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SPECIAL REPORT

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Proposal to optimize evaluation and treatment of Febrile infection-related epilepsy syndrome (FIRES): A Report from FIRES workshop

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Abstract

Febrile infection-related epilepsy syndrome (FIRES) is a rare catastrophic epileptic encephalopathy that presents suddenly in otherwise normal children and young adults causing significant neurological disability, chronic epilepsy, and high rates of mortality. To suggest a therapy protocol to improve outcome of FIRES, workshops were held in conjunction with American Epilepsy Society annual meeting between 2017 and 2019. An international group of pediatric epileptologists, pediatric

neurointensivists, rheumatologists and basic scientists with interest and expertise in FIRES convened to propose an algorithm for a standardized approach to the diagnosis and treatment of FIRES. The broad differential for refractory status epilepticus (RSE) should include FIRES, to allow empiric therapies to be started early in the clinical course. FIRES should be considered in all previously healthy patients older than two years of age who present with explosive onset of seizures rapidly progressing to RSE, following a febrile illness in the preceding two weeks. Once FIRES is suspected, early administrations of ketogenic diet and anakinra (the IL-1 receptor antagonist that blocks biologic activity of IL-1β) are recommended.

KEYWORDS

anakinra, cytokines, epileptic encephalopathy, immune activation, neuroinflammation, new-onset refractory status epilepticus

1 | INTRODUCTION

Key points

- Consensus to optimize operational best practice on diagnosis and treatment of FIRES (febrile infectaion-related epilpsy syndrome)
- Recognize FIRES in a new explosive onset seizures progressing to status epilepticus following a febrile illness in the preceding two weeks
- Once infectious, metabolic, toxic and structural etiologies excluded within the first 48 hours, consider immunomodulatory therapies
- Targeted therapy for FIRES include anakinra, ketogenic diet, canabidiol and tocilizumab

The first report of the acute encephalopathies of obscure origin in infants and children was in 1961. Previous names also include "devastating epileptic encephalopathy in school age children (DESC)," "Fever induced refractory encephalopathy in school age children" and "acute encephalitis with refractory repetitive partial seizures (AERRPS)." Now known as "febrile infection-related epilepsy syndrome" (FIRES), FIRES is a subcategory of New-Onset Refractory Status Epilepticus (NORSE) and affects previously healthy children and adults suddenly and explosively.[1] FIRES is rare with an estimated incidence of one per million and a prevalence of one per 100 000.[2] The historical mortality rate of FIRES during the acute phase is between 9%–18%. Additionally, only 18% of children retain normal cognitive function following the acute phase, and over 90% develop refractory epilepsy requiring lifelong treatment.[2-5]

In an effort to unify clinicians and streamline research around the NORSE and FIRES, the consensus defining group convened and set standard definitions for NORSE and FIRES (funded by NORSE institute and endorsed by Critical Care EEG Monitoring Research Consortium (CCEMRC)).[6] NORSE was defined as a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other pre-existing relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic, or metabolic cause. FIRES is thus defined as a "subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at onset of SE."[6] Unlike NORSE, FIRES affects slightly more male children, and the median age of onset is roughly 8 years.[4,6,7]

Presentation of FIRES often begins with new-onset intermittent or stuttering seizures that progress in a crescendo-like pattern. Over a period of 2-7 days, seizures generally increase in frequency and duration, and progress to refractory status epilepticus (RSE) with minimal response to conventional anti-seizure medications (ASM). Some reported common features on the electroencephalograms (EEGs) of children with FIRES include 1) extreme delta brush, 2) a gradual increase in seizure burden and 3) focal seizure activity often with an onset low amplitude fast (>10 Hz) activity that evolves and shifts from one hemisphere of the brain to the other, eventually ending in the contralateral hemisphere.[8] Eventually, the seizure activity wanes in patients who survive, and there is progressive recovery of varying degrees of consciousness. Unfortunately, surviving patients are often left with significant cognitive deterioration and chronic intractable epilepsy.[3,9]

Improved understanding of the underlying pathophysiology of FIRES may help guide treatment options and improve outcomes. Preliminary data suggest a dysregulated innate immune system activation in FIRES.[6,10,11] An unopposed

pathological inflammatory state in the central nervous system (CNS) driven by over active proinflammatory cytokines and chemokines has been reported in children with this disorder.[12] This may contribute to seizure activity as these molecules have proconvulsant activity.[7] Additionally, a key role of interleukin-1 (IL-1) in epilepsy has been demonstrated in animal models.[13] Others have hypothesized that mesial temporal damage may contribute to the drug-resistant epilepsy.[3,4,12]

2 | OBJECTIVES

Given the high morbidity and mortality in FIRES, and the potential role of inflammatory process that may allow for targeted therapy, an international group of pediatric epileptologists, pediatric neurointensivists, rheumatologists and basic scientists with clinical interest and expertise in FIRES was convened with a goal of:

- Formulating a rational consensus driven approach for the evaluation of children with super-refractory status epilepticus in order to increase the recognition of patients with FIRES
- Developing a schema for early treatment of children meeting the current definition of FIRES with a goal of improving outcomes
- Creating a collaboration of providers for potential future research or trials for patients with FIRES

3 | METHODS

The FIRES workshops were held in conjunction with the 2017-2019 American Epilepsy Society meeting. These were organized by Sookyong Koh, MD, PhD. Persons who had published or presented work in this area were invited and encouraged to invite colleagues who also had expertise in FIRES. Twenty-five participants attended the first FIRES Workshop in 2017 and represented five countries (USA, UK, Sweden, Italy, and France). An initial draft protocol was outlined based on a group consensus at the initial meeting. Additional experts were invited and eventually included, resulting in this writing group. The group met annually at the American Epilepsy Society for the following two years to develop this final consensus document.

4 | RESULTS

4.1 | Pathogenesis of FIRES

The exact pathogenesis of FIRES remains elusive, but appears to involve a fulminant neurogenic inflammation in the brain.[2,10] Neurogenic inflammation has been proposed to describe an inflammatory response occurring in CNS cells, not only in neurons but also in glia and vascular cells of the blood-brain barrier (BBB) which is evoked by enhanced levels of neuronal activity.[14] A nonspecific, febrile infectious process occurs within two weeks preceding presentation with RSE; however, a single, causative pathogenic agent has not been identified.[3] Rather, it is likely that a nonspecific infection, not causal to the syndrome, triggers an inflammatory cascade.[3] The hypothesis, supported by increased CSF levels of inflammatory molecules and the therapeutic response of unremitting seizures to anti-cytokines treatments in FIRES patients, is that the progressive febrile infection primes the brain of a predisposed individual by inducing inflammatory response thereby reducing seizure threshold. Days to weeks after the febrile infection, the reduced threshold favors precipitation of seizures which in turn provoke a massive neurogenic inflammatory response. This neurogenic response contributes to seizure recurrence and status epilepticus.

Thus, FIRES may be considered a postinfectious immune system dysregulation in healthy, yet vulnerable individuals. While there have been no consistent single gene mutations reported in patients with FIRES, a genetic predisposition to inflammation may be important. In 2016, a potential link to the cytokine pathway was identified in patients with FIRES. Candidate gene analyses of 19 Japanese children with FIRES, focusing on polymorphisms of cytokine-related genes, found a significant association between the frequency of tandem repeats of the RN2 allele of IL-1RN and FIRES.[15] Variation in this allele results in higher levels of IL-1β and lower levels of IL-1Ra. A potential imbalance of intrinsic functional deficiency in endogenous IL-1 receptor antagonist (IL1-RA) and active IL-1β could lead to an unopposed pathologic inflammatory state. Sakuma et al found proinflammatory cytokines and chemokines markedly elevated in FIRES patients while T-cell associated and homeostatic cytokines were not.[10,12] Low rates of multiple autoantibodies, including GluR2, GluR3, glutamine decarboxylase (GAD), anti-voltage-gated potassium channel complex (VGKC), and neuropil, have been detected in FIRES cases. However, these rare positive findings likely reflect secondary epiphenomena due to breakdown of the BBB.[3,16]

4.2 | Preclinical and clinic evidence of IL-1β-IL-1R1 axis as a therapeutic target

IL-1 is a master cytokine of local and systemic inflammation. IL-1Ra is the endogenous competitive antagonist of IL-1 receptor type 1 (IL-1R1); this receptor transduces the cellular signal upon agonist activation. It is well known that > 100-fold molar excess of IL-1Ra is needed to efficiently inhibit IL-1 activity.[17] Anakinra is the human recombinant form of IL-1Ra and was the first to be introduced in 1993. Anakinra

currently has an established safety profile, known pharmakokinetics with short half-life and is effective in CNS.[18] The availability of specific IL-1-targeting agents, such as anakinra, has revealed a pathological role of IL-1-mediated inflammation in a growing list of autoinflammatory diseases.[17] Anakinra is approved for use in various rheumatological disorders, including rheumatoid arthritis, neonatal onset multisystem inflammatory disease,[18] and other cryopyrin-associated period fever syndromes. Anakinra is standard of care in systemic juvenile arthritis and macrophage activation syndrome. There have been two published phase II clinical studies evaluating the use of anakinra for neurological disease including patients with acute stroke and traumatic brain injury. In these studies, patients demonstrated the drug's tolerability even in exceptionally high doses.[19,20]

There is established and growing evidence for the activation of the IL-1β-IL-1R1 signaling pathway in human pharmacoresistant epilepsies in both children and adults, as shown by immunohistochemical and biochemical studies carried out in surgically resected epileptogenic foci.[21-25] Similar findings are reported in both immature and adult animal models of acute symptomatic seizures, febrile and non-febrile SE, as well as in models of acquired epilepsies, absence epilepsy, and progressive myoclonic epilepsy.[26-29] Notably, the activation of this signaling in animals significantly contributes to seizure generation in both acute and chronic models[28] and is involved in epileptogenesis evoked by SE.[30-32] The activation of the IL-1 signaling pathway, a pivotal part of the neuroinflammatory response, in chronic epileptogenic tissue[33,34] suggests that this signaling is inefficiently controlled. Indeed, IL-1Ra, which is the key molecule modulating the effects of IL-1β, is expressed to a lower extent than IL-1β in epileptic foci from drug-resistant epilepsy patients[22] and in animal models.[35] There is also a lower level of IL-1Ra in blood of children with febrile seizures compared to children with fever without seizures.[36] Thus, the ratio IL-1Ra:IL-1β is likely to be involved in determining seizure threshold. Recent evidence showed that circulating IL-1Ra in children with FIRES is less effective in blocking the IL-1β-signals as compared to native IL-1Ra, as assessed in a cell-based reporter system, denoting a functional inefficiency in IL-1Ra inhibitory activity.[12]

In support of the hypothesis that an imbalance between IL-1β and IL-1Ra contributes to recurrent seizure mechanisms, there are pharmacological studies in animal models showing that the intracerebral injection of IL-1Ra blocks the ictogenic effects of IL-1β[37] and is anticonvulsive per se by decreasing seizure number by 50% in kainate-injected adult rats.[38] Additional studies have shown that adult mice overexpressing the human recombinant form of IL-1Ra in astrocytes by 15-fold were intrinsically more resistant to seizures.[39] Further studies of anakinra in adult rodent models have demonstrated an effect on the incidence, severity and duration of SE.[40,41] Anakinra also mediates neuroprotection[42] and inhibited seizures induced by bicuculline in an isolated guinea pig brain. Its anticonvulsive effect was associated with rescue of blood-brain barrier (BBB) permeability dysfunction and decreased IL-1β expression in astrocytes.[43] Inhibition of IL-1β biosynthesis using the caspase-1 inhibitor VX-765 was also effective in reducing drug-resistant recurrent seizures in adult epileptic mice.[44]

Since FIRES affects mostly children, it is relevant to underscore that the activation of IL-1-IL-1R1 axis has been demonstrated in forebrain astrocytes and neurons in immature rodent models of seizures, such as in postnatal day 14-15 mice exposed to hyperthermia-induced status epilepticus.[45] This axis was shown to contribute to both acute seizures and epiletogenesis in this model.[30,45] Another model incorporates an inflammatory challenge induced by the bacterial product lipopolysaccharide (LPS) in immature rats but seizure precipitation requires a concurrent convulsive agent at a subcovulsive dose: both the induction of the seizure and its long term neurological sequelae involve inflammatory processes.[46] Additionally, anakinra reduced kindling epileptogenesis in immature rats promoted by LPS,[47] and anakinra co-administered with a COX-2 antagonist to juvenile P21 rats after SE reduced the ensuing epilepsy severity since rats developed a milder form of epilepsy with strong reduction (up to 70%-90%) of spontaneous seizure frequency, neuroprotection, and rescue of neurological comorbidities.[48] Notably, immature rats exposed to kainate-induce seizures displayed age-dependent seizure-induced neuroinflammation in forebrain which occurs at about 2 weeks of age and approaches the adult pattern at P21.[49] This age-dependent pattern may be ascribed to uncoupling between kainate-seizures and activation of transcriptional factors promoting inflammation such as AP-1 or NFkB. This evidence supports that the rodent brain becomes susceptible to seizure-associated neuroinflammation at an age compatible with the occurence of FIRES in humans.[50]

In summary, the experimental data show that the cytokine pathway, specifically mediated through IL-1β is involved in both humans and animal models of epilepsy, including FIRES. Dysregulation of the balance of IL-1β activation and inhibition influences epilepsy and epileptogenesis. These factors can be modified or targeted by therapeutics, including anakinra, which has evidence of potent anti-seizure actions in a variety of experimental models of seizures, affords neuroprotection, and has potential anti-epileptogenic effects.

4.3 | Therapeutic options for FIRES

4.3.1 | Anti-seizure medications

Anti-seizure medications (ASM) are poorly efficacious in FIRES.[3] Many children are treated with prolonged anesthetic

coma given their seizure burden; however, there is concern that longer durations of barbiturate-induced, burst suppression coma correlate with worse cognitive outcomes.[51] Cannabidiol (CBD) has been approved as Epidiolex® (GW Pharma) for the treatment epilepsy in patients with Dravet Syndrome or Lennox-Gastaut Syndrome.[52] CBD may have an anti-inflammatory effect. Small case series of patients with FIRES treated with CBD (mostly in the chronic phase) documented improvement in seizure frequency and duration in 6/7 cases after four weeks (90% reduction) and 48 weeks (65% reduction) of treatment.[4]

4.3.2 | Ketogenic diet

Several small case series suggest a benefit of ketogenic diet in children with FIRES,[53,54] with one study documenting efficacy in 7/9 children within 4-6 days after diet onset.[53] Notably, the β-hydroxybutyrate, one main ketone body generated by the KD, inhibits the proteolytic activity of caspase-1 thereby reducing the release of biologically active IL-1β.[55] The ketogenic diet exhibits anti-inflammatory properties in animal studies, with animals showing less fever and lower proinflammatory cytokines after just 14 days of dietary therapy than controls.[56]

4.3.3 | Immunomodulatory/anti-inflammatory therapies

Patients with FIRES are often treated with high-dose steroids, intravenous immunoglobulin (IVIG), or both; however, there is little evidence of efficacy for such treatments. In a retrospective study of 29 patients given steroids for FIRES, most of whom were treated with pulse methylprednisolone, no significant benefit was seen in any subject.[3] Similarly, limited data support efficacy for plasmapheresis and no convincing benefit was noted in 30 patients given IVIG.[3] In one study of 8 children, IVIG was partially efficacious in 2 cases; however, both of these subjects had oligoclonal bands found in CSF electrophoresis, which is atypical for FIRES.[57] Therapeutic hypothermia is known to have anti-inflammatory and neuroprotective property and has been shown to be beneficial in patients with FIRES.[7] The KD might also be active through an anti-inflammatory mechanism as detailed above.[55,56]

There are several case reports of children with FIRES treated with anakinra that showed significant reduction in seizures.[11,12,58-62] In a 32-month old girl with FIRES, cytokine analysis was performed on both CSF and serum. While no significant abnormalities were detected in serum, both IL-8 and IL-6 were markedly increased in the CSF pretreatment but normalized on treatment. IL-1β analysis was attempted but deemed unreliable.

There is little data on the use of other immunomodulatory therapies, although some of these also have a direct effect on the cytokine pathway. Canakinumab, a monoclonal antibody against IL-1β has shown benefit in single report of a FIRES patient also treated with anakinra.[13] Tocilizumab blocks IL-6-mediated signaling and was reported to improve NORSE symptoms in one study; however, adverse events were reported following tocilizumab use in a fraction of patients within the study. Tocilizumab has a longer half-life than anakinra and its CNS penetration is unclear.[63] Rituximab is an anti-CD20 monoclonal antibody that depletes circulating B-cells. It has shown no benefit in two reported cases of FIRES.[64,65] Tacrolimus inhibits T-cell activation and proliferation and has been used in two cases with mixed results. Sato et al documented efficacy in a single patient who was also found to have anti-glutamate receptor ε2 antibodies, suggesting this was probably not cryptogenic FIRES;[66] however, there was no benefit in one other case.[2]

5 | PROPOSED DIAGNOSTIC HEURISTIC AND THERAPEUTIC CONSIDERATIONS

FIRES is a devastating diagnosis that does not respond to treatment with conventional therapies and has a high rate of morbidity and mortality. New randomized trial data is unlikely to be feasible due to the low prevalence of FIRES. Given the available preclinical and case report data, we propose a shift in therapy toward early targeted immune therapy for FIRES, as our group no longer felt there was equipoise for treating FIRES without targeted therapies. To aid in the rapid identification of patients with FIRES and potential early targeted therapy, we compiled a typical case presentation of a child with FIRES (Box 1) as well as a diagnostic heuristic and approach to therapies (Figure 1). The recommendations made are expert opinion based on our experiences in treating children with FIRES, published case studies, and discussions with other clinicians in this field of study.

5.1 | How can FIRES be recognized early in the clinical course with reasonable certainty?

FIRES should be clinically suspected in any child presenting with new-onset seizures, without a clear acute or active structural, toxic, or metabolic cause, which are rapidly increasing in frequency and severity following a nonspecific febrile illness in the last 2 weeks to 24 hours, consistent with the proposed definition approved by the CCEMRC.[6] The most critical differential diagnoses that must be excluded are central nervous system infections and autoimmune encephalitis.

BOX 1 Case Presentation

A previously healthy, developmentally normal 6-year-old girl initially presented to the emergency department (ED) with a 2-week history of cough and rhinorrhea and a 24-hour history of abdominal pain, dizziness, and fever, without headache, neck stiffness, or altered level of consciousness. A urinalysis in the ED was suggestive of a urinary tract infection, and she was prescribed an oral antibiotic and discharged. The prescription for the antibiotic was not filled because of a holiday weekend, and her mother brought her back to the ED the following day, where she was febrile to 39.4°C. She received an intramuscular dose of ceftriaxone and was again discharged home. Three days after her initial presentation, the patient again had a fever to 38.8°C, and her mother witnessed acute-onset gaze deviation and head turn towards the left, progressing to generalized stiffness. Upon arrival to ED, the patient was awake and interactive; however, she was soon noted to have a decreased level of responsiveness with fluttering eyelid movements and oral automatisms. She was given intravenous lorazepam, and these movements stopped. She then became hypoxic and required emergent intubation with mechanical ventilation. Head computed tomography was unremarkable, and continuous video electroencephalogram (cvEEG) indicated subclinical SE, which persisted despite administration of 2 additional doses of intravenous lorazepam. She was given intravenous fosphenytoin (20 mg/kg), started on a midazolam infusion, and transferred to the pediatric intensive care unit (PICU).

In the 12 hours following patient's arrival to the PICU, she had 9 multifocal onset electroclinical seizures, characterized by rhythmic twitching in the right face, arm, and leg. Midazolam infusion was discontinued and replaced by a pentobarbital infusion, which was titrated to a burst-suppression EEG pattern. Empiric broad-spectrum antibiotic coverage was initiated, including vancomycin, ceftriaxone, and acyclovir. A lumbar puncture (LP) was performed to rule out meningoencephalitis, and CSF analysis revealed 15 white blood cells (WBC)/mm^3 with slightly elevated glucose and normal protein. CSF polymerase chain reactions for enterovirus, adenovirus, and herpes simplex virus were all negative. On hospital day 2, levetiracetam was initiated. Efforts to wean pentobarbital resulted in additional subclinical seizures, so this was continued, to target a burst-suppression EEG pattern.

Additional investigation (see Appendix A) were unrevealing with negative infectious testing and a brain MRI with nonspecific findings of bilateral hippocampal and left thalamic T2 signal hyperintensity, with a loss of normal architecture in these regions. She received additional ASM including lacosamide, isoflurane, lidocaine infusion, perampanel, ketamine infusion, and cannabidiol oil. Additional therapies trialed included the ketogenic diet, hypothermia, magnesium infusion and intravenous immunoglobulin. Despite these aggressive therapies, the patient continued to have RSE. By hospital days 16, she developed many complications including refractory hypotension requiring continuous vasopressors and hydrocortisone, and anuria with renal failure requiring continuous venovenous hemofiltration (CVVH). The patient expired on hospital day 23 of respiratory failure.

Common treatable infectious, metabolic, toxic, and structural etiologies can typically be excluded within the first 48 hours (Table 1).

As confirmation of specific antibodies that cause autoimmune encephalitis, such as anti-NMDA receptor antibody, may be delayed for 1-2 weeks, empiric treatment with IV methylprednisolone or IVIG is often undertaken after infectious causes are excluded, or in addition to empiric anti-infective coverage. The common prodrome with behavior changes, mutism, and movement disorders may suggest that anti-NMDA R encephalitis is a more likely etiology in the correct clinical context[67] and can help guide specific treatment for this diagnosis. Seizures are common (~70%), but rarely frequent, while the other two major symptoms, psychiatric features and movement disorders are even more prevalent (>90%).[67,68] Lack of clinical improvement after 2-5 days of immunotherapy, including methylprednisolone, IVIG and plasmapheresis, should prompt increased clinical suspicion for FIRES. Unfortunately, there are no definitive confirmatory laboratory markers for FIRES. Laboratory evaluations are thus to exclude other identifiable etiology for RSE.

5.2 | When to start empiric therapy for FIRES?

Once other potential common treatable causes are excluded with reasonable certainty, presumptive treatment for FIRES should be initiated, ideally, within one week of initial presentation. While research studies have demonstrated elevations in various inflammatory cytokines, such studies are very limited in the clinical sphere, and if performed, results are often available only after a significant delay. Our working group felt strongly that definitive treatment for FIRES should not be delayed given the lack of an established role in confirmatory cytokine testing.

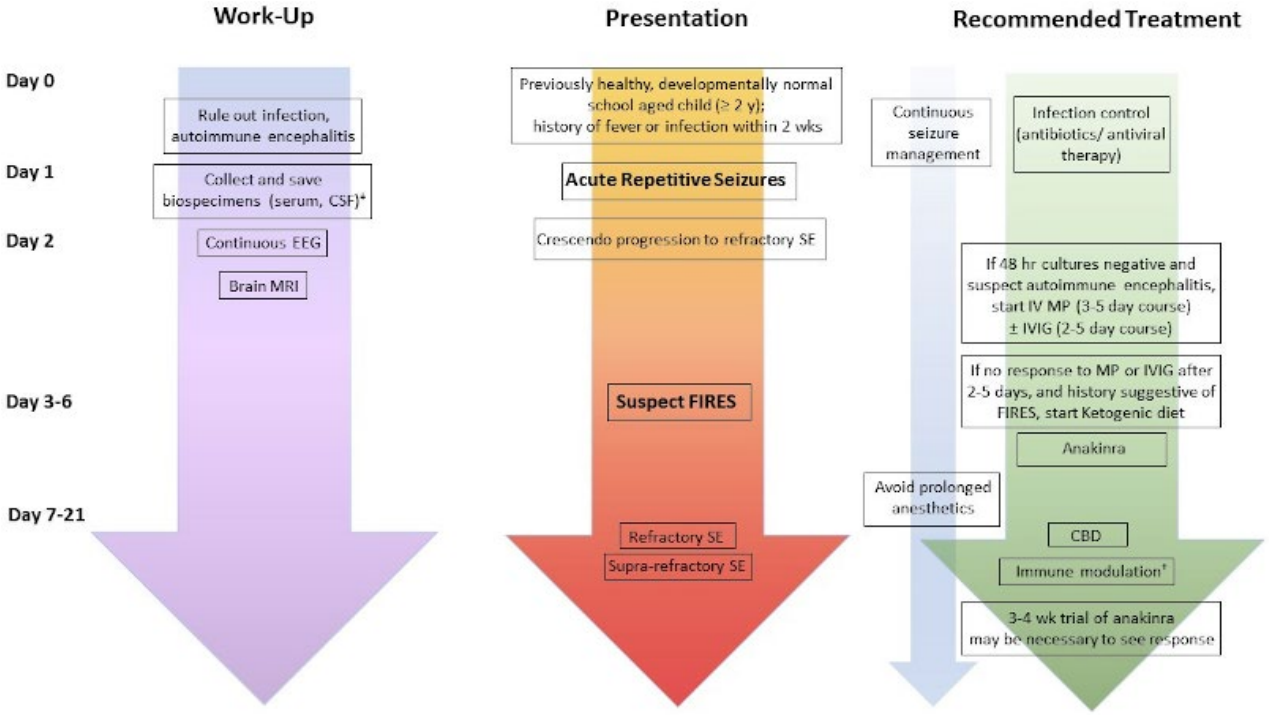

FIGURE 1 FIRES Recommended Diagnostics and Therapeutics ‡For cytokine assays, biorepository. EEG, electroencephalography; MRI, magnetic resonance imaging; CSF, cerebral spinal fluid; SE, status epilepticus; MP, methylprednisolone; CNS, central nervous system; ASM, anti-seizure medications. *Suspect diagnosis:* New-onset acute repetitive seizures and intermittent SE in a previously healthy, normal developing child older than 2 years of age; preceding febrile illness within 2 weeks of seizure onset. *First 24 hours:* First tier work up to exclude active bacterial and viral CNS infection via lumbar puncture. Confirm no other structural etiology via brain MRI. Continuous EEG monitoring needed. Save serum and CSF for autoimmune panel. Escalating ASM with benzodiazepines, fosphenytoin, phenobarbital, levitiracetam, valproic acid, midazolam drip followed by barbiturate coma—burst suppression. *Day 2-6:* Establish FIRES determination—super-refractory SE (SRSE); strongly consider FIRES by day 6. Start ketogenic diet. Tolerate brief breakthrough seizures; try lift or avoid barbiturate-induced burst suppression. If suspicion of autoimmune encephalitis is high, then consider methylprednisolone (30 mg/kg daily, max 1 g, for 3 days) ± IVIG (2 g/kg divided over 2-3 days). blood, serum, and CSF, if available, for cytokine assays including neopterin, Il-6 and IL-1β (see Table 1). Consider anakinra (subcutaneous injection 10 mg/kg divided twice to 4 times daily up to 400 mg/day). Consider other ASM including CBD *Day 7-21:* Start ketogenic diet and anakinra if not done already. Avoid prolonged anesthetics, such as pentobarbital coma, propofol, lidocaine, isoflurane, or ketamine infusion. Extended trial of anakinra (3-4 weeks) may be necessary before response is seen; alternatively, or if no response to anakinra after 4 weeks, consider other †immunomodulation such as tocilizumab (subcutaneous or intravenous injection 8-12 mg/kg) or canakinumab (subcutaneous injection 2-3 mg/kg) for patients weighing between 15-40 kg. Continue immunomodulatory therapy if positive response noted. Consider alternate therapy, such as plasmapheresis, rituximab, cyclophosphamide, if autoimmune antibody detected. *Resources*: NORSE Institute (www.norseinstitute.com) *NORSE Prospective Study*Nicolas.gaspart@erasme.ulb.ac.be*or*alrence.hirsch@yale.edu*Norse Family Resgistry*Teneille.gofton@lhsc.on.ca

5.3 | What are potential therapeutic options in a child with SRSE, in whom FIRES is suspected?

Targeted therapy includes treatment with anakinra, initiation of the ketogenic diet where available, cannabidiol, and additional anti-inflammatory therapies.

5.3.1 | Anakinra considerations

As described above, preclinical data are compelling and early clinical data suggest that anakinra is beneficial in many FIRES patients. This is an established, effective medication used in rheumatologic disorders in children and is well-tolerated and safe. [2,12,58,62] If seizures remain refractory after empiric treatment with corticosteroids and/or IVIG and if anesthetic agents are unable to be weaned, adding Anakinra for IL-1 blockade should be considered within the first two weeks of presentation. Our group felt that there was not adequate therapeutic equipoise to justify a placebo-controlled study, but that a well-designed open-label study should be done, comparing outcome in anakinra-treated subjects to previously reported cases in the literature. Given that fulminant neurogenic inflammation is likely injurious to the brain, our group agreed that initiation of anakinra is likely time-sensitive, with the potential for improved outcomes both regarding seizure control and neurocognitive function with earlier therapy. Thus, anakinra should optimally be started prior to or within the first two

TABLE 1 Diagnostic testing during evaluation for suspected FIRES

	Blood/Serum	CSF	Other Testing
Infectious	Bacterial culture Additional infectious testing based on travel and season	CSF cell count Bacterial Culture HSV PCR Meningoencephalitis Panel (PCR) CSF arboviral Panel (Immunoassay)	MRI with and without contrast Continuous video EEG
Autoimmune	Autoimmune Encephalopathy Panel ANA, SLE panel ESR, CRP, Procalcitonin	Autoimmune Encephalopathy Panel	
Autoinflammatory	B, T, NK cell number, ferritin Immunoglobulins, IgE Cytokine Panel (Cincinatti Children's Laboratory) Neopterins	Cytokine Panel (Cincinatti Children's Laboratory) Neopterins	
Metabolism	Based on history consider specific testing Pre-Ketogenic diet laboratories including: electrolytes, hepatic panel, amylase, lipase, NH3, lactic acid, pyruvic acid, amino acids, organic acids, carnitine, acyl-carnitine, and beta-hydroxybutyrate levels		

weeks (7-14 days) after initial seizure presentation. Though rapid decreases in seizure burden have been experienced by our group (within 1-2 days), extended trials of 3-4 weeks may be needed particularly for patients with protracted courses. Several authors have identified and reported patients with increased seizures when anakinra is stopped and improved seizure control after re-initiation. Extended therapy may be helpful during the chronic epilepsy phase of FIRES.

5.3.2 | Ketogenic diet considerations

If it is possible to safely initiate the ketogenic diet at the patient's hospital, early initiation can start within the first week. As per each institution's ketogenic diet protocol in general, metabolic diseases should be excluded. Testing may include (based on clinical history): electrolytes, hepatic panel, amylase, lipase, NH3, lactic acid, pyruvic acid, amino acids, organic acids, carnitine, acyl-carnitine, and beta-hydroxybutyrate levels. If there is nothing suggestive of a metabolic disorder from the history or initial studies, the ketogenic diet can be initiated while testing is pending and stopped if metabolic parameters worsen. A metabolic disease is less likely the older the onset of FIRES.[3]

5.3.3 | CBD Considerations

Initiation of CBD may be considered at any time during the course of FIRES, but should not delay anakinra therapy, as there is limited data regarding the use of CBD in the acute phase of treatment.

5.3.4 | Additional targeted anti-inflammatory therapy

Tocilizumab and canakinumab may have therapeutic roles; however, the group felt they had lesser evidence and potentially greater side effects than anakinra and decreased CSF penetration, and thus should only be considered if anakinra is ineffective. Our group recommended caution combining tocilizumab and anakinra due to combined immune suppression and potential additive adverse effects.

6 | DISCUSSION

FIRES is a devastating epilepsy syndrome that has significant associated morbidity and mortality necessitating early diagnosis and targeted treatment. Early administration of immune modulatory drugs, including the IL-1 receptor antagonist, anakinra, that blocks biologic activity of IL-1β, may be beneficial. Canakinumab, another IL-1β inhibitor[13] and tocilizumab, an IL-6 inhibitor,[63] have also been used with promising results in FIRES and NORSE cases, though more data are available with anakinra in children with FIRES at this time. Initiation of a ketogenic diet is strongly recommended due to established anti-inflammatory effects; additionally, positive results in children with FIRES given a ketogenic diet have been reported.[6,53] CBD has been presented as a possible alternative therapy for uncontrolled seizures in a small case study in children with FIRES and is approved for other refractory epilepsy syndromes. This may be considered in conjunction with other therapies, although there is limited data regarding use in the acute phase of FIRES. Unfortunately, prolonged

use of high-dose barbiturates and anesthetics to induce coma may contribute to poor cognitive outcomes in patients with FIRES.[3,7] Tolerating brief breakthrough seizures or a low seizure burden may allow for weaning from continuous anesthetic anti-seizure medications.

Though FIRES is a rare syndrome, its effect on children and their families is truly devastating. Randomized trials are not likely given the rarity and severity of this condition. Open communication among treating clinicians and establishment of a database and biorepository are underway to facilitate research into the underlying cause and pathogenesis of NORSE and FIRES (NORSE Institute www.norseinstitute.com). Delays in diagnostics and administration of appropriate therapeutics may contribute to poor prognoses.[7] We present these proposed expert recommendations and describe international collaborative efforts with the hope of helping future patients with FIRES and in memory of the children lost.

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CONFLICT OF INTEREST

Sookyong Koh applied and received unrestricted educational grant from Sobi to hold FIRES Workshops. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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APPENDIX A

Other Testing (Case Presentation)

Additional available data from the case presentation are listed below.

TSH low at 0.26, T4 low at 0.40, ANA-negative, HIV-negative, dsDNA-negative, ANCA: neg, tissue transglutaminase IgA-negative, issue transglutaminase IgG normal, TPO Ab-negative, thyroglobulin-negative, RPR nonreactive, ACE-negative, arbovirus panel: negative, VRP: Adenovirus +. Repeat on 7/17 negative, adenovirus CSF: negative, CSF cytology: neg, NMDA serum: neg, *Ehrlichia* spp. titers: neg, Cat Scratch (*Bartonella henselae*) IgG/IgM: neg, genetic metabolic panel: Nonspecific changes not indicative of a metabolic disease.