
Tocilizumab	IL-6 Receptor Antagonist	Day 28 (Rescue)	Transient cessation of seizures (48 h); allowed partial anesthetic wean	Profound Neutropenia; Worsening Sepsis
IVIG	Immune modulation	Day 32 (Rescue)	No significant response	None documented

Phase 3: Systemic decompensation and outcome (Days 31–39)

Despite transient seizure control, the patient's systemic condition deteriorated. She developed refractory septic shock requiring escalating dual vasopressor support, progressive acute kidney injury, hepatic dysfunction, and hematological abnormalities, culminating in multiple organ dysfunction syndrome (MODS). The cumulative cardio-depressant effects of high-dose propofol and thiopentone, prolonged immobility, and profound immunosuppression (contributed to by infection, critical illness, and cytokine blockade) were considered major drivers of this systemic collapse [2, 3, 15]. On day 37, she suffered a cardiac arrest (pulseless ventricular tachycardia/asystole). Return of spontaneous circulation (ROSC) was achieved; however, neurological examination remained poor. She experienced a subsequent bradycardic cardiac arrest and was pronounced dead on day 39.

DISCUSSION

Adult-onset FIRES is a devastating encephalopathy driven by innate immune dysregulation and a central nervous system cytokine storm, rather than classical antibody-mediated autoimmunity [7–9, 16]. Microglial NLRP3 inflammasome overactivation and elevated interleukin-6 (IL-6) create a pro-convulsive milieu, explaining the marked pharmaco-resistance typical of this syndrome [7, 13]. Our patient's presentation—explosive SRSE, inflammatory CSF, negative autoantibodies, and basal ganglia hyperintensities—strongly aligns with this pathophysiology [4, 5, 16]. Seizure control remained precarious despite quadruple CIVAs, underscoring the urgent need to avoid iatrogenic destabilization.

The carbapenem‑valproate interaction proved catastrophic in this context. Carbapenems inhibit acylpeptide hydrolase, preventing the deconjugation of valproate-glucuronide. This accelerates clearance, causing a 60‑100% reduction in active valproate within 24‑48 h [10-11]. This rapid decline is often refractory to valproate dose escalation. In our patient, initiating meropenem caused an immediate loss of burst-suppression. While lack of therapeutic drug monitoring (TDM) precluded numerical confirmation of the serum valproate trough, the instantaneous clinical deterioration perfectly mirrored established pharmacokinetic timelines for this interaction. Concurrent use of carbapenems and valproate is contraindicated in SRSE. If carbapenems are mandatory for multidrug-resistant infections, valproate must be proactively substituted [10, 11, 17].

First-line immunotherapies targeting adaptive immunity (plasmapheresis, rituximab) yielded no benefit, consistent with the seronegative nature of FIRES [4-6, 16]. Conversely, IL-6 receptor blockade with tocilizumab produced a striking 48 h electroclinical remission, supporting the role of IL-6-driven neuroinflammation [7, 13, 14]. However, administering tocilizumab late (day 28) diminished its net benefit. The subsequent severe neutropenia and septic shock highlight the narrow therapeutic window for cytokine blockade. International consensus advocates initiating targeted therapies (anakinra or tocilizumab) within two weeks if first-line interventions fail, before entrenched multi-organ failure occurs [5, 13, 14].

SRSE mortality is frequently driven by systemic complications from prolonged anesthesia rather than uncontrolled seizures [2, 3, 15]. Our case exemplifies this trajectory. Quadruple CIVA effectively suppressed electrographic seizures but precipitated profound immunosuppression, ventilator-associated pneumonia, and cardiovascular collapse. Furthermore, adjunctive therapies faced practical barriers. The ketogenic diet failed due to critical illness-induced feeding intolerance and hypoglycaemia [9, 13, 18]. Alternative ASMs with novel mechanisms were extensively utilized. For instance, high-dose enteral perampanel (10 mg every 24 hourly) was administered to target glutamate-mediated excitotoxicity [19-21]. However, its absorption and efficacy were likely blunted by the patient's intermittent feeding intolerance and severe ileus. Brivaracetam was not trialed due to the prioritization of broad-spectrum structural ASMs, maximum CIVAs, and immunomodulation. To counteract potential drug resistance, we implemented the off-label use of verapamil to inhibit P-glycoprotein efflux at the blood-brain barrier [12]. Ultimately, high-risk features-cryptogenic etiology, requirement for four concurrent anesthetics, and mechanical ventilation exceeding 39 days—accurately predicted a fatal outcome according to standard scoring systems like END-IT [22, 23].

CONCLUSION

This fatal adult-onset FIRES case highlights critical lessons for neurocritical care practice. Concurrent use of carbapenem antibiotics and valproic acid in epilepsy or SE should be contraindicated. The interaction rapidly renders valproate ineffective, precipitating breakthrough seizures. When carbapenems are indispensable for life-threatening sepsis, alternative ASMs must be optimized proactively. Furthermore, in NORSE/FIRES with negative antibody panels, management should not rely solely on escalating anesthetics. Early cytokine-targeted immunotherapy (anakinra or tocilizumab) within 7‑14 days may provide better seizure control with a more favorable risk-benefit balance versus delayed rescue.

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AI USE STATEMENT

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AUTHORS CONTRIBUTIONS

Both authors contributed to patient management, data collection, literature review, and manuscript preparation. Both authors read and approved the final manuscript.

CONFLICT OF INTERESTS

Declared none

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