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SPECIAL REPORT

International consensus recommendations for management of new onset refractory status epilepticus including febrile infection-related epilepsy syndrome: Statements and supporting evidence

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Abstract

Objective: This study was undertaken to develop consensus-based recommendations for the management of adult and pediatric patients with new onset refractory status epilepticus (NORSE)/febrile infection-related epilepsy syndrome (FIRES) based on best evidence and experience.

Methods: The Delphi methodology was followed. A facilitator group of nine experts was established, who defined the scope, users, and suggestions for recommendations. Following a review of the current literature, recommendation statements concerning diagnosis, treatment, and research directions were generated, which were then rated on a scale of 1 (strongly disagree) to 9 (strongly agree) by a panel of 48 experts in the field. Consensus that a statement was appropriate was reached if the median score was ≥7 and inappropriate if the median score was ≤3. The analysis of evidence was mapped to the results of each statement included in the Delphi survey.

International NORSE Consensus Group members are shown in Appendix A.

Results: Overall, 85 recommendation statements achieved consensus. The recommendations are divided into five sections: (1) disease characteristics; (2) diagnostic testing and sampling; (3) acute treatment; (4) treatment in the postacute phase; and (5) research, registries, and future directions in NORSE/FIRES. The detailed results and discussion of all 85 statements are outlined herein. A corresponding summary of findings and practical flowsheets are presented in a companion article.

Significance: This detailed analysis offers insight into the supporting evidence and the current gaps in the literature that are associated with expert consensus statements related to NORSE/FIRES. The recommendations generated by this consensus can be used as a guide for the diagnosis, evaluation, and management of patients with NORSE/FIRES, and for planning of future research.

KEYWORDS

adult, antiseizure medication, Delphi, epilepsy, immunotherapy, ketogenic diet, pediatric, refractory status epilepticus, status epilepticus

1 | INTRODUCTION

New onset refractory status epilepticus (NORSE) is a rare and devastating condition characterized by de novo onset of refractory status epilepticus (RSE) without an identifiable acute or active structural, toxic, or metabolic cause. It is a clinical presentation rather than a specific diagnosis, as suggested by a recent consensus definition paper.[1] Febrile infection-related epilepsy syndrome (FIRES), per the same consensus definition paper, is considered a subcategory of NORSE rather than a separate entity as previously suggested.[2] This is supported by evidence of NORSE and FIRES both occurring in all age groups and by difficulties with clearly delineating them as separate clinical entities.[1,3] The FIRES diagnosis requires prior febrile illness starting between 2 weeks and 24 h before onset of RSE (with or without fever at onset of status epilepticus [SE]).[1,4] Both terms thus apply to all age groups. If a specific diagnosis is subsequently reached, including autoimmune and infectious causes, it is still considered NORSE (with or without also qualifying as FIRES). If no explanation for the clinical presentation of NORSE is found, it is considered cryptogenic NORSE (or NORSE of unknown etiology).

The current evidence for appropriate diagnostic evaluation, treatment, and follow-up of patients with NORSE stems from case reports, case series, and limited observational studies. Although a number of reviews have been published on this topic,[4–8] no randomized controlled trials or consensus guidelines for the management of NORSE/FIRES are available. A recent systematic review of the relevant literature identified 197 studies of 1334 adult and pediatric patients.[7] Nonetheless, many aspects of clinical care in NORSE remain unaddressed, and the existing treatment approaches are still heterogeneous. This is illustrated by a survey among neurocritical care practitioners in the United States in which it was reported that two thirds of institutions did not have a protocol to evaluate and treat NORSE patients.[9]

Key Points

- As solid evidence for diagnosis and treatment of NORSE/FIRES is scarce, a Delphi consensus approach was employed to develop recommendations
- A total of 85 recommendations concerning diagnosis, treatment, and follow-up were developed to aid clinicians in patient care
- Supporting evidence and current gaps in the literature associated with the expert consensus statements for NORSE/FIRES are presented

The present study, performed using a Delphi methodology, aimed to map the existing literature to an exhaustive list of consensus recommendations for the treatment of NORSE/FIRES in all age groups. The recommendations were designed to be pragmatic and relevant, and to serve as a practical decision support tool for clinicians confronted with this rare and challenging condition. Given the limited evidence supporting most treatment statements, the present document is intended as recommendations or considerations rather than strict guidelines. By including the background and evidence

for every statement included in the Delphi survey, we aim to additionally demonstrate where the current literature supports current recommendations and where there are gaps in understanding that require future research. A practice-focused summary of relevant recommendations with diagnostic and management tools for acute care of NORSE is provided in a companion article in this issue of *Epilepsia*.

2 | MATERIALS AND METHODS

2.1 | Participant selection

Following the initiation of this work at the 2019 Annual Meeting of the American Epilepsy Society, a steering committee of nine experts (R.W., O.T., R.D., E.T.P., N.S., R.N., S.K., N.G., and L.J.H.) was established. This committee acted as facilitator group for the Delphi project and also participated as panelists. A panel of 39 experts with recognized experience in the field was then identified and invited to complete the survey, leading to a total group of 48 persons (later referred to as "the panel"). The experts were chosen based on their portfolios of indexed relevant publications and participation in specific congresses as well as their leadership in clinical care for NORSE/FIRES. Experts, including those from the facilitator group, were specialists in (multiple specialties possible): adult neurology ($n = 16$), pediatric neurology ($n = 15$), adult epileptology ($n = 19$), pediatric epileptology ($n = 18$), adult neurocritical care ($n = 7$), pediatric neurocritical care ($n = 5$), and pediatric rheumatology ($n = 2$). Experience was ≥13 years for 78% of respondents, 10–12 years for 8%, 7–9 years for 6%, and 4–6 years for 8%. Geographically, the panelists represented North America ($n = 27$), South America ($n = 1$), Europe ($n = 18$), Asia ($n = 1$), and Oceania ($n = 1$). A patient representative from the NORSE Institute provided continuous input during the development of recommendations. Seminal articles on NORSE were selected by the facilitator group and distributed to the panel members as background information at the time of the survey. Because of the significant lack of data from randomized controlled trials or large studies, GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) of the evidence was not performed.

2.2 | Development of Delphi method

A two-step survey was preceded by a pre-Delphi questionnaire, which was introduced to develop the consensus on relevant statements. The pre-Delphi questionnaire (Supplement S1) surveyed the data on the respondents' demographics, site data, and agreement on core definitions. Furthermore, it addressed the important question of whether the subsequent Delphi process should be conducted separately for NORSE and FIRES, as well as for adults and children. The prequestionnaire was sent out to the panel members in March 2020 using SurveyMonkey, a web-based survey tool (www.SurveyMonkey.com). The data collected using this prequestionnaire were applied to compile the Delphi 1 survey. The Delphi 1 questionnaire was comprised of 81 Delphi statements and seven open questions and was distributed in January 2021. Following the assessment of the consensus on these statements, 28 statements were carried forward to the Delphi 2 survey, which was distributed in April 2021. The statements were divided into five sections: (1) disease characteristics of NORSE/FIRES, (2) tests and sampling in NORSE/FIRES, (3) treatment of NORSE/FIRES–acute phase, (4) treatment of NORSE/FIRES–postacute phase, and (5) research and registries in NORSE/FIRES. In addition to statements and recommendations, open questions were included in the questionnaires to aid in the development of further statements.

In each survey, panel members were asked to rate each statement according to a 9-point Likert scale (1 = strongly disagree, 9 = strongly agree) and provide free text comments on the statement. Consensus that a statement is appropriate was defined as reached if the median score was ≥7, and that it was inappropriate if the median score was ≤3. The level of agreement (LA), defined as the percent of raters giving a score of 7–9, and the level of disagreement (LD), defined as the percent of raters giving a score of 1–3, were calculated for each statement. Consensus statement for a specific recommendation was considered in disagreement if LD was found in at least one third of respondents. Such a finding would mean that consensus had not been reached. Each recommendation that did not achieve consensus was either discarded or revised and carried forward; this decision was made via discussions in the facilitator group. A complete list of statements and open questions for both rounds can be seen in Supplement S1 and the process of arriving at the statements is outlined in Supplement S2. Furthermore, a breakdown of responses between adult and pediatric caregivers was made to facilitate the understanding of different views and opinions in two groups of clinicians. The median responses (M) for both age groups as well as those for adult (MA) and pediatric (MP) caregivers were calculated on the 1–9-point Likert scale for each statement.

3 | RESULTS

3.1 | Pre-Delphi questionnaire

Forty-seven of 48 experts responded to the prequestionnaire. There was consensus that the survey should address NORSE and FIRES jointly (median = 8, LA = 84.0%, and LD = 9%). Of the five participants who disagreed, three were pediatric neurologists and two were adult neurologists. There was also consensus that the survey should address adult and pediatric care jointly (median = 7.5, LA = 60.5%, and LD = 18.6%). Of the eight members who disagreed, four were pediatric neurologists and four were adult neurologists. The subsequent Delphi questionnaires were therefore developed to jointly address all questions. Additional analyses of responses from adult and pediatric health care physicians were made and are provided in the document.

3.2 | Delphi 1 and 2 questionnaires

All 48 invited panelists completed the Delphi 1 questionnaire. Consensus was reached for 70 of 81 statements, but comments warranted rephrasing in 13 of 70 statements. In addition, six statements that did not reach consensus were rephrased for a subsequent round, and nine new statements were added based on the feedback and responses to open questions, yielding 28 statements that were included in Delphi 2. Again, a full response (48/48) was achieved and consensus was reached for all 28 statements. Collectively, 85 statements reached consensus, and are described herein, including a discussion concerning the level of evidence and rationale for the statement. An overview of the recommendation statements, including practical flowsheets for diagnosis and treatment, is available in a summary article in this volume of *Epilepsia*.

3.3 | Disease characteristics of NORSE/FIRES

1. **A diagnosis of NORSE may be given for persons of all ages** (M = 9, MA = 9, MP = 9, LA = 90.7%, LD = 4.7%).
   Although it appears clear that NORSE can affect people of all ages, the etiologies may vary markedly with age, leading to differences in evaluation and treatment, as discussed below. However, NORSE should be viewed as a clinical presentation with new onset of RSE without a clear acute or active structural, toxic, or metabolic cause regardless of the age of the patient. If no cause is found after an extensive evaluation, the disorder should be considered cryptogenic (i.e., NORSE of unknown etiology).
2. **The definition of FIRES as a subcategory of NORSE is appropriate** (M = 9, MA = 9, MP = 9, LA = 88.7%, LD = 0%).
   Rather than being an independent disease entity, it was proposed in the consensus definitions[1] that FIRES should be defined as a subcategory of NORSE that requires a prior febrile infection. The fever can start between 2 weeks and 24 h prior to the onset of RSE, and it may or may not persist at the onset of seizures. However, FIRES is also recognized as a distinct syndrome as defined by the International League Against Epilepsy (ILAE) nosology task force, and identifying NORSE cases that fulfill FIRES criteria is therefore important. To what extent FIRES (i.e., NORSE with prior fever) actually differs from NORSE without prior fever remains to be elucidated, but given the wide use and extensive prior literature on FIRES, it is important to maintain this term as further research addressing the question is performed.
3. **A diagnosis of FIRES may be given for persons of all ages** (M = 9, MA = 9, MP = 8, LA = 84.1%, LD = 2.3%).
   Although initially considered a pediatric condition, it has become increasingly clear that not all children with NORSE fulfill FIRES criteria and conversely that many adult patients with NORSE do. Although the mechanisms underlying RSE may be distinct in adult and pediatric patients, FIRES can thus develop at any age. It was recently demonstrated that FIRES is distinguishable from febrile SE in children not only by the timing of fever (part of the definition), but also by younger age and shorter SE duration in febrile SE.[10]
4. **NORSE/FIRES has no evident geographical trend** (M = 8, MA = 7, MP = 9, LA = 81.2%, LD = 2.1%).
   No studies have systematically assessed the geographical distribution of NORSE/FIRES.
   A recent systematic review of literature on pediatric FIRES reported that the incidence of NORSE was higher in certain parts of Asia. The authors speculated that this may reflect an association with geographical locations or ethnic groups.[11] However, given that the review was based on the case reports and case series, this may also represent a publication bias. Future research is needed to assess the geographical distribution of NORSE and establish whether there are genetic factors

or endemic infections that may contribute to the development of this refractory seizure syndrome.

5. **NORSE/FIRES has no demonstrated seasonal trend, but more research is needed to exclude such variation** (M = 8, MA = 8, MP = 7.5, LA = 75.0%, LD = 2.1%).
   There are no published data to support the role of a seasonal trend in NORSE/FIRES. Whereas anecdotal experience from the panel was that only a few cases had been encountered by members during summer months, preliminary data from the Yale biorepository together with the NORSE family registry do not support this. In contrast, cases are fairly evenly distributed through the year, with summer being the most frequently represented season. This may be an important area for future research, as infectious pathogens may be important triggers for certain autoimmune encephalitis syndromes associated with NORSE,[12] and a seasonal trend following viral infections could theoretically be of importance.
6. **In NORSE/FIRES patients with chronic autoimmune conditions, a primary autoimmune etiology should be suspected** (M = 8, MA = 8, MP = 8, LA = 83.3%, LD = 2.1%).
   Because both chronic autoimmune conditions and primary autoimmune-driven NORSE are relatively uncommon in children and adolescents,[5,10] the discussion on autoimmune etiology of this condition mainly concerns adult patients. It should also be noted that patients receiving immunosuppressive therapies are at higher risk for infections and that an extensive workup for relevant pathogens therefore is warranted.
7. **In NORSE/FIRES patients with non-central nervous system (CNS) malignancies, a paraneoplastic etiology should be suspected** (M = 8, MA = 8, MP = 8, LA = 87.5%, LD = 0%).
   The prevalence of malignancies among NORSE/FIRES patients is unknown, but cancer needs to be ruled out as a cause for autoimmune paraneoplastic disease. In a large retrospective cohort of adult patients with NORSE, paraneoplastic encephalitis was identified in 18% of cases.[13] As the prevalence of noninfectious etiologies is overall lower in children compared to adults,[5,14] this will be more relevant for the latter age group.
8. **Postinfectious immune activation is likely an important cause for NORSE/FIRES** (M = 8, MA = 8, MP = 8.5, LA = 91.6%, LD = 2.1%).
   An etiological role of infections was established in approximately 20% of pediatric[14] and 10% of adult[15] NORSE cases, and a comprehensive evaluation for infectious pathogens is therefore important to direct therapy. In addition to conventional methods, metagenomic next generation sequencing of cerebrospinal fluid (CSF) or brain tissue, with its capacity to assess for a wide spectrum of potential pathogens, will add power as it becomes more available in clinical practice.[16] Several mechanisms linking an infectious etiology with immune activation and SE have been proposed, including an imbalance between pro- and anti-inflammatory mediators causing activation of innate immune pathways in multiple cell types and resulting in an uncontrolled neuroinflammatory cascade.[17,18] A diminished toll-like receptor response in peripheral monocytes with decreased numbers of naïve and regulatory T cells has also been observed in children with FIRES. This may increase the susceptibility to viral infections and hinder pathogen eradication but also negatively affect a normal suppression of the autoimmune or innate immune response.[19] Thus, although it is unclear to what extent infections directly cause and perpetuate seizures in NORSE, the postinfectious inflammatory response is considered to be a major component of the pathogenic mechanisms and should be targeted during the treatment. However, most histopathological studies in NORSE and FIRES have demonstrated neuronal cell loss and reactive gliosis rather than inflammatory cellular infiltrates,[20–23] although mild T-cell-related inflammatory changes,[24] nonspecific reactivation of microglia,[20] and bilateral hippocampal inflammation[25] have also been described. Further research on the role of immunological mechanisms in cryptogenic NORSE is warranted to understand the pathophysiological processes to design new treatments and aid in the development of relevant cellular and animal models.
9. **Inflammatory activation in the CNS is likely to precede the development of seizures in NORSE/FIRES** (M = 8, MA = 7, MP = 8, LA = 79.2%, LD = 0%).
   Emerging studies support the hypothesis of neuroinflammation being involved in the pathogenesis of NORSE/FIRES rather than merely being a result of sustained seizure activity. Consistent with that, levels of CSF inflammatory cytokines in FIRES were found to be higher than those in afebrile SE.[26,27] Moreover, there was a reciprocal relation between neuroinflammation and recurrence of seizures[17] such that the release of cytokines in the CNS results in immune cell

infiltration and contributes to the hyperexcitable state with refractory seizures.[28,29] Although inflammatory mechanisms are likely to be involved in all NORSE cases, FIRES appears to have a different pattern, with lower inflammatory cell infiltration.[30] Therefore, it is possible that unknown autoantibodies are not the initial triggers of immune activation in cryptogenic NORSE/FIRES, and that the innate immune responses are more predominant than the adaptive immunity.[31]

10. **Inflammatory activation in the CNS likely contributes to the persistence of seizures in NORSE/FIRES** (M = 8, MA = 7.5, MP = 9, LA = 97.9%, LD = 0%).
A vicious cycle where inflammation promotes seizures which in turn upholds an inflammatory state, leading to network reorganization and refractory seizures, has been proposed.[17] Although the pathophysiology is not fully known, this is supported by several lines of animal experiments linking neuroinflammation and blood–brain barrier disruption to epilepsy refractoriness.[30,32] The involvement of immune mechanisms is further supported by reports of successful response to therapies targeting interleukin (IL)-1[24,33–35] or IL-6 receptor-mediated signaling.[36,37] Patients who responded to these therapies had seizures refractory to corticosteroids (CS), intravenous immunoglobulins (IVIG), and therapeutic plasma exchange (TPE), as well as second-line therapies, including rituximab. Following the acute phase, sustained seizures and epileptogenesis are likely supported by other pathophysiological mechanisms such as structural changes in the hippocampus and neocortex. However, agents targeting the IL-1-mediated signaling have also been used successfully in late stages of NORSE, which may support their disease-modifying activity.[38]
11. **Differences in initial clinical manifestations can provide clues for specific etiologies of NORSE/FIRES** (M = 8, MA = 7, MP = 8, LA = 77.1%, LD = 2.1%).
Although certain well-defined autoimmune encephalitis syndromes may manifest with characteristic clinical features (e.g., facial brachial seizures in LGI1 encephalitis or psychiatric symptoms in anti-N-methyl-D-aspartate [NMDA] receptor encephalitis),[5] such distinct symptoms are frequently absent in cryptogenic NORSE/FIRES. The latter syndrome is characterized by hyperacute onset and monosymptomatic course without neurobehavioral or memory alterations before the onset of SE.[39]
12. **Cryptogenic NORSE/FIRES cases usually have a higher seizure burden (i.e., seizure frequency × duration) than cases with an established etiology** (M = 7, MA = 7, MP = 7, LA = 70.1%, LD = 4.2%).
In a review of 130 NORSE cases, the duration of SE was longer in cryptogenic NORSE than in that with an established etiology.[13] Furthermore, NORSE cases that were highly resistant to antiseizure medications (ASMs) were more likely to be cryptogenic.[31,40] Future and more standardized investigations will be important for corroborating these findings.
13. **Patients with cryptogenic NORSE/FIRES are more likely to develop permanent cognitive disability than noncryptogenic cases** (M = 7, MA = 7, MP = 7, LA = 68. 8%, LD = 4. 2%).
More than 90% of patients with NORSE/FIRES will develop cognitive disabilities largely characterized by frontal lobe dysfunction with lack of motor and speech initiatives, perseveration, and poor attention.[22,41] Many patients with NORSE also manifest signs of temporal lobe dysfunction,[42] which may be particularly prominent in those who develop mesial temporal sclerosis in the course of SE.[43] Furthermore, recovering patients suffer from attention-deficit/hyperactivity disorder and other behavioral disturbances.[44] Seizures in patients with cryptogenic NORSE/FIRES respond poorly to immunotherapies; therefore, seizure-related irreversible brain damage has been suggested as causing more profound cognitive impairment in these patients compared to those with antibody-positive NORSE.[31,45] The higher seizure burden in cryptogenic NORSE may also lead to more severe inflammation, which may contribute to subsequent cognitive impairment. Although the expression of the inflammatory markers in the CSF and serum has not been directly compared in patients with cryptogenic and antibody-positive NORSE, there was no substantial infiltration of the brain with inflammatory cells and no complement activation in the latter group.[46]
14. **Patients with cryptogenic NORSE/FIRES are more likely to develop a more severe epilepsy following discharge from hospital as compared to noncryptogenic cases** (M = 7, MA = 7, MP = 7, LA = 70.8%, LD = 4.2%).
There are scarce data on the long-term epilepsy outcomes in patients with NORSE and FIRES. A large retrospective study suggests that cryptogenic and noncryptogenic cases do not differ in that regard, with >92% requiring long-term ASM.[13]

Smaller case series in both adults and children, and the authors' own experience, also suggest that drug-resistant epilepsy is an almost inevitable part of the long-term consequences of cryptogenic NORSE/FIRES, although this might in part result from various identification and publication biases. This contrasts with the observation that chronic epilepsy does not appear to be a necessary outcome after autoimmune or viral encephalitis, with the risk of postencephalitis epilepsy varying according to etiology and being potentially mitigated by early treatment.[47–49]

3.4 | Workup and diagnosis of NORSE/FIRES

Published data indicate that more than half of adult and pediatric patients with NORSE/FIRES do not have an established etiology after the comprehensive diagnostic workup, thereby representing cryptogenic NORSE.[10,13,14,30] In our expert group, the ability to confirm etiology of NORSE/FIRES was seen differently by adult and pediatric clinicians. Among pediatric providers, 69.2% stated that fewer than one quarter of their patients are likely to receive an established etiology. In contrast, only 22.7% of adult providers perceived establishment of etiological diagnosis as so rare ($p = .001$, chi-squared test). This difference in perceptions between the clinicians from two age groups was also reflected concerning etiologies, where 100% of adult providers perceived primary autoimmune causes as the most commonly established etiology of NORSE/FIRES compared to 61.5% of pediatric providers. Among the latter, paraneoplastic autoimmune and infectious etiologies were perceived as the most commonly established etiologies by 11.5% and 26.9% of respondents, respectively. Among adult providers, 72.8% of respondents stated that the majority of NORSE/FIRES patients could be identified within 48 h. The proportion of pediatric panel members who agreed with this statement was lower at 50%.

15. **It is appropriate to perform the same investigations in NORSE cases regardless of whether they also fulfill FIRES criteria** (M = 8, MA = 8, MP = 8, LA = 89.6%, LD = 0%).
    Fever that is detected in a patient with FIRES makes infectious investigations obvious. Similar to that, a young age of patients will likely prompt the clinician to search for metabolic and genetic testing more often than in older age. Although all medical care needs to be tailored to the individual patient, a comprehensive standardized diagnostic workup was recommended to minimize risk of missing essential data in critically ill patients who may benefit from early targeted interventions including immune therapies.
16. **Early testing for autoimmune antibodies is of great importance** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).
    Although autoimmune encephalitis might be a rare cause of NORSE/FIRES in children, distinguishing cases secondary to autoimmune encephalitis from cryptogenic NORSE is important, as it will aid in guiding the treatment and establishing the prognosis.[31] Cryptogenic cases possibly respond less robustly to the first-line immunotherapies compared to cases associated with autoimmune antibodies; thus, an early focus on the second-line therapies for SE may be more appropriate for the patients in the former category.[30] In a recent systematic review of literature on etiology of NORSE, diagnostic evaluation for paraneoplastic and autoimmune antibodies was performed in only 60.9% of all patients included in the published studies.[7] Furthermore, in a systematic review of data in pediatric FIRES, antibody panels and CSF cytokine measurements were obtained in only 21.4% of patients.[11] Although this likely reflects that the diagnostic yield of antibody testing in children is perceived as low, other factors, such as variable familiarity with NORSE, could play a role. For example, in a survey among neurointensivists in the United States, 25% of respondents stated they would not initiate an autoimmune workup if there were no concerning features in patients' history or physical examination. Moreover, the majority of clinicians preferred not to test for antineuronal antibodies during the initial evaluation for NORSE.[9] New emerging etiologies of NORSE associated with neuronal and glial autoantibodies have been identified, including autoimmune encephalopathy with antithyroid antibodies[50] and myelin oligodendrocyte glycoprotein antibody-associated disease.[14]
17. **Having access to rapid autoimmune antibody analysis is important, as results will affect management decisions** (M = 9, MA = 9, MP = 9, LA = 93.8%, LD = 0%).
    Given that treatment of NORSE will differ depending on autoantibody status, rapid laboratory analysis of serum and CSF specimens is of great importance. However, in clinical reality the results are frequently not available in the early stages of SE. It was therefore emphasized by the panel that the decision to initiate immunotherapy should be made on clinical suspicion, if antibody

results are not immediately available. A clinical score (c-NORSE) was recently developed to predict likelihood of cryptogenic NORSE at the initial presentation of SE.[39] This score predicts the probability of a negative antibody result based on the presence of prodromal high fever of unknown origin before the onset of SE, absence of prodromal behavioral or memory alterations before SE onset, absence of sustained orofacial–limb dyskinesias despite a profoundly decreased level of consciousness, and symmetric brain magnetic resonance imaging (MRI) abnormalities.

18. **The value of evaluating inborn errors of metabolism (including mitochondrial disease) is unclear in teenagers and adults** (M = 7, MA = 7, MP = 7, LA = 62.5%, LD = 6.3%).

Mitochondrial disorders are uncommon causes of NORSE, but mutations in genes encoding the presynaptic dynamin 1-like protein (*DNM1L*) and mitochondrial DNA polymerase gamma (*POLG1*) have been described in a few patients.[14,51–53] Therefore, relevant evaluation may still be warranted in cryptogenic cases in adolescents and adults, as penetrance in mitochondrial disorders is variable and some patients may not manifest seizures until adulthood.[54] However, there was no consensus on the panel concerning the screening for mitochondrial disorders in adult patients without a history suggestive of such underlying disease. It is important to acknowledge that clinical diagnosis of mitochondrial disorder may be difficult in the settings of normal serum and CSF lactate levels and unrevealing muscle biopsy as seen in *DNM1L* variants.[51,55]

19. **In addition to regular testing in SE (as per local guidelines) the following SERUM investigations are needed during the initial 48 h of admission in most or all patients with NORSE/FIRES:**
    a. **Comprehensive rheumatologic evaluation** (M = 8, MA = 8, MP = 8, LA = 100%, LD = 0%);
    b. **Comprehensive infectious evaluation including cultures, and viral and bacterial serology relevant in the geographical region and season** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%);
    c. **Evaluation for inborn errors of metabolism in young children** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%);
    d. **Autoimmune and onconeural antibody panels** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%);
    e. **Extra blood samples for storage for future analysis (e.g., cytokine and genetic analyses)** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).

Because NORSE is a severe life-threatening disease, an extensive and complete workup is warranted for all patients. This includes a comprehensive rheumatological evaluation, which should be undertaken especially if other symptoms and signs of autoimmune disorder (e.g., cytopenia, proteinuria, or peripheral organ dysfunction) are presents at onset of SE. Given that sporadic autoimmune and paraneoplastic encephalitis represents the single most frequent etiological category in noncryptogenic NORSE/FIRES in adults[13] and also occurs in children,[10] antibodies should be actively looked for, in both serum and CSF. Widespread and less common CNS infections are also a possible cause of NORSE/FIRES that will require specific treatment. They should thus be actively looked for according to local, seasonal, and geographical trends, and accounting for individual exposure, as recommended by guidelines from infectious diseases societies.

20. **In addition to regular testing in SE (as per local guidelines) the following CSF investigations are needed during the initial 48 h of admission in most or all patients with NORSE/FIRES:**
    a. **Comprehensive infectious evaluation relevant in the geographical region and season** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%);
    b. **Evaluation for inborn errors of metabolism in young children (e.g., lactate, pyruvate, amino acids)** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%);
    c. **Autoimmune antibody panels** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%);
    d. **Extra CSF samples for storage for future analysis (e.g., cytokine analyses)** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).

The severity of disease in NORSE/FIRES warrants initial CSF investigations for early and accurate diagnosis. In young children, CSF samples may be indispensable for diagnosis of inborn errors of metabolism. As for serum samples, CNS infections should be actively looked for and individualized for the patient, and such pursuit may be expanded to metagenomics analysis. The value of repeated samples to monitor disease progression or response to treatment is likely to increase

with a developing understanding of biomarkers in NORSE/FIRES. Obtaining additional volume of CSF during lumbar puncture is important and can allow later analyses of stable proteins such as antibodies.

21. **Brain MRI should be performed during the initial 48 h of admission in most or all patients with NORSE/FIRES** (M = 9, MA = 9, MP = 9, LA = 97.9%, LD = 0%).
    A brain MRI with and without contrast should be performed in the early acute phase of disease to rule out other etiologies of SE such as structural malformations, stroke, metabolic disorders, and neoplasms. Additional magnetic resonance angiography and magnetic resonance venography are options that increase the sensitivity for vascular etiologies. It should be noted that brain imaging findings may be normal in the initial phase of the disease. In a systematic review of 131 pediatric FIRES patients, 61% had a normal initial MRI, whereas temporal lobe signal abnormalities were seen in 25%. Other abnormal findings include abnormalities in the temporal lobes, basal ganglia, thalami, or brainstem and diffuse cerebral edema.[56] A variety of radiological findings on brain MRI has also been demonstrated in adult NORSE patients, including claustrum involvement,[57] mesial temporal involvement,[58] and involvement of the limbic area.[13]
22. **Gadolinium contrast enhancement should be included with MRI evaluation** (M = 9, MA = 9, MP = 9, LA = 91.7%, LD = 2.1%).
    Gadolinium contrast enhancement indicates blood–brain barrier disruption that may be caused by inflammation and could be in part responsible for seizure recurrence.[59,60] It should be noted, however, that gadolinium enhancement might also be induced by focally increased perfusion as a response to hypermetabolism in RSE,[61] and it should be interpreted with caution.
23. **Brain Spectroscopy (magnetic resonance spectroscopy [MRS]) can be of diagnostic use in NORSE/FIRES cases where inborn errors of metabolism (including mitochondrial disease) are suspected** (M = 7, MA = 7, MP = 7.5, LA = 64.6%, LD = 2.1%).
    MRS may be of importance for excluding inborn errors of metabolism, but its use may be hindered by logistical problems, as it is not readily available at all health care facilities. Also, results may be confounded by ongoing SE. Results therefore need to be interpreted with caution and in an adequate clinical context.
24. **Whole body positron emission tomography (PET) can be useful in NORSE/FIRES cases where a paraneoplastic etiology is suspected** (M = 8, MA = 8.5, MP = 7.5, LA = 85.4%, LD = =2.1%).
    Cases of paraneoplastic autoimmune etiology are very rare in children, and use of whole body PET is more often employed by adult physicians. This modality is thus likely to be of more importance in the adult age group. It should also be noted that availability of inpatient PET scanning may vary. As emerging data have demonstrated specific brain PET patterns in some NORSE etiologies (e.g. autoimmune encephalitis),[62] the indications for PET, in particular in the postacute phase, may increase in the future.
25. **Malignancy screening (computed tomography [CT] of chest, pelvis, and abdomen) should be performed in a majority of patients with cryptogenic NORSE/FIRES** (M = 9, MA = 9, MP = 7.5, LA = 77.1%, LD = 4.2%).
    Malignancy screening should be considered in the diagnostic workup in all patients with cryptogenic NORSE but is of particular importance in adults, as the prevalence of paraneoplastic etiologies is substantially lower in children.[7]
26. **Malignancy screening should include whole body PET when other testing, including CT of chest, pelvis, and abdomen, remains negative** (M = 8, MA = 8, MP = 7, LA = 89.2%, LD = 2.7%).
    In a recent review on NORSE that included 197 publications, whole body PET was performed in 4.6% of patients.[7] Although this imaging modality may not be available at all institutions, an early use of whole body PET may obviate the need for serial CT imaging of the chest, abdomen, and pelvis. This is in line with current guidelines for paraneoplastic disorders where PET increases sensitivity for several, albeit not all, conditions.[63]
27. **Malignancy screening should include testicular/ovarian ultrasound** (M = 9, MA = 9, MP = 9, LA = 95.8%, LD = 0%).
    The correlation between anti-NMDA receptor encephalitis and ovarian teratomas is well established.[64] Therefore, gonadal imaging is warranted to exclude tumors in adult and pediatric patients with anti-NMDA receptor antibodies, especially in girls and women. However, absence of these antibodies or other classical paraneoplastic antibodies does not exclude a paraneoplastic process. For example, a case of limbic encephalitis and NORSE in a patient with recurrent neuroendocrine testicular tumor and unrevealing CSF and serum antibody

profiles has recently been reported.[65] Therefore, pelvic ultrasound or MRI and scrotal ultrasound serve as important adjunctive imaging modalities for adult patients with cryptogenic NORSE.

28. **Genetic testing can be helpful in the diagnostic evaluation of cryptogenic NORSE/FIRES** (M = 7.5, MA = 7, MP = 8, LA = 77.1%, LD = 2.1%).
Several gene mutations have been identified in NORSE/FIRES, including genes encoding neuronal channels, such as *SCN1A*, *SCN2A*, *SCN10A*, *KCNT1*, and *CACNA1A*.[14,66–69] Of particular interest, a polymorphism in the *IL1RN* gene has been described in FIRES patients.[70] As this gene encodes the IL-1 receptor antagonist (IL-1RA), which inhibits IL-1α and IL-1β-mediated signaling, this deficiency will lead to unopposed aberrant inflammatory responses, which is in line with the proposed inflammatory mechanisms of seizures in NORSE. Other gene variants have been suggested, but the clinical significance of these findings remains uncertain. Whole exome sequencing (WES) in 50 children with FIRES found no pathogenic variants in established genes for epilepsies or neurodevelopmental disorders and failed to identify prominent human leukocyte antigen alleles.[71] However, with the rapid development and availability of WES, the opportunities to obtain genetic testing and awareness of its importance for clinical care are continuing to grow. From the clinical perspective, genetic testing may be of importance to understand the etiology of NORSE/FIRES, differentiate patients with noncryptogenic SE, and determine prognosis. Although genetic testing rarely affects the management of patients in acute phase of disease, increased clinical availability of rapid turnaround genetic analyses may provide the genetic diagnosis within weeks.[51]
29. **Genetic testing should be performed in the majority of cases of cryptogenic NORSE/FIRES** (M = 8, MA = 7, MP = 9, LA = 68.8%, LD = 4.2%).
In a recent review of the literature on NORSE that included 197 reports, genetic testing was performed in only 18.3% of patients.[7] Among panel members, the yield of testing was perceived as fairly low among those working with adult patients, but considered important by pediatric physicians. As discussed above, this knowledge is unlikely to affect the initial management of SE but is of great importance for understanding the safety of ASMs in certain genetic syndromes and delineating the prognosis for seizure recurrence. A combination approach starting with a customized neuroinflammation panel[72] combined with mitochondrial gene testing, which if negative can be expanded to WES, is an alternative.
30. **Genetic testing should be considered early in young children** (M = 9, MA = 8, MP = 9, LA = 93.8%, LD = 0%).
Most metabolic and genetic disorders will manifest during infancy or childhood. Therefore, the importance of searching for such etiologies is higher in younger patients; however, as discussed above, late onset genetic or metabolic disease may be found also in adults. We therefore recommend that, in addition to all cases being interpreted individually, special vigilance is taken in cases younger than 4 years.
31. **Continuous electroencephalographic (EEG) monitoring is needed to manage seizures in NORSE/FIRES** (M = 9, MA = 9, MP = 9, LA = 95.8%, LD = 2.1%).
The use of continuous EEG monitoring (cEEG) is recommended by most professional societies for the management of all patients with RSE,[73–76] which allows expansion of the application of this modality to NORSE/FIRES. It is important to recognize that most seizures that occur in critically ill patients, once continuous sedation and neuromuscular blockade have been initiated, lack any obvious clinical manifestations.[77,78] Because electrographic seizure burden has been repeatedly linked to adverse neurological outcomes[79,80] and cEEG is the only available method to accurately identify electrographic seizures, it represents the only approach to guide the course of treatment for SE.
32. **If etiology remains unclear and if MRI indicates a targetable lesion, a brain biopsy should be considered** (M = 8, MA = 8, MP = 8, LA = 85.4%, LD = 0%).
Obtaining tissue samples from the brain may ultimately be the only way to rule out important etiologies of SE such as small vessel angiitis or hemophagocytic lymphohistiocytosis or to perform metagenomic analyses for potential pathogens. However, there is no evidence to support routine use of brain biopsy in evaluation for NORSE. In a recent review of literature on NORSE that included 197 publications, a brain biopsy was performed in only 7.6% of NORSE patients.[7] Furthermore, in a series of 22 children with FIRES, only 31.2% of patients had biopsies that revealed nonspecific findings such as gliosis without inflammation.[21] Other rare findings in brain specimens of patients with NORSE included angiitis and neutrophilic leucocytes, T cells, and microglial infiltration with severe spongiosis.[57,81] In a cohort from 2001, one

case of human herpesvirus-6 was detected on brain biopsy in addition to gliosis, necrosis, and leptomeningeal inflammation.[82]

33. **A brain biopsy should not be performed unless MRI indicates a targetable lesion** (M = 8, MA = 7, MP = 8, LA = 79.2%, LD = 0%).
The diagnostic yield of biopsies in the absence of targetable lesions was considered low by the panel. There are case reports of biopsies with diagnostic value in a few patients with NORSE who either had multifocal lesions on the brain imaging or had unrevealing radiological workup. Following a biopsy, multifocal scattered small lesions in the white matter were diagnosed as small vessel vasculitis.[83] In other reports, meningoencephalitis was found in biopsy[81] or brain autopsy specimens of NORSE patients who succumbed to multiorgan failure and for whom the development of CNS inflammation later in the disease could be attributed to other factors.[84] Ultimately, the decision will depend on the clinical scenario and the associated risks.

34. **CSF cytokines may be useful, as they are potential biomarkers for disease progression or response to treatment** (M = 8, MA = 7.5, MP = 8, LA = 79.2%, LD = 2.1%).
Several cytokines involved in the innate immune response are increased in CSF in FIRES. Of particular interest has been the proinflammatory alteration in CSF cytokine profile, suggesting that these mediators along with the respective signaling pathways could be involved in the pathogenesis of SE and serve as targets for therapies.[33,81,85] The immunological pattern, with high levels of IL-6, C-X-C motif chemokine ligand 10, and IL-8 in both serum and CSF, may help to differentiate FIRES from other forms of encephalitis.[26,27] A larger increase of IL-6 in CSF compared to serum has also been demonstrated, suggesting a CNS-specific response.[27,85] Anti-inflammatory cytokines IL-1RA and IL-10 have been demonstrated to be increased in some patients with NORSE/FIRES.[26,33,81,85,86] In NORSE, changes in cytokines involved in the responses in the adaptive immune system have also been reported, including IL-6, tumor necrosis factor α, IL-2, IL-12, IL-4, and IL-10.[87] Such immune activation was not specific to NORSE or FIRES, as higher levels of IL-6, IL-8, and neopterin have also been seen in febrile SE as compared to noninflammatory neurologic conditions or chronic epilepsy. However, FIRES patients had a different cytokine profile than those with febrile or afebrile SE, suggesting distinct pathophysiological mechanisms involved in the development of seizures in these conditions.[26] This also indicates that there may be a bidirectional relationship between the cytokine alterations and tendency to have recurrent seizures in SE.
There are no consistent quantitative and qualitative data on the measurements of cytokines in NORSE/FIRES at the present time, although certain patterns are emerging.[30] Overall, the role of specific cytokines and chemokines in initiating and sustaining seizures in SE remains unclear. Likewise, the prognostic implications of cytokine alterations in NORSE/FIRES remain to be elucidated, although evidence from studies in other refractory forms of SE suggests that certain proinflammatory profiles may be associated with more severe outcomes.[88]

35. **CSF cytokines are potentially useful for guiding treatment choice** (M = 7, MA = 7, MP = 8, LA = 66.7%, LD = 4.2%).
Clinically available diagnostic panels of cytokines in CSF and serum are currently being developed and may aid in the initial treatment decisions in NORSE/FIRES in the future.[30] However, the utility of cytokines in evaluating the response to treatment of SE has not been well studied. The reduction of refractory seizures following the administration of IL-1R antagonists such as anakinra,[33] monoclonal IL-1 blockade with canakinumab,[89] and IL-6 antagonist tocilizumab[37] in NORSE/FIRES has been reported, but only one study documented a reduction in IL-8 and IL-6 levels in CSF and serum.[33] Consistent with this, the CSF and serum levels of endogenous IL-1R antagonist were shown to increase following the administration of anakinra, also resulting in seizure termination and long-term neuroprotection.[86] Although this represents limited evidence, the data indicate that serial measurements of CSF cytokines may be useful to guide treatment of NORSE. Further research is warranted to link the patients' cytokine profiles with their specific electroclinical patterns.

36. **Repeated MRI has an important role in monitoring disease progression** (M = 9, MA = 9, MP = 8, LA = 87.5%, LD = 0%).
There was a broad consensus on the panel that serial MRI is recommended, although the clinical and prognostic value of this method for delineating disease progression is unclear. Brain atrophy can be caused by severe seizures or immunological treatments, but the degree of atrophy does not affect treatment decisions. Instead, serial MRI studies may be important to ensure that no other disease processes are evolving.

3.5 | Treatment of NORSE/FIRES in the acute phase

37. **Management of all patients with NORSE/FIRES should be carried out in a tertiary center with expertise in NORSE/FIRES, with available multidisciplinary expertise in epileptology, rheumatology, and immunology, and intensive care** (M = 9, MA = 9, MP = 9, LA = 95.8%, LD = 0%).
    Depending on the clinical setting, patients with RSE are usually managed by neurologists with expertise in epilepsy or neurocritical care or by intensive care physicians from other subspecialties. The management of patients with NORSE/FIRES extends beyond the management of RSE, as it entails additional workup for the diagnosis of rare autoimmune disorders and requires familiarity with use of immune therapies. The latter may be beyond the scope of practice for most epileptologists and (neuro)intensive care physicians. The warranted combination of expertise is rarely found beyond large tertiary centers. If practically feasible, patient transfer to such tertiary centers should be considered.
38. **In addition, management of adults with NORSE/FIRES should be carried out by neurointensivists** (M = 7.5, MA = 7.5, MP = 7.5, LA = 62.5%, LD = 4.2%).
    In addition to the specific treatment of the underlying autoimmune or inflammatory conditions, the management of RSE requires a solid knowledge of available ASMs, anesthetic drugs, and life-support therapies, as well as aggressive screening for complications of these treatments and those of prolonged state of unconsciousness. Depending on the prevailing model of care, this is likely best achieved by neurointensive care physicians (if such a subspecialty is recognized in one's country) or by a multidisciplinary team of intensive care physicians and neurologists with expertise in RSE. There is some evidence that both models seem to provide the same level of care.[90]
39. **The acute treatment of seizures with ASMs in NORSE/FIRES should be similar to acute treatment of seizures in other conditions** (M = 8, MA = 8, MP = 8, LA = 85.4%, LD = 4.2%).
    The efficacy of ASMs in NORSE/FIRES is generally low, and no concrete evidence exists to recommend a preferential use of specific drugs. Based on their mechanism of action and having an immunological effect, sodium channel blockers have been suggested to be more effective than midazolam, high-dose phenobarbital, or cannabidiol in several cases and case series.[11,91,92] Given the severity of seizures in NORSE, ASMs that allow instant loading and rapid achievement of therapeutic concentrations are preferred. The recommendation of the panel is that in the early stages of SE (i.e., during the initial 24–48 h), ASM treatment should follow the established guidelines for SE. When a diagnosis of NORSE/FIRES is established, an aggressive escalation of ASM regimens, initiation of ketogenic diet (KD), and immunotherapy should be instituted as soon as possible.
40. **Treatment of seizures in NORSE/FIRES with anesthetic drugs should follow the same principles as treatment of SE in other conditions during the initial 48 h** (M = 8, MA = 8, MP = 8, LA = 87.5%, LD = 4.3%).
    In line with the discussion above, the use of anesthetic drugs during the initial 24–48 h should follow the established guidelines. Longer exposure to these agents has been associated with higher mortality and increased risk of complications,[93–95] but it is difficult to discern whether this reflects a causal relationship or merely a need for prolonged treatment in more severe cases. However, prolonged anesthesia and burst-suppression on EEG has been associated with worse seizure and neuropsychological outcomes in pediatric FIRES,[96,97] and concern has been raised also for adults.[94] In adult RSE patients, continuous midazolam administration was shown to be as efficacious as thiopental infusion and with fewer adverse events.[78] The recommendation of this panel was to follow established guidelines for anesthetic drug use during the initial phase of SE and prioritize initiation of KD or immunotherapy as soon as the diagnosis of NORSE/FIRES is made.
41. **First-line immunological treatment should be started during the first 72 h** (M = 9, MA = 8.5, MP = 9, LA = 95.8%, LD = 4.2%).
    Despite the lack of concrete evidence of its efficacy, there was a high level of agreement that first-line immunotherapy, which includes CS, IVIG, and TPE, should be initiated within the first 72 h of seizures. Of note, the majority of respondents also advocated starting these therapies as early as 48 h after onset of seizures or as soon as common infectious etiologies were ruled out. This differs from management approaches reported in a survey of neurocritical care practitioners in the United States, of whom 29% stated that they would not

consider IVIG and 24% would not use TPE in the course of treatment for NORSE.[9] Because NORSE patients who do not fulfill criteria for FIRES appear to have a higher burden of CNS inflammatory infiltrate[20,81] and their cytokine profiles are consistent with the concomitant involvement of the adaptive immune system,[26] it is expected that these patients will respond favorably to first-line immunotherapies such as CS and IVIG. Taken collectively, existing studies support the premise that delaying immunotherapy leads to worse outcomes in NORSE.

There were large differences in the views of the panel members on utilization of TPE as an alternative to CS as first-line immunotherapy. Some argued that the risks of eliminating the ASMs associated with TPE were not acceptable, considering the lack of evidence for its superior efficacy. Institution of TPE is associated with more frequent and severe infections than use of IVIG.[98,99] Other panelists advocated using TPE early in severe cases or as an alternative to IVIG in patients with severe SE, either in conjunction with CS or sequentially, to ensure a rapid effect. We therefore give no recommendation concerning TPE beyond that it should not delay initiation of treatments that are more likely to succeed (i.e., KD and immunotherapy).

42. **Steroids are the first-line immunological treatment in NORSE/FIRES** (M = 8, MA = 8, MP = 8, LA = 87.5%, LD = 2.1%).

    Although often ineffective in cryptogenic NORSE/FIRES,[4,31] CS should be initiated pending autoantibody panel report as soon as the most common viral, bacterial, and fungal infections have been ruled out. In pediatric FIRES cases, a correlation between CS use in the acute phase and good outcome has been reported.[11] Similarly, CS have among other first-line immunotherapy options been found to be beneficial for adults with NORSE.[58]

43. **If given, steroids should be administered in the form of methylprednisolone in a dose of 20–30 mg/kg per day (maximum = 1 g) for 3–5 days** (M = 9, MA = 8, MP = 9, LA = 93.8%, LD = 0%).

    This type and dose recommendation follows general treatment practice for CS treatment, but there is no evidence available specific to NORSE/FIRES. Some centers use dexamethasone, which penetrates the blood–brain barrier more easily, whereas others prefer high-dose methylprednisolone up to 2 g/day.

44. **Enteral steroids should not be used as an alternative to intravenous methylprednisolone** (M = 8, MA = 9, MP = 8, LA = 81.3%, LD = 6.3%).

    Due to lack of studies and the risk of poor absorption in comatose patients with decreased gastrointestinal motility, enteral administration of CS is generally not recommended. However, if intravenous administration is not possible, enteral preparations could be given.

45. **IVIG can be given as an alternative to steroids as first-line immunological treatment** (M = 7, MA = 7, MP = 7, LA = 65.6%, LD = 4.2%).

    Although using IVIG alone as first-line immunological treatment was considered acceptable by the panel, most members indicated that they prefer to use IVIG as a complement to CS instead of as an alternative. IVIG may have a role if infections (primarily bacterial) cannot be safely ruled out. Importantly, diagnostic sampling of autoantibodies in serum and CSF needs to be performed prior to initiation of IVIG.

46. **If given, the preferred dose regimen for a course of IVIG is (a total of) 2 g/kg over 2–5 days** (M = 9, MA = 8.5, MP = 9, LA = 95.8%, LD = 2.1%).

    Similar to the statement regarding the use of CS, current recommendations for IVIG administration follow the established practices. However, there is no evidence to support a specific dosing or frequency regimen for this agent in NORSE/FIRES. It should be noted that there is evidence to support a single or repeated doses of IVIG (2 mg/kg) in Kawasaki disease.[100]

47. **IVIGs and steroids can be administered simultaneously** (M = 8, MA = 8, MP = 9, LA = 89.6%, LD = 2.1%).

    Most panelists use the approach of a simultaneous administration of IVIG and CS during the initial round of immunotherapy for early initiation of immunological treatment, but a sequential approach may also be used. Diagnostic workup including serum, CSF, and autoantibodies should be completed prior to the initiation of treatment.

48. **KD should be initiated in the first week** (M = 8, MA = 6.5, MP = 9, LA = 77.1%, LD = 4.2%).

    The use of KD as an adjunctive treatment in NORSE/FIRES was initially explored in pediatric patients for whom an attenuation of seizures was seen within 4 days of ketonuria.[47,101] Similar encouraging results were demonstrated in super-refractory SE (SRSE) in adults, including those with NORSE, where nine of 10 patients achieved

ketosis, with subsequent cessation of SE in all patients within a median of 3 days.[102] There were differences in opinion between adult and pediatric clinicians on the panel with respect to how quickly the KD should be initiated. Although consensus for this statement was achieved, there was a gap between the median consensus score of 6.5 in the adult group and 9 in the pediatric group. A major impeding factor for the initiation of KD was thought to be its limited availability as well as lack of experience in its administration. Both concerns were primarily voiced by the panelists from the adult group. Of note, a technical concern was that the use of CS during the initial 72 h may hinder the establishment of ketosis. Among panelists, 95.8% (46/48) responded that they were able to start KD in the intensive care units at their institutions. Access to KD expertise in adult neurology is likely to increase in the coming years, as an increasing number of patients with genetic epilepsies receiving KD are able to reach adult age.

49. **If not already given, KD should be considered in prolonged and severe cases** (M = 9, MA = 8, MP = 9, LA = 95.8%, LD = 0%).
    A very high level of consensus for this statement with no disagreements underlined the perceived importance of KD among panelists. This is in line with results from a meta-analysis of pediatric FIRES cases, where KD in the acute phase of SE was the only treatment that was clearly associated with favorable outcome.[11,22] Several panelists have emphasized the importance of starting KD very early in the course of NORSE.
50. **If enteric KD is not possible, KD should be started by parenteral application, assuming local availability and expertise** (M = 8, MA = 7, MP = 9, LA = 79.2%, LD = 0%).
    A recommendation was discussed for parenteral delivery of KD in cases where enteric treatment is not feasible in critically ill patients. The panel agreed that although such route of administration is appealing, many centers lack such practical experience, especially in adult epilepsy centers. We therefore added that local availability and expertise should be prerequisites for this recommendation. We believe that this consensus will allow increasing availability and enhancing experience with KD delivered via both enteral and parenteral routes.
51. **Current evidence does not clearly support the usefulness of cannabidiol in the acute phase of NORSE/FIRES** (M = 9, MA = 8, MP = 8, LA = 72.9%, LD = 4.2%).
    The available evidence for use of cannabidiol was not perceived to be sufficient to recommend its use in NORSE/FIRES. In children with FIRES, cannabidiol is one of few treatments for which a favorable effect on seizures was documented in a case series.[103] Similar to the experience with other acute interventions for SE, discerning the specific contribution of cannabidiol from that of other therapies is challenging in clinical practice. A special caution should be given to the drug–drug interactions with cannabidiol.
52. **Cannabidiol should not be used as a first-line treatment** (M = 8.5, MA = 8, MP = 9, LA = 81.2%, LD = 0%).
    Consistent with the discussion in the previous statement, there was a broad consensus that evidence did not support the use of cannabidiol as first-line treatment, as it may delay delivery of other treatments (i.e., immunotherapy and KD) that are likely to be of importance for the success of seizure control in NORSE.
53. **Current evidence does not clearly support the usefulness of hypothermia in the acute phase of NORSE/FIRES** (M = 8, MA = 8.5, MP = 7.5, LA = 87.5%, LD = 0%).
    The available evidence for effects of hypothermia on seizures was not perceived as sufficient to recommend its use in NORSE/FIRES. However, there are case series describing favorable effects of hypothermia in pediatric FIRES. In two children, moderate therapeutic hypothermia at 33°C resulted in a fast and sustained control of RSE.[104] Furthermore, in a retrospective case series, 11 children with RSE treated with hypothermia had a decrease of seizure duration and showed improved long-term outcomes compared to those without hypothermia. However, the specific effect of hypothermia on seizures in FIRES was difficult to ascertain; therefore, any definitive conclusions are difficult to draw.[105] A review of case series of SRSE in adults and children found hypothermia to be effective in controlling seizures in 82% of patients irrespective of their etiology. This was, however, followed by recurrence of seizures in 49% of cases after rewarming.[106]
54. **Hypothermia should not be used as a first-line treatment** (M = 9, MA = 9, MP = 8.5, LA = 79.2%, LD = 4.2%).
    There was a strong consensus that evidence does not support the use of therapeutic hypothermia as first-line treatment for NORSE/FIRES, as it may delay other treatments (i.e., immunotherapy and KD) that are likely to be of greater importance.

55. **In noninfectious NORSE/FIRES with inadequate response to first-line immunological treatment, second-line immunological treatment should be started within 7 days of seizure onset** (M = 8, MA = 8, MP = 8, LA = 81.2%, LD = 0%).
Escalation to second-line immunotherapy in patients who do not respond to first-line treatment is an important cornerstone in immunological treatment in general. Likewise, earlier aggressive treatment is generally associated with better outcomes, but there are insufficient data to provide a specific timeline for escalation of such therapy. Whereas some panelists advocated a "the earlier the better" approach, others expressed concern that precipitous escalation may lead to inability to fully assess response to the first-line treatment and result in overmedication. Interestingly, in many published reports where immunotherapy failed, only first-line treatments were tried, without escalation to second-line treatment,[22,107] possibly due to concerns of potential side effects. Our consensus statement is that escalation to second-line immunological treatment should be started within 7 days of seizure onset, provided that first-line treatment was initiated without delays.
56. **Second-line immunological treatment has the potential to improve outcome even when initiated late (several weeks) after seizure onset** (M = 7, MA = 7, MP = 7, LA = 70.8%, LD = 2.1%).
There is no evidence at the present time to support this statement beyond anecdotal experience, which may represent the natural history of disease rather than a treatment effect. However, given that adequate immunotherapy with appropriate escalation is associated with improved outcomes in other forms of neuroinflammatory disease, there is reason to believe that this may also be the case in NORSE/FIRES. Furthermore, the panel argued that potential beneficial effects of this approach would outweigh potential risks, including adverse events associated with administration of these agents. However, as mentioned previously, earlier initiation of any immunological treatment is likely to be more beneficial than delaying the therapy.
57. **Current evidence does not clearly support use of any specific second-line immunological treatment over others** (M = 8, MA = 8, MP = 7, LA = 75.0%, LD = 12.5%).
In the first Delphi round, the panel was asked to indicate in which order they would consider various second-line immunotherapy options in acute NORSE/FIRES. The answers clearly differed between adult practitioners, who indicated rituximab as their first choice (59%) followed by the IL-6 antagonist tocilizumab (32%), and pediatric clinicians, who stated that IL-1RAs (96%) should be followed by IL-6 antagonists (73%). These differences clearly reflect the distinct patterns of etiology of NORSE in adults and children, with antibody-mediated encephalitis being more prevalent in the former group.[10,13] On the other hand, such differences in opinions could also reflect anecdotal evidence and a selection bias, with preferences merely following established practices, with IL-6 antagonists being administered more often in adults and IL-1RAs more often in children. Of note, the data to support the use of any second-line therapy for NORSE are insufficient and were largely derived from case reports and small case series.
58. **Second-line immunological treatment should be based on suspected etiology** (M = 8, MA = 8, MP = 7, LA = 79.2%, LD = 4.2%).
Following first-line treatment with CS or IVIG, a suspected or confirmed etiology may be used to guide therapeutic considerations, as indicated in the following statements.
59. **If a pathogenic antibody is identified or highly suspected, rituximab treatment should be initiated** (M = 8, MA = 8, MP = 8, LA = 83.3%, LD = 0%).
Following first-line immunotherapy, patients in whom pathogenic antibodies are identified or suspected should be treated with rituximab if escalation is warranted or following established antibody-specific autoimmune encephalitis protocols.
60. **In cryptogenic NORSE/FIRES without clinical features of autoimmune encephalitis, IL-1RAs or IL-6 antagonists should be initiated** (M = 8, MA = 7, MP = 8, LA = 81.2%, LD = 2.1%).
In both children and adults, treatment with anticytokine therapies, such as the IL-1RA anakinra[24,33,34] and the IL-6 antagonist tocilizumab,[36,37] has been demonstrated to be effective in seizures refractory to first-line treatment and second-line therapies like rituximab. Thus, in patients who remain etiologically unexplained and who failed to respond to the first-line immunotherapy, anticytokine agents should be considered. There were no comparative trials to recommend a preferential use of either agent. Risk–benefit discussions of these two agents should be conducted by a clinician comfortable with their usage.

3.6 | Treatment in the postacute phase (following the resolution of epileptic seizures)

61. **Current evidence does not clearly support efficacy of any specific antiseizure medication in the postacute phase of NORSE/FIRES** (M = 8, MA = 8, MP = 8, LA = 85.4%, LD = 12.5%).
The postacute and chronic phases of NORSE/FIRES are frequently characterized by drug-resistant epilepsy with clustering of seizures and moderate to severe cognitive impairment.[41,97] To manage these refractory seizures, polypharmacy is nearly universal, and it is therefore challenging to establish the efficacy of specific ASMs in improving seizure or cognitive outcomes. Among adult clinicians on the panel, 54.5% responded that they did not feel that any ASM could be preferentially recommended in the postacute phase of NORSE. Among pediatric clinicians, this opinion was shared by only 26.9% of panelists. Of those who answered that specific ASMs should be recommended, the most frequently listed medications by the adult clinicians were clobazam (27.3%), lacosamide (22.7%), and phenobarbital (22.7%). These were followed by levetiracetam, perampanel, and topiramate. In contrast, the most frequently selected medications by the pediatric clinicians were phenobarbital (46.2%) and clobazam (23.1%), followed by topiramate, felbamate, and perampanel. Of note, lacosamide was recommended by only 7.8% of pediatric clinicians. It is likely that the choice of ASMs in the postacute period will depend upon the choice of agents used during the initial treatment of seizures in NORSE.
62. **If effective in the acute phase, KD should be continued in the postacute phase** (M = 8, MA = 7, MP = 8.5, LA = 87.5%, LD = 0%).
The association between the use of KD in the postacute phase and positive disease outcomes has been suggested in a recent meta-analysis of pediatric FIRES cases, where univariate analysis was statistically significant, but where it did not remain as an independent determinant according to multivariate logistic regression.[11] Subject to individual considerations and patient compliance, we therefore recommend that KD is considered and continued also in the postacute phase of NORSE/FIRES. Although a sustained adherence to KD for a prolonged period of time may be challenging, the diet should still be recommended in the postacute phase of NORSE for patients who have benefited from it during the early stage of disease.
63. **Duration of follow-up KD in the postacute phase should be at least 3 months** (M = 8, MA = 7, MP = 8, LA = 75.0%, LD = 0%).
As noted in the discussion for the previous statement, there are no studies to support a recommendation for a particular duration of KD, but if it is well tolerated, a period of 3 months was considered appropriate by the panel.
64. **If effective in the acute phase, follow-up treatment during the postacute phase should include immunomodulation** (M = 8, MA = 8, MP = 8, LA = 87.5%, LD = 0%).
If immunomodulation was initiated and perceived as potentially effective during the acute phase of NORSE/FIRES, it is reasonable to continue treatment in the postacute phase. This may include a slowly tapering course of CS or anticytokine agents. The latter would be particularly important in cases where cytokine increase was documented in the acute phase of disease.
65. **Duration of follow-up immunomodulation in the postacute phase should be at least 3 months** (M = 8, MA = 8, MP = 8.5, LA = 81.2%, LD = 2.1%).
Although no studies exist on which to base a recommendation for duration of immunomodulation in NORSE/FIRES, a consensus was reached for a minimum of 3 months of therapy. Some panelists advocated for only 4–6 weeks.
66. **If symptoms significantly worsen in the postacute phase upon immunotherapy withdrawal, the previous immunological treatment should be resumed** (M = 9, MA = 8, MP = 9, LA = 93.7%, LD = 0%).
There was a strong consensus for the statement on resumption of immunotherapy in case of symptom worsening upon withdrawal. The rationale for this was not based on any scientific evidence but was derived from the practical observations.
67. **IL-1 or IL-6 blockade may have a therapeutic role in a severe or recurring postacute epilepsy situation even if they were not previously tried in the acute phase** (M = 7, MA = 7, MP = 7, LA = 81.2%, LD = 0%).
Inhibition of IL-1 receptor-mediated signaling with anakinra has been reported to reduce the relapse risk of highly refractory and recurrent seizures at 1.5 years after FIRES onset.[24] This supports the hypothesis that ongoing inflammation and activity in the IL-1 pathway may be of importance also in

the chronic stages of the disease and that targeting these activated pathways may be potentially disease-modifying. Future studies on the postacute phase of NORSE/FIRES are needed to find evidence of residual ongoing neuroinflammation and to clarify the therapeutic role of IL-1 or IL-6 blockade in the long-term follow-up.

68. **Steroid pulses may have a therapeutic role in a severe or recurring postacute epilepsy situation** (M = 7, MA = 7, MP = 7.5, LA = 81.2%, LD = 0%).
The role of pulse CS in the postacute phase is unclear, but in line with use in other forms of refractory epilepsy, it may also be of potential use in NORSE/FIRES. In pediatric FIRES, an association between steroids in the postacute phase and good outcomes has been suggested, although its independent contribution to the positive outcome was not supported by multivariate logistic regression analysis.[11] As with KD and anticytokine therapy, the potential use of pulse CS could be considered in patients for whom the steroids were effective to reduce seizures in the acute phase of disease.
69. **Maintenance steroids should be avoided in the postacute phase** (M = 7, MA = 7, MP = 7, LA = 62.5%, LD = 14.6%).
The views on using maintenance steroids in the postacute phase of NORSE/FIRES differed among panelists. Whereas some adult and pediatric clinicians argued that patients who had a good response to steroids in the acute phase should continue this therapy in the postacute phase, other panelists argued against it because of the risk of developing side effects. Most panelists who supported the use of steroids in the later stages of disease were also proponents of medication taper to minimize adverse effects; several members speculated that repeated steroid pulses would be acceptable and beneficial. The consensus recommendation for this statement is therefore to avoid continuous high-dose steroids and to transition to low-dose steroid regimens including alternate-day scheduling. Of note, there was a relatively weak level of agreement (62.5%) with a corresponding high level of disagreement (14.6%) for this statement, although it reached the formal consensus threshold as defined in this study.
70. **Epilepsy surgery evaluation is indicated in a refractory postacute epilepsy situation** (M = 7, MA = 7, MP = 7, LA = 72.9%, LD = 12.5%).
The general experience among panelists was that seizures in the postacute phase often are largely multifocal and thus not amenable to surgical intervention or with a low chance of obtaining good seizure outcome. However, there was a consensus that in patients with focal onset seizures from unilateral or bilateral temporal regions, an evaluation for epilepsy surgery should be considered.
71. **Vagus nerve stimulation may be effective for postacute epilepsy** (M = 7, MA = 7, MP = 7, LA = 75.0%, LD = 2.1%).
There are very few available data to evaluate the efficacy and safety of vagus nerve stimulation (VNS) in the postacute phase of NORSE/FIRES. One case report of successful rapid titration of VNS parameters in a pediatric patient has been published,[108] and two case reports in adults also report positive effects in the acute[109] and postacute[110] phases. However, based on the possible anti-inflammatory effect of VNS[111] and the long-term use in several other forms of therapy-refractory epilepsies, including RSE,[112–114] neuromodulation with VNS can also play a role in NORSE/FIRES and should be considered. Likewise, recent case reports of positive effects using brain-responsive neurostimulation in FIRES[115] and in autoimmune encephalitis[116] as well as a recent review on neuromodulation in SRSE[117] indicate a need for further studies in these areas.
72. **Current evidence does not support the usefulness of deep brain stimulation (DBS) for postacute epilepsy** (M = 8, MA = 8, MP = 7.5, LA = 70.8%, LD = 6.3%).
The use of DBS in NORSE has been highlighted in a case report where centromedian thalamic nuclei DBS (in combination with anakinra) reduced the burden of generalized seizures but had no effect on focal seizures in a patient with medically intractable epilepsy following FIRES.[118] With such limited experience and scarce published data, the panel did not believe that it was feasible to provide a recommendation until further evidence is available. It should, however, be noted that there is no evidence of DBS lack of efficacy.
73. **All patients who are able to do so should undergo neuropsychological evaluation** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).
As cognitive impairment is a common sequela in patients, there was unanimous consensus that neuropsychological evaluation should be part of follow-up care in NORSE/FIRES to identify cognitive deficits and plan relevant interventions. Given the timeline of clinical recovery in the postacute phase, it was also recommended that evaluation is periodically repeated.

74. **All patients should be screened for mood and psychiatric disorders** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).
As mood disorders are common in refractory epilepsy,[119] there was unanimous consensus that all patients should be screened for mood and psychiatric disorders to receive appropriate treatment.
75. **All patients should be screened for sleep disorders** (M = 9, MA = 9, MP = 9, LA = 93.7%, LD = 0%).
As sleep plays a role in epilepsy modulation, clinicians need to be vigilant for sleep complaints in patients with epilepsy.[120] There was unanimous consensus that all patients should be screened for sleep disorders.
76. **Most patients need to undertake an intensive program of motor and cognitive rehabilitation** (M = 9, MA = 9, MP = 9, LA = 97.9%, LD = 0%).
There were no data to support the recommendation to introduce intensive motor and cognitive rehabilitation in patients recovering from NORSE/FIRES. However, as cognitive and motor sequelae of patients are often severe, but usually with a potential to improve at follow-up,[13] there was unanimous consensus that patients should undergo an intensive program of motor and cognitive rehabilitation.
77. **Rehabilitation should be combined with social service interventions to promote social activities, return to school or work, and quality of life of the patients and their families** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).
The ultimate goal of rehabilitation is to help disabled individuals to develop the emotional, social, and intellectual skills needed to live, learn, and work in the community with the least amount of professional support. There was a unanimous consensus that postacute rehabilitation should be offered together with social service interventions in the long-term to promote their return to social activities, school, or work and to promote quality of life as much as possible.
78. **If the etiology for NORSE/FIRES remains unexplained, repeated malignancy screening should be considered** (M = 8, MA = 8, MP = 7, LA = 77.1%, LD = 6.3%).
Depending on patients' age and their initial antibody status, repeated malignancy screening at set intervals (e.g., annually) may be warranted. The risk for occult malignancy in autoimmune encephalitis differs from very low in young children to much higher in adults and also differs depending on the antibody type.[63] There are no reported cases of a paraneoplastic etiology in pediatric NORSE/FIRES, nor any anecdotal evidence known to the panelists. Our recommendation, although not based on any solid evidence, is therefore to repeat malignancy screening on an annual basis up to 5 years in adults and in the case of worsened clinical symptoms and in particular in cases with positive autoantibodies but negative malignancy screening in the acute phase in adults and children.

3.7 | Research and registries in NORSE/FIRES

79. **Due to the rarity of disease, multicenter international efforts are essential to understand the mechanisms of NORSE/FIRES and to improve diagnosis and treatment** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).
Developing multicenter international collaborations of clinical researchers with the capacity to perform both observational studies and clinical trials is vital for furthering the knowledge in the area. There are several ongoing initiatives, including both national and international efforts, and aligning these efforts into joint projects holds great potential. An outspoken aim of this consensus collaboration was to lay a foundation for such a research consortium.
80. **Development of an international, web-based, high-quality clinical registry and database should be a priority** (M = 9, MA = 9, MP = 9, LA = 100%, LD = 0%).
A joint database of clinical data, including biomarkers, interventions, and outcome analysis, should be established urgently and regardless of the progress in clinical trials. The NORSE biorepository at Yale University is an example of such a database, which is also combined with a biobank open to researchers in the field. If the legal or regulatory restrictions do not allow the international sites to utilize this database, the data must be aligned across various existing international databases to allow comparisons. Importantly, such standardization will only be possible if common data elements (CDEs) for NORSE/FIRES are developed, including parameters for multiple outcomes. To ensure conformity, the development of CDEs should be performed together with relevant stakeholders in SE such as the ILAE.
81. **In addition to ongoing observational studies, an intervention trial of immunological treatment should be initiated** (M = 9, MA = 9, MP = 9, LA = 95.8%, LD = 0%).
There was a very strong consensus on the panel that clinical intervention trials are needed. However, the panel also recognized the concerns and practical difficulties in organizing such a trial, where the limited knowledge of the pathophysiology of NORSE/FIRES complicates choices of what therapies to study.

Furthermore, polypharmacy will complicate interpretation of the outcomes and will necessitate the development of innovative study designs. Learning from other rare disease communities that utilize quality improvement efforts and real comparative effectiveness trials may be necessary.

82. **As it is not ethical to randomize to a placebo arm in an immunological treatment trial, alternative study designs are needed** (M = 9, MA = 9, MP = 9, LA = 95.8%, LD = 2.1%).
The panel considers use of immunotherapy in NORSE/FIRES to be part of current standard care, thus rendering placebo trials unethical. Alternative study designs are therefore warranted, discussed further below as Statement 84.
83. **In an immunological treatment research trial, collection of CSF before and after the study intervention is indicated to assess changes in inflammatory markers** (M = 9, MA = 9, MP = 9, LA = 93.7%, LD = 4.2%).
Although concerns were raised that it may affect inclusion in clinical trials, the panel considered repeated CSF testing at standardized time points including pre- and postintervention to be important for understanding the pathophysiology of NORSE/FIRES and assessment of the response to treatment. CSF testing was considered to have major importance in the acute phase of disease, whereas its sampling in the postacute phase was viewed to be more problematic or even unethical.
84. **A head-to-head randomized comparison between two selected interventions is the most appropriate form of treatment trial** (M = 8, MA = 8, MP = 8, LA = 83.3%, LD = 4.2%).
As a placebo-controlled intervention trial is not considered feasible, some variant of comparative effectiveness research (CER) is warranted. However, the design of such a study is complicated by the lack of uniform agreement on what constitutes the standard of care. We believe that the current consensus document may serve as such a standard of care, to which it would be possible to add one or more interventions and perform CER studies. An alternative could be to establish several potential standardized treatment algorithms and allow the clinical teams to choose the most appropriate plan. This will increase the autonomy of clinicians but will also introduce a selection bias in the study design. The rarity of disease also makes outcome adaptive designs feasible. Finally, the possibility of having biomarker-driven studies was considered interesting but not feasible until more data emerge on relevant biomarkers.
85. **In a head-to-head randomized treatment trial, the prioritized treatments should be IL-1RAs and IL-6 antagonists** (M = 8, MA = 6, MP = 8, LA = 66.7%, LD = 8.3%).
Although the panel reached consensus as a group that the prioritized treatments in a clinical trial should be IL-1RAs and IL-6 antagonists, no agreement was reached specifically among adult clinicians on this issue. Beyond the relevant question of study design as discussed in Statement 84, the rationale for studying two treatments targeting cytokine signaling pathways was questioned. Instead, many adult clinicians advocated that a clinical trial should include rituximab. Until an acceptable standard of care algorithm required for CER design is developed, a differential approach to adult and pediatric patients may be required.

4 | CONCLUSIONS

The recommendations developed in this study address many aspects that need to be considered by the clinical teams in the diagnosis, evaluation, and treatment of NORSE/FIRES in adults and pediatric patients. The consensus recommendations also emphasize the importance of adequate follow-up in surviving patients, including neurorehabilitation and seizure control. This consensus report has some limitations. As the expert panel was selected based on the experience and expertise of the facilitator group, this may have created a possible selection bias. However, care was taken to involve both pediatric and adult experts and to have representatives from a broad international community. There could also be a bias in the selection of particular focus areas or specific survey questions. However, despite these potential limitations, we believe that these consensus statements may provide foundation for further actions to improve clinical care and solidify the ongoing research efforts in NORSE/FIRES.

As this is a field with limited evidence, emerging studies may alter our current understanding of NORSE/FIRES; therefore, it is important to stay current with these developments. The NORSE institute resources (https://www.norseinstitute.org/) can provide valuable tools for medical professionals and aid in locating the most recent publications and conference abstracts on NORSE and FIRES curated by experts in the field.

AUTHOR CONTRIBUTIONS

Project conception, design, and modification: All main authors. Literature review: All main authors. Recommendations draft preparation: All main authors. Data analysis: Ronny Wickstrom. First draft: Ronny Wickstrom, Olga Taraschenko, Nicolas Gaspard,

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CONFLICT OF INTEREST

R.W. has served on scientific advisory boards for GW Pharma and Octapharma; and has received speaker honoraria from Eisai and Sanofi. O.T. was supported by a research grant from the National Institutes of Health (P20GM130447). R.D. has received a speaker honorarium fee from Sobi. E.T.P. has received a speaker honorarium from Eisai. S.K. has served on scientific advisory boards for Zogenix and Neurelis. L.J.H. has received consultation fees for advising from Accure, Aquestive, Ceribell, Eisai, Marinus, Medtronic, Neurelis, Neuropace, and UCB; royalties from Wolters-Kluwer for authoring chapters for *UpToDate–Neurology* and from Wiley for coauthoring the book *Atlas of EEG in Critical Care* by Hirsch and Brenner; and honoraria for speaking from Neuropace, Natus, and UCB. NS has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, BioMarin, LivaNova, and Sanofi; and has served as an investigator for Zogenix, Marinus, BioMarin, UCB, and Roche. R.N. and N.G. have no disclosures for this study. The present study is not industry-sponsored. 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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

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