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SPECIAL REPORT

International consensus recommendations for management of new onset refractory status epilepticus (NORSE) including febrile infection-related epilepsy syndrome (FIRES): Summary and clinical tools

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Abstract

Objective: 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 available evidence and expert opinion.

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 that were then voted on using 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 greater than or equal to 7, and inappropriate if the median score was less than or equal to 3.

International NORSE Consensus Group memberes are present 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 post-acute phase; and (5) research, registries, and future directions in NORSE/FIRES. These are summarized in this article along with two practical clinical flowsheets: one for diagnosis and evaluation and one for acute treatment. A corresponding evidence-based analysis of all 85 recommendations alongside responses by the Delphi panel is presented in a companion article.

Significance: 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, anti-seizure medication, Delphi, epilepsy, immunotherapy, ketogenic diet, pediatric, refractory, 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 as a separate entity, as suggested previously.[2] The FIRES diagnosis requires a prior febrile illness starting between 2 weeks and 24 hours before the onset of RSE (with or without fever at onset of status epilepticus).[1,3] Both definitions thus apply to all age groups. 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. Indeed, although a number of reviews have been published on this topic,[3–7] no randomized controlled trials or consensus guidelines for the management of NORSE/FIRES are available. 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 patients with NORSE.[8]

The present study was performed using a Delphi methodology with the aim of creating 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 who were confronted with this rare and challenging condition. Given the limited evidence supporting most of the treatment statements, the present document is intended to serve as recommendations rather than strict guidelines. This article is intended as concise summary recommendations for use during acute care of NORSE/FIRES, whereas the evidence for statements included in the Delphi survey is described in a companion article in this issue of *Epilepsia*.

Key points

- As solid evidence for diagnosis and treatment of new-onset refractory status epilepticus (NORSE)/febrile infection-related epilepsy syndrome (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.
- As immunological activation is likely, first-line immunotherapy should be considered within 72 hours of seizure onset in cryptogenic cases.
- In cases that remain cryptogenic, second-line immunotherapy and ketogenic diet should be considered within 7 days of seizure onset.
- This summary includes two practical clinical flowsheets: one for diagnosis and evaluation and one for acute treatment.

2 | METHODS

The methodology of participant selection and the different Delphi rounds is presented in detail in the companion article that details both the evidence-based analysis and corresponding Delphi responses for all questions. Briefly, an international panel of 48 experts was selected based on portfolios of indexed relevant publications and participation in specific congresses as well as their leadership in clinical care for NORSE/FIRES. The group included specialists (multiple specialties possible) in 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%. Participants completed two rounds to develop a set of consensus statements following an initial pre-questionnaire (details concerning how consensus statements were reached can be found in the longer and complete document).[9] NORSE and FIRES were considered jointly for all ages. The statements were divided into five sections. A statement was defined as reaching consensus as appropriate if the median score was greater or equal to 7, and as inappropriate if the median score was less than or equal to 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. Furthermore, a breakdown of responses between adult and pediatric caregivers was made to facilitate the understanding of different views and opinions in these two groups of providers. 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 Likert scale for each statement.

TABLE 1 Disease characteristics of NORSE/FIRES

Statements reaching consensus	Median value (adult/pediatric)	Level of agreement[a] (n total voting)	Level of disagreement[a]
1. A diagnosis of NORSE may be given for persons of all ages.	9 (9/9)	90.7% (43)	4.7%
2. The definition of FIRES as a subcategory of NORSE is appropriate.	9 (9/9)	88.7% (44)	0%
3. A diagnosis of FIRES may be given for persons of all ages.	9 (9/8)	84.1% (45)	2.3%
4. NORSE/FIRES has no evident geographical trend.	8 (7/9)	81.2% (48)	2.1%
5. NORSE/FIRES has no demonstrated a seasonal trend, but more research is needed to exclude such variation.	8 (8/7.5)	75.0% (48)	2.1%
6. In NORSE/FIRES patients with chronic autoimmune conditions, a primary autoimmune etiology should be suspected.	8 (8/8)	83.3% (48)	2.1%
7. In NORSE/FIRES patients with non-CNS malignancies, a paraneoplastic etiology should be suspected.	8 (8/8)	87.5% (48)	0%
8. Postinfectious immune activation is likely an important cause of NORSE/FIRES.	8 (8/8.5)	91.6% (48)	2.1%
9. Inflammatory activation in the CNS is likely to precede the development of seizures in NORSE/FIRES.	8 (7/8)	79.2% (48)	0%
10. Inflammatory activation in the CNS likely contributes to the persistence of seizures in NORSE/FIRES.	8 (7.5/9)	97.9% (48)	0%
11. Differences in the initial clinical manifestations can provide clues for the specific etiologies of NORSE/FIRES.	8 (7/8)	77.1% (48)	2.1%
12. Cryptogenic NORSE/FIRES cases usually have a higher seizure burden (i.e., seizure frequency x duration) than cases with an established etiology.	7 (7/7)	70.1% (48)	4.2%
13. Patients with cryptogenic NORSE/FIRES are more likely than noncryptogenic cases to develop permanent cognitive disability.	7 (7/7)	68.8% (48)	4.2%
14. Patients with cryptogenic NORSE/FIRES are more likely to develop a more severe epilepsy following discharge from the hospital as compared to noncryptogenic cases.	7 (7/7)	70.8% (48)	4.2%

[a]Level of agreement defined as the percent of raters voting 7–9 on a 9-point scale and level of disagreement defined as the percent of raters voting 1–3 on a 9-point scale.

TABLE 2 Workup and diagnosis in NORSE/FIRES

Statements reaching consensus	Median value (adult/pediatric)	Level of agreement[a] (n total voting)	Level of disagreement[a]
1. It is appropriate to perform the same investigations in NORSE cases regardless of whether they also fulfill FIRES criteria or not.	8 (8/8)	89.6% (48)	0%
2. Early testing for autoimmune antibodies is of great importance.	9 (9/9)	100% (48)	0%
3. Having access to rapid autoimmune antibody analysis is important as results will affect management decisions.	9 (9/9)	93.8% (48)	0%
4. The value of evaluating inborn errors of metabolism (including Mitochondrial disease) is unclear in teenagers and adults.	7 (7/7)	62.5% (48)	6.3%
5. In addition to regular testing in status epilepticus (as per local guidelines) the following SERUM investigations are needed during the initial 48 hours of admission in most or all patients with NORSE/FIRES.			
Comprehensive rheumatologic evaluation	8 (8/8)	100% (48)	0%
Comprehensive infectious evaluation including cultures and viral and bacterial serology relevant in the geographical region and season	9 (9/9)	100% (48)	0%
Evaluation for inborn errors of metabolism in young children	9 (9/9)	100% (48)	0%
Autoimmune and onconeural antibody panel	9 (9/9)	100% (48)	0%
Extra blood samples for storage for future analysis (e.g., cytokine and genetic analyses)	9 (9/9)	100% (48)	0%
6. In addition to regular testing in status epilepticus (as per local guidelines) the following CSF investigations are needed during the initial 48 hours of admission in most or all patients with NORSE/FIRES.			
Comprehensive infectious evaluation relevant in the geographical region and season	9 (9/9)	100% (48)	0%
Evaluation for inborn errors of metabolism in young children[b] (e.g., lactate, pyruvate, amino acids)	9 (9/9)	100% (48)	0%
Autoimmune antibody panel	9 (9/9)	100% (48)	0%
Extra CSF samples for storage for future analysis (e.g., cytokine analyses)	9 (9/9)	100% (48)	0%
7. Brain MRI should be performed during the initial 48 hours of admission in most or all patients with NORSE/FIRES.	9 (9/9)	97.9% (48)	0%
8. Gadolinium contrast enhancement should be included with MRI evaluation.	9 (9/9)	91.7% (48)	2.1%
9. Brain spectroscopy (MRS) can be of diagnostic use in NORSE/FIRES cases where inborn errors of metabolism (including mitochondrial disease) are suspected.	7 (7/7.5)	64.6% (48)	2.1%
10. Whole-body PET can be useful in NORSE/FIRES cases where a paraneoplastic etiology is suspected.	8 (8.5/7.5)	85.4% (48)	2.1%
11. Malignancy screening (CT of chest, pelvis, and abdomen) should be performed in a majority of patients with cryptogenic NORSE/FIRES.	9 (9/7.5)	77.1% (48)	4.2%
12. Malignancy screening should include whole-body PET when other testing, including CT of C/A/P, remains negative.	8 (8/7)	89.2% (37)	2.7%
13. Malignancy screening should include testicular/ovarian ultrasound.	9 (9/9)	95.8% (37)	0%

TABLE 2 (Continued)

Statements reaching consensus	Median value (adult/pediatric)	Level of agreement[a] (n total voting)	Level of disagreement[a]
14. Genetic testing can be helpful in the diagnostic evaluation of cryptogenic NORSE/FIRES.	7.5 (7/8)	77.1% (48)	2.1%
15. Genetic testing should be performed in the majority of cases of cryptogenic NORSE/FIRES.	8 (7/9)	68.8% (48)	4.2%
16. Genetic testing should be considered early in young children.[b]	9 (8/9)	93.8% (48)	0%
17. Continuous EEG monitoring is needed to manage seizures in NORSE/FIRES.	9 (9/9)	95.8% (48)	2.1%
18. If etiology remains unclear and if MRI indicates a targetable lesion, a brain biopsy should be considered.	8 (8/8)	85.4% (48)	0%
19. A brain biopsy should not be performed unless MRI indicates a targetable lesion.	8 (7/8)	79.2% (48)	0%
20. CSF cytokines may be useful as they are potential biomarkers for disease progression or response to treatment.	8 (7.5/8)	79.2% (48)	2.1%
21. CSF cytokines are potentially useful for guiding treatment choice.	7 (7/8)	66.7% (48)	4.2%
22. Repeat MRI has an important role in monitoring disease progression.	9 (9/8)	87.5% (48)	0%

Abbreviation: C/A/P, chest, pelvis and abdomen; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography.

[a]Level of agreement defined as the percent of raters voting 7–9 on a 9-point scale and level of disagreement defined as the percent of raters voting 1–3 on a 9-point scale.

[b]No clear age cut-off exists, but the younger the child, the more these conditions should be considered (applies to genetic testing and evaluation for inborn errors of metabolism).

3 | RESULTS

Following the completion of the pre-questionnaire, two Delphi surveys were distributed (complete questionnaires including all original and subsequently rephrased statements can be found in Appendix S1). All 48 invited panelists completed the two questionnaires. A total of 85 statements and recommendations were developed and reached consensus, as presented in Tables 1–5. Table 1 describes statements of disease characteristics of NORSE/FIRES that reached consensus support. Table 2 shows the recommendations for evaluation and diagnosis. Table 3 shows the recommendations for treatment of NORSE/FIRES in the acute phase, whereas Table 4 shows the recommendations for treatment in the post-acute phase (defined as following the resolution of status epilepticus [SE]). Finally, Table 5 outlines the development of registries and research priorities in the NORSE/FIRES field. A detailed discussion of the evidence associated which each statement alongside the corresponding individual recommendations is presented in an accompanying article in this volume of *Epilepsia*. Based on these consensus statements and previous algorithms, two practical clinical tools were developed: a flowsheet for diagnosis and evaluation (Figure 1) and a flowsheet for acute treatment in NORSE including FIRES (Figure 2).

4 | DISCUSSION

In this article, we present the first international, consensus-based treatment guidelines for the diagnostic evaluation and treatment of NORSE/FIRES, developed by using the Delphi methodology. Two initial major questions were whether to address NORSE as one disease group or to separate FIRES in this process, and also whether adults and children should be discussed separately. This was addressed in a pre-questionnaire using the same Delphi methodology, and a consensus was reached to perform a combined analysis for NORSE/FIRES of all ages, but also to carry out secondary analyses of stratified responses from adult and pediatric physicians. One important argument for this was to learn from differences in treatment practices that may be associated with patient age.

TABLE 3 Treatment in the acute phase of NORSE/FIRES

Statements reaching consensus	Median value (adult/pediatric)	Level of agreement[a] (n total voting)	Level of disagreement[a]
1. 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.	9 (9/9)	95.8% (48)	0%
2. In addition, management of adults with NORSE/FIRES should be carried out by neurointensivists.	7.5 (7.5/7.5)	62.5% (48)	4.2%
3. The acute treatment of seizures with ASMs in NORSE/FIRES should be similar to acute treatment of seizures in other conditions.	8 (8/8)	85.4% (48)	4.2%
4. 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 hours.	8 (8/8)	87.5% (48)	4.2%
5. First-line immunological treatment should be started during the first 72 hours.[b]	9 (8.5/9)	95.8% (48)	4.2%
6. Steroids are the first-line immunological treatment in NORSE/FIRES.	8 (8/8)	87.5% (48)	2.1%
7. If given, steroids should be given in the form of methyl prednisone in a dose of 20–30 mg/kg per day (maximum 1 g) for 3–5 days.	9 (8/9)	93.8% (48)	0%
8. Enteral steroids should not be used as an alternative to IVMP.	8 (9/8)	81.3% (48)	6.3%
9. IVIG can be given as an alternative to steroids as first-line immunological treatment.	7 (7/7)	65.6% (48)	**8.3%**
10. If given, the preferred dosage for a course of IVIG is (a total of) 2 g/kg over 2–5 days.	9 (8.5/9)	95.8% (48)	2.1%
11. IVIG and steroids can be administered simultaneously.	8 (8/9)	89.6% (48)	2.1%
12. Ketogenic diet should be initiated in the first week.[c]	8 (6.5/9)	77.1% (48)	4.2%
13. If not already given, ketogenic diet should be considered in prolonged and severe cases.	9 (8/9)	95.8% (48)	0%
14. If enteric ketogenic diet is not possible, ketogenic diet should be started by parenteral application assuming local availability and expertise.	8 (7/9)	79.2% (48)	0%
15. Current evidence does not clearly support the usefulness of cannabidiol in the acute phase of NORSE/FIRES.	8 (8/8)	72.9% (48)	4.2%
16. Cannabidiol should not be used as a first-line treatment.	8.5 (8/9)	81.2% (48)	0%
17. Current evidence does not clearly support the usefulness of hypothermia in the acute phase of NORSE/FIRES.	8 (8.5/7.5)	87.5% (48)	0%
18. Hypothermia should not be used as a first-line treatment.	9 (9/8.5)	79.2% (48)	4.2%
19. In noninfectious NORSE/FIRES with inadequate response to first-line immune treatment, second-line immunological treatment should be started within 7 days of seizure onset.	8 (8/8)	81.2% (48)	0%
20. Second-line immunological treatment has the potential to improve outcome even when initiated late (several weeks) after seizure onset.	7 (7/7)	70.8% (48)	2.1%
21. Current evidence does not clearly support the use of any specific second-line immunological treatment over others.	8 (8/7)	75.0 (48)	**12.5%**
22. Second-line immunological treatment should be based on suspected etiology.	8 (8/7)	79.2% (48)	4.2%
23. If a pathogenic antibody is identified or highly suspected, rituximab treatment should be initiated.	8 (8/8)	83.3% (48)	0%
24. In cryptogenic NORSE/FIRES without clinical features of autoimmune encephalitis, IL-1 receptor antagonists or IL-6 antagonists should be initiated.	8 (7/8)	81.2% (48)	2.1%

Abbreviation: ASM, antiseizure medication; IVIG, Intravenous immunoglobulins; IVMP, intravenous methyl prednisone; SE, status epilepticus.

[a]Level of agreement defined as the percent of raters voting 7–9 on the 9-point scale and Level of disagreement defined as the percent of raters voting 1–3 on the 9-point scale.

[b]The majority in fact advocated starting as early as by 48 h (applies to question 5).

[c]Note that this statement did not reach consensus in adult group (applies to question 12).

TABLE 4 Treatment in the post-acute phase of NORSE/FIRES

Statements reaching consensus	Median value (adult/pediatric)	Level of agreement[a] (n total voting)	Level of disagreement[a]
1. Current evidence does not clearly support the efficacy of any specific antiseizure medication in the post-acute phase of NORSE/FIRES.	8 (8/8)	85.4% (48)	**12.5%**
2. If effective in the acute phase, the ketogenic diet should be continued in the post-acute phase.	8 (7/8.5)	87.5% (48)	0%
3. The duration of follow-up of the ketogenic diet in the post-acute phase should be at least 3 months.	8 (7/8)	75.0 (48)	0%
4. If effective in the acute phase, follow-up treatment during the post-acute phase should include immunomodulation.	8 (8/8)	87.5% (48)	0%
5. The duration of follow-up immunomodulation in the post-acute phase should be at least 3 months.	8 (8/8.5)	81.2% (48)	2.1%
6. If symptoms significantly worsen in the post-acute phase upon immunotherapy withdrawal, the previous immune treatment should be resumed.	9 (8/9)	93.7 (48)	0%
7. IL-1 receptor or IL-6 antagonists may have a therapeutic role in a severe or recurring post-acute epilepsy situation even if they were not previously tried in the acute phase.	7 (7/7)	81.2% (48)	0%
8. Steroid pulses may have a therapeutic role in a severe or recurring post-acute epilepsy situation.	7 (7/7.5)	81.2% (48)	0%
9. Maintenance steroids should be avoided in the post-acute phase.	7 (7/7)	62.5% (48)	**14.6%**
10. Epilepsy surgery evaluation is indicated in a refractory post-acute epilepsy situation.	7 (7/7)	72.9% (48)	**12.5%**
11. Vagus nerve stimulation may be effective for post-acute epilepsy.	7 (7/7)	75.0 (48)	2.1%
12. Current evidence does not support the usefulness of deep brain stimulation for the post-acute epilepsy.	8 (8/7.5)	70.8% (48)	6.3%
13. All patients that are able to do so should undergo neuropsychological evaluation.	9 (9/9)	100% (48)	0%
14. All patients should be screened for mood and psychiatric disorders.	9 (9/9)	100% (48)	0%
15. All patients should be screened for sleep disorders.	9 (9/9)	93.7 (48)	0%
16. Most patients need to undertake an intensive program of motor and cognitive rehabilitation.	9 (9/9)	97.9 (48)	0%
17. 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.	9 (9/9)	100% (48)	0%
18. If the etiology for NORSE/FIRES remains unexplained, repeated malignancy screening should be considered.	8 (8/7)	77.1% (48)	6.3%

Abbreviation: ASM, antiseizure medication.

[a]Level of agreement defined as the percent of raters voting 7–9 on a 9-point scale and level of disagreement defined as the percent of raters voting 1–3 on a 9-point scale.

4.1 | Disease characteristics

Our recommendations begin with general statements concerning disease characteristics, important aspects of cryptogenic NORSE/FIRES, and the putative role of inflammation (Table 1). An important point is that both NORSE and FIRES are diagnoses that can occur at any age. Several lines of evidence support a role of inflammation in the pathological mechanisms in NORSE/FIRES, although the etiologies for such an immune activation may differ with age.

4.2 | Recommendations for evaluation and diagnosis

Thereafter follows recommendations for diagnostic evaluation of NORSE/FIRES in which a very high level of

TABLE 5 Research and registries in NORSE/FIRES

Statements reaching consensus	Median value (adult/pediatric)	Level of agreement[a] (n total voting)	Level of disagreement[a]
1. Due to the rarity of disease, multicenter international efforts are essential to understand the mechanisms of NORSE/FIRES and to improve diagnosis and treatment.	9 (9/9)	100% (48)	0%
2. Development of an international web-based, high-quality clinical registry and database should be a priority.	9 (9/9)	100% (48)	0%
3. In addition to ongoing observational studies, an intervention trial of immunological treatment should be initiated.	9 (9/9)	95.8% (48)	0%
4. As it is not ethical to randomize to a placebo arm in an immunological treatment trial, alternative study designs are needed.	9 (9/9)	95.8% (48)	2.1%
5. In an immunological treatment research trial, collection of CSF before and after the study intervention is indicated to assess changes in inflammatory markers.	9 (9/9)	93.7% (48)	4.2%
6. A head-to-head randomized comparison between two selected interventions is the most appropriate form of treatment trial.	8 (8/8)	83.3% (48)	4.2%
7. In a head-to-head randomized treatment trial, the prioritized treatments should be IL-1 receptor antagonists and IL-6 antagonists.[b]	8 (6/8)	66.7% (48)	**8.3%**

[a]Level of agreement defined as the percent of raters voting 7–9 on a 9-point scale and level of disagreement defined as the percent of raters voting 1–3 on a 9-point scale.

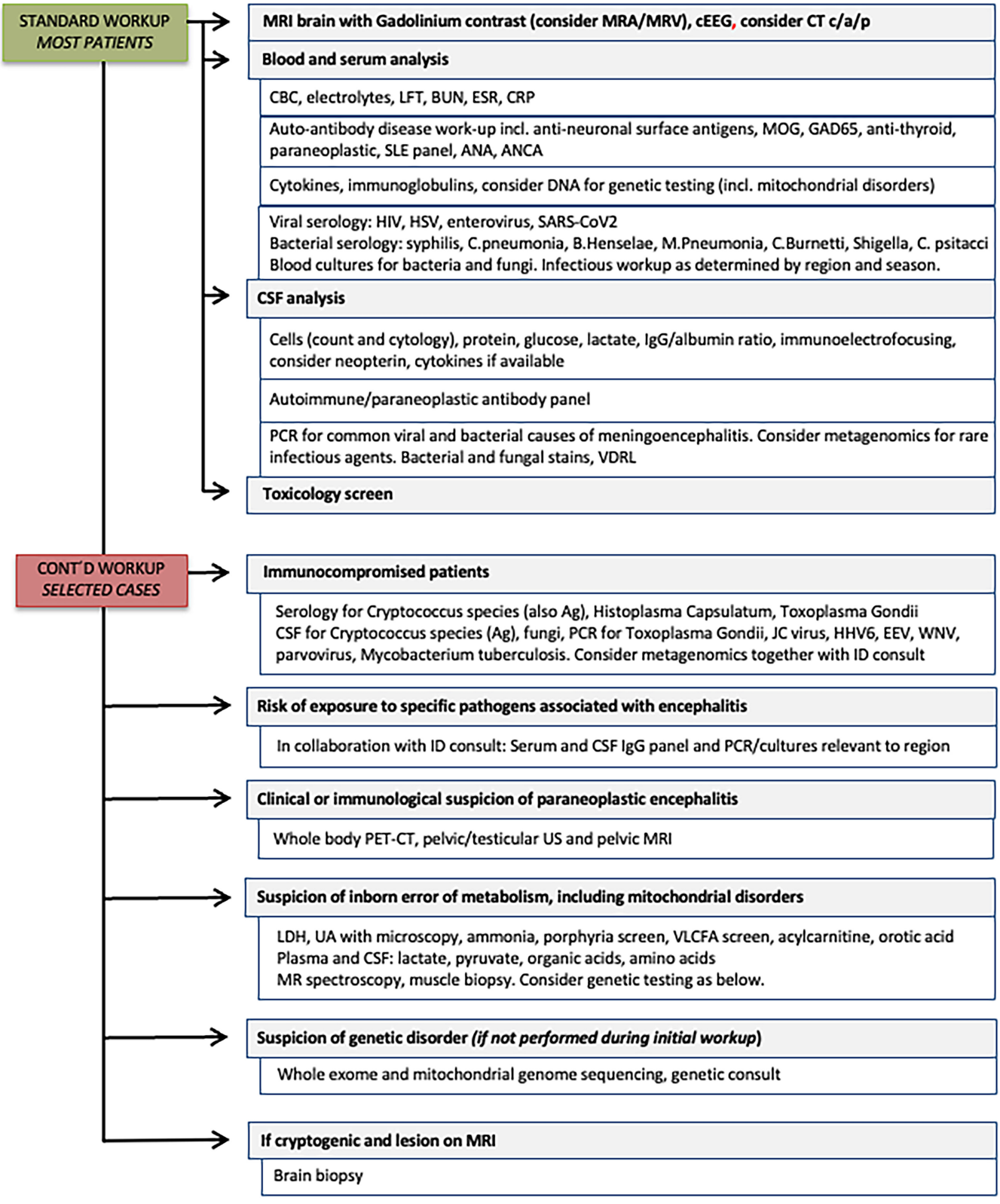
[b]Note that this statement did not reach consensus in adult group (applies to question 7).

agreement was generally achieved (Table 2). Overall, it was considered appropriate to perform the same investigations in NORSE cases regardless of whether they also fulfill FIRES criteria. The age of the patient affects, but rarely excludes, the likelihood of specific etiological diagnoses. Although autoimmune encephalitis with a known auto-antibody may be a rare cause of NORSE/FIRES in children, distinguishing cases secondary to identifiable autoimmune encephalitis from cryptogenic NORSE is important as it will likely aid in guiding the treatment and establishing the prognosis.[11] Conversely, the value of evaluating for inborn errors of metabolism (including mitochondrial diseases) was considered unclear in teenagers and adults. The diagnostic evaluation was thus divided into a general part with a standard set of investigations, and a targeted evaluation with selected investigations individually tailored to the patient (Figure 1).

4.3 | Treatment in the acute phase

Regarding therapy in the acute phase (Table 3 and Figure 2), there was consensus that the treatment of seizures with ASMs and anesthetic drugs during the initial 48 hours should be similar to acute treatment of RSE in other conditions. There was also agreement that the management of NORSE/FIRES patients should be carried out in a tertiary center with the appropriate resources and

FIGURE 1 Algorithm for diagnostic workup in NORSE including FIRES. Adapted from NORSE Institute website (https://www.norseinstitute.org/) and Sculier et al.[4] Ag, antigen; ANA, anti-nuclear antibodies, ANCA, anti-neutrophil cytoplasmic antibodies; *B. henselae*, *Bartonella henselae*; BUN, blood urea nitrogen; *C. burnetii*, *Coxiella burnetii*; *C. pneumoniae*, *Chlamydia pneumoniae*; *C. psittaci*, *Chlamydia psittaci*; CBC, complete blood count; cEEG, continuous EEG; CGH, comparative genomic hybridization; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; EBV, Epstein–Barr virus; EEEV, eastern equine encephalitis virus; EEG, electroencephalography; ESR, erythrocyte sedimentation rate; GAD, glutamic acid decarboxylase; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ID, infectious disease; IgG, immunoglobulin G; JC, John Cunningham; LDH, lactate dehydrogenase; LFT, liver function test; *M. pneumoniae*, *Mycoplasma pneumoniae*; MOG, myelin oligodendrocyte glycoprotein; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PCR, polymerase chain reaction; PET-CT, positron emission tomography–computed tomography; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; UA, urine analysis; US; ultrasound; VLCFA, very long chain fatty acid; VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus; WNV, West Nile virus.



multidisciplinary expertise in epileptology, rheumatology and immunology, and intensive care. Furthermore, the panel agreed on a recommendation that the acute management of adults with NORSE/FIRES should be carried out by neurointensivists with available multidisciplinary expertise as above.

An important difference from most treatment algorithms in RSE is that we recommend that in NORSE/FIRES, first-line immunotherapy—which may include corticosteroids (CS), intravenous immunoglobulins (IVIG), or therapeutic plasma exchange (TPE)—should be initiated within the first 72 hours of onset of SE. Of

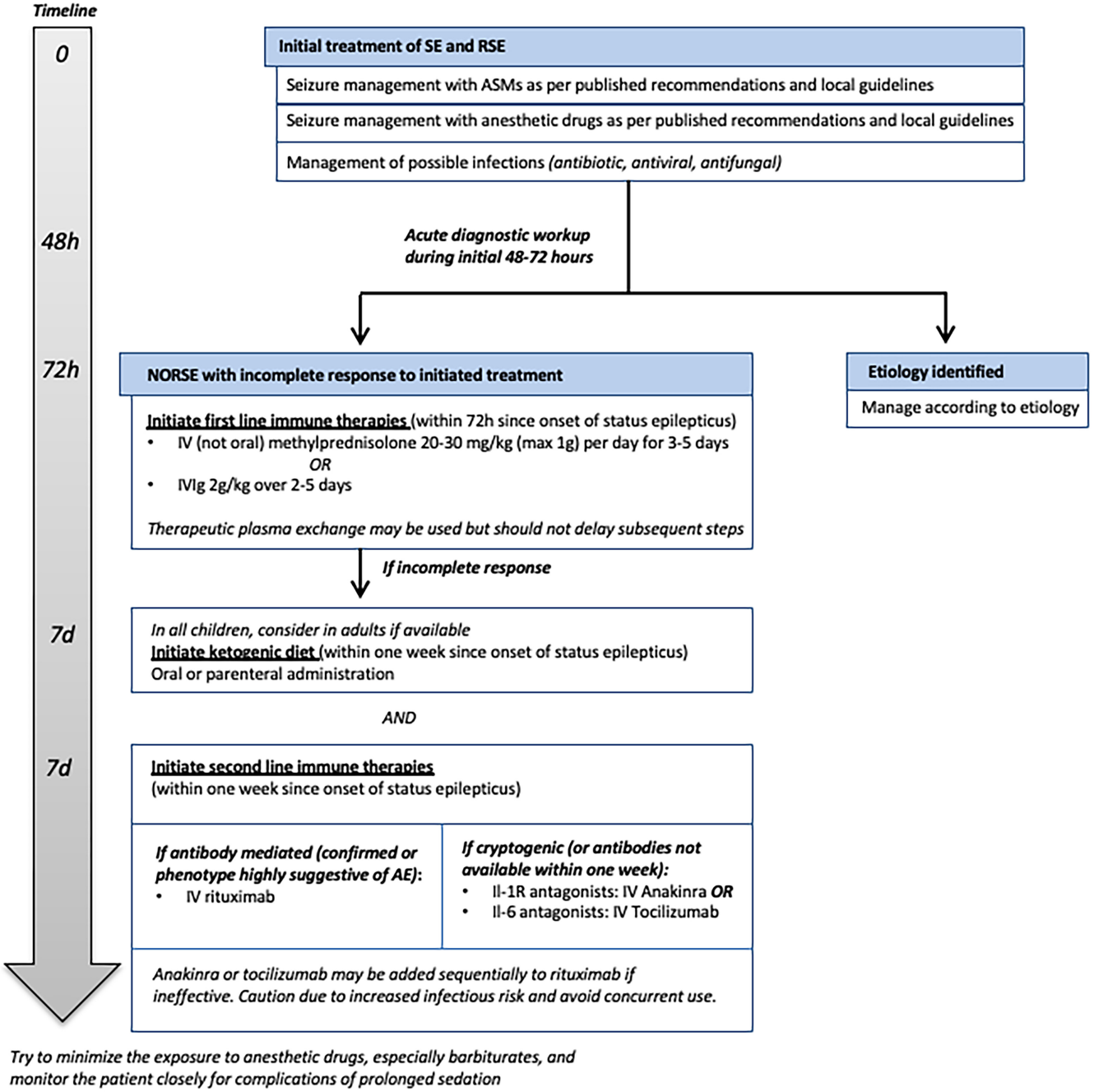


FIGURE 2 Suggested treatment algorithm for NORSE including FIRES (expert opinion). Adapted from Gaspard et al.[3] van Baalen et al.[10] and Sculier et al.[4] AE, autoimmune encephalitis; ASM, anti-seizure medication; IV, intravenous; IVIG, intravenous immunoglobulins; RSE, refractory status epilepticus; SE, status epilepticus.

note, the majority of respondents also advocated starting these therapies as early as 48 hours after onset or as soon as common infectious etiologies were ruled out. There were large differences among panel members concerning utilization of TPE, and this consensus document therefore gives no recommendation concerning TPE beyond that it should not delay initiation of subsequent treatments. Based on the likely involvement of immune mechanisms in sustaining seizures, we further recommend that the ketogenic diet and second-line immunotherapies are initiated within 1 week in noninfectious NORSE/FIRES with inadequate response to first-line immune treatment. Because current evidence does not clearly support the use of any specific second-line immunological treatment over others, the choice should be based on suspected etiology. If a pathogenic antibody is identified or an autoimmune process highly suspected, rituximab treatment should be the preferred treatment in most cases. In cryptogenic NORSE/FIRES without clinical features of a specific autoimmune encephalitis syndrome, interleukin 1 (IL-1)

receptor antagonists or IL-6 blockers should be strongly considered.

4.4 | Treatment in the post-acute phase

Following the resolution of SE, recommendations concerning treatment in the post-acute phase addressed both continued treatment and adequate rehabilitation (Table 4). Current evidence was not considered to support the efficacy of any specific ASM in the post-acute phase of NORSE/FIRES. In contrast, immunomodulation and the ketogenic diet were recommended to be continued in the post-acute phase if effective during the acute phase. Furthermore, the importance of neuropsychological evaluation, screening for mood and sleep disorders, and intensive programs for motor and cognitive rehabilitation was emphasized by the panel.

4.5 | Research and registries

The final section addressed future directions for research where the need for multicenter international efforts was emphasized, including the development of an international web-based, high-quality clinical registry and database. There was a very strong consensus in the panel that clinical intervention trials are needed. However, the panel also recognized the concerns and practical difficulties in organizing such trials at the current time and a further discussion on innovative, adaptive trial designs is needed.

This consensus report has some important limitations. The rarity of NORSE/FIRES inevitably makes any recommendation or guideline concerning treatment limited due to a lack of high-quality evidence. Because 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 with variable areas of expertise. To clearly demonstrate to what extent there was disagreement as well as agreement, the LD is also given for all statements and LD values >7% are highlighted in the tables. 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 will provide a foundation for further actions to improve clinical care and solidify the ongoing research efforts in NORSE/FIRES.

This is the first effort to generate an international consensus-based recommendation aimed at supporting the clinician in the diagnosis and treatment of NORSE/FIRES. It is our hope that this will not only improve patient care but will also initiate the important task of standardizing sampling and developing common data elements (CDEs) including outcome parameters, that is, standardized key terms or concepts that once established may be used in clinical research across sites and over time.

Although the evidence is limited at the present time, new studies may alter our current understanding of NORSE/FIRES, and it is therefore important to be familiar with these research developments. The NORSE institute website (www.norseinstitute.org) can serve as a resource for medical professionals and provides an updated bibliography on NORSE and FIRES curated by experts in the field.

AUTHOR CONTRIBUTIONS

Project conception, design, and modification: All authors. Literature review: All authors. Recommendations draft preparation: All authors. Data analysis: RW. First draft: RW, OT, NG, RD, and LJH. Editing and approval of final draft: All authors and collaborators.

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CONFLICT OF INTEREST

RW has served on scientific advisory boards for GW Pharma and Octapharma and has received speaker honoraria from Eisai and Sanofi. OT was supported by research grant from the National Institutes of Health (NIH) (P20GM130447). RD has received speaker honorarium fee from Sobi. ETP has received a speaker honorarium from Eisai. RN has no disclosures for this study. SK has served on scientific advisory boards for Zogenix and Neurelis. NG has no disclosures for this study. LJH 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 co-authoring 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. RW, OT, RN, SK, NG, and LJH are members of the Scientific Board of the NORSE Institute. 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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