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CONTEMPORARY ISSUES

New onset refractory status epilepticus research

What is on the horizon?

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Abstract

New-onset refractory status epilepticus (NORSE) is a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurologic disorder, with new onset of refractory status epilepticus (RSE) that does not resolve after 2 or more rescue medications, without a clear acute or active structural, toxic, or metabolic cause. Febrile infection-related epilepsy syndrome is a subset of NORSE in which fever began at least 24 hours prior to the RSE. Both terms apply to all age groups. Until recently, NORSE was a poorly recognized entity without a consistent definition or approach to care. We review the current state of knowledge in NORSE and propose a roadmap for future collaborative research. Research investigating NORSE should prioritize the following 4 domains: (1) clinical features, etiology, and pathophysiology; (2) treatment; (3) adult and pediatric evaluation and management approaches; and (4) public advocacy, professional education, and family support. We consider international collaboration and multicenter research crucial in achieving these goals.

Introduction

Refractory status epilepticus (RSE) is defined as status epilepticus (SE) resistant to adequate doses of an initial benzodiazepine and a second acceptable antiseizure medication.[1,2] Super-refractory SE (SRSE) is defined as RSE that persists or recurs after 24 hours of anesthetic therapy (including recurrence upon reduction or withdrawal or anesthetic).[3] Nonepileptiform mimics of SRSE exist in comatose patients and these possibilities should be carefully considered at the time of diagnosis. Possible mimics include some forms of postanoxic myoclonus, drug overdose, or anesthetic drug withdrawal with associated epileptiform EEG discharges. About 5%–35% of patients with SE will develop RSE[4–6] (10%–40% in children[7]), and approximately 50% of these will progress to SRSE[5] (SRSE makes up 7% of all SE in children[8]). SRSE is associated with a high morbidity and mortality.[9] The mortality associated with RSE is approximately 22% and rises to 36% in SRSE and 63% in patients over age 75 with SRSE,[4] or 50% of all patients with SRSE.[5] SRSE is associated with an intensive care unit length of stay of approximately 9 days[4] and an overall hospital length of stay of approximately 21–37 days.[10,4] The cost per admission for patients with SRSE is much higher in patients with SRSE (€32,000 or $37,000) when compared to those with RSE (€4,500 or $5,200).[10] Data suggest that a longer duration of SE is associated with a higher risk of subsequent epilepsy[11] and that the degree of disability as a result of SE is higher among patients with RSE or SRSE as compared to responsive SE.[5] In one study, only 20% of patients with RSE or SRSE regained their baseline function.[5]

New-onset refractory SE (NORSE) is "a clinical presentation in a patient without active epilepsy or other preexisting relevant neurologic disorder, with new onset of refractory status epilepticus, without a clear acute or active structural, toxic, or metabolic cause." [12] Febrile infection-related epilepsy syndrome (FIRES) is "a subset of NORSE that requires a prior febrile

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Glossary

FIRES = febrile infection-related epilepsy syndrome; **GCSE** = generalized convulsive status epilepticus; **IVIg** = IV immunoglobulin; **NCSE** = nonconvulsive status epilepticus; **NORSE** = new-onset refractory status epilepticus; **RSE** = refractory status epilepticus; **SE** = status epilepticus; **SRSE** = superrefractory status epilepticus.

infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory status epilepticus, with or without fever at onset of status epilepticus".[12] Both NORSE and FIRES include patients of all ages. Ten years ago, NORSE was a poorly recognized entity without a consistent definition or approach to care. Over the last several years, NORSE has become increasingly well-recognized and defined, and recently consensus definitions have been suggested.[12] NORSE may be considered as a separate subtype of RSE and SRSE in order to guide early approaches to diagnostic evaluation and therapy when the cause of new-onset RSE or SRSE remains unidentified and to prospectively identify this subset of patients for future research.

In nearly 50% of cases, the probable cause of NORSE can eventually be determined.[13] The most commonly identified etiologies include autoimmune (19%) and paraneoplastic encephalitis (18%) or infection-related (8%).[13] In the other half of cases, NORSE remains unexplained (known as "cryptogenic NORSE" or "NORSE of unknown etiology"). Cases of cryptogenic NORSE last longer than cases with an identified etiology.[13] NORSE is a relatively uncommon disorder, and has been recognized as a rare disorder by the National Organization for Rare Disorders.[14] As such, collaboration between institutions is necessary to make multicenter research both possible and successful. The majority of the medical literature that treating intensivists and neurologists/epileptologists currently rely upon stems from broader research investigating the management of RSE, and not specifically NORSE.

Management of RSE

Guidelines are currently available for the treatment of convulsive SE or nonconvulsive SE following convulsive seizures.[2,15] By definition, however, patients in RSE fail to respond to first- and second-line therapies, and therefore require continuous IV medications to control ongoing seizures.[1] Many recommendations for the management of SRSE are supported by little evidence, and are mostly based on expert opinion.[16]

Current guidance recommends the administration of a continuous infusion of an anesthetic drug for the management of generalized convulsive SE (GCSE).[2,15] The same guidance also recommends that conventional antiseizure medications be trialed before inducing pharmacologic coma in nonconvulsive SE (NCSE), even though anesthetics will be required to effectively control seizures in many cases of refractory NCSE.[2,15] Current research provides evidence for the continuous infusion of midazolam, propofol (in adults), and barbiturates,[17] as well as possibly ketamine.[18] Previous systematic review of findings published prior to 2002 reported that patients treated with continuous infusion of midazolam had higher rates of therapeutic failure than those treated with pentobarbital, and also reported higher rates of seizures.[17] However, since continuous EEG was reported more frequently in studies of pentobarbital infusion, the incidence of nonconvulsive seizures may be underrepresented in results for other agents. These results are also limited by the fact that midazolam was usually administered at doses below 0.4 mg/kg/h, while a later study found that higher doses were often required to control RSE, and a protocol allowing these higher doses when needed was associated with lower mortality.[19] Implementation of midazolam or pentobarbital loading boluses may also vary in current clinical practice, potentially affecting efficacy. A recent controlled and randomized trial investigated responses to propofol and barbiturates in patients with RSE, although a low enrollment rate led to the early termination of the study.[20] While results from this limited study were not able to demonstrate differences between the 2 treatment protocols, it was observed that a longer period of mechanical ventilation was required for patients treated with barbiturates.[20] The authors inferred that the difference in responses is a result of the relatively shorter half-life of propofol and midazolam when compared to barbiturates, which are much longer-acting agents. Alternatively, minor differences in RSE etiology between groups may have also contributed. The administration of barbiturates is also of concern due to its powerful depressant effect that often leads to cardiovascular complications such as hypotension and the need for vasopressors,[21] and due to a higher rate of hematologic and infectious complications,[22] and at times more frequent gastrointestinal complications. Finally, prolonged treatment with high doses of propofol has been linked to propofol infusion syndrome, and may lead to more frequent complications and higher mortality when compared with other drugs, such as midazolam,[17] at least for children and in patients with suspected metabolic or mitochondrial disorders.

SRSE is managed in a similar manner to RSE; however, the duration of treatment is often longer and there is a greater risk of complications associated with prolonged critical illness, anesthesia, and possibly continued cerebral injury resulting from the primary pathology. These include, but are not limited to, progressive brain atrophy, as well as cardiovascular, gastrointestinal, hepatic, hematologic, infectious, neuroendocrine, and ophthalmologic complications.[23,24]

Novel agents and approaches are being considered in the management of SRSE including the ketogenic diet,[25]

ketamine,[26–28] lidocaine,[29] hypothermia,[30] vagus nerve stimulation,[31] transcranial magnetic stimulation,[32] electroconvulsive therapy,[33] and epilepsy surgery in selected cases,[34] among others. Of these interventions with limited evidence base, ketamine and the ketogenic diet appear to have most promise. Animal studies suggest a likely synergistic action of ketamine when combined with midazolam and valproic acid.[35]

Inhalational anesthetics may play a role in the management of RSE and SRSE, but are associated with hypotension and may carry a risk of MRI changes with prolonged exposure,[36] the clinical significance of which is uncertain. A preliminary report suggests that inhalational anesthetics may be associated with higher rates of hippocampal signal abnormalities when compared to noninhalational anesthetics in RSE.[37]

Uncommon causes of SE and work-up of NORSE

At times, finding the cause of RSE is straightforward. Finding the cause of SRSE may not be, and there is a greater proportion of NORSE or encephalitis-like syndromes among patients with SRSE as compared to RSE or SE.[38] The common factors leading to RSE are well-known to most clinical neurologists, and include noncompliance with or recent alterations to antiseizure treatment, toxic–metabolic disturbances, alcohol withdrawal, acute or remote stroke, and brain tumor.[1,39,40] However, a patient's medical history and preliminary laboratory studies may not pinpoint the cause of RSE in a large minority of patients; these are cases of NORSE. Such cases often involve children or previously healthy young adults,[40] and a lengthy diagnostic investigation may at times arrive at a definitive diagnosis.[13] Uncovering the etiology of SRSE in such cases is useful both prognostically and therapeutically, and it helps families and treating medical teams to have an identified and clear cause. Unlike many other neurologic disorders, the management of SRSE initially focuses on symptom management in order to control seizures before diagnosing a specific underlying cause. Indeed, better patient outcomes with less accumulated disability are associated with the early control of GCSE and NCSE.[41] Delays in the management and control of SE are associated with longer convulsions and worse clinical outcomes.[42] However, even after seizures have been controlled, especially if they persist despite treatment with standard seizure control interventions, diagnosis and therapeutic management of the underlying causes of seizure must be a priority early in the hospitalization. In some cases, management of seizures may only be possible through the direct treatment of the underlying cause or causes. Increasingly, clinical research is demonstrating that the underlying cause of seizures is among the strongest determinants of patient outcomes subsequent to SE.[43,44] Therefore, reversible systemic causes, such as acute poisoning or withdrawal, may lead to less long-term disability or epilepsy among patients recovering from SE than for patients with undiagnosed causes or for etiologies that are difficult to treat, such as acute viral encephalitis. Furthermore, in some situations, SE may portend an underlying, undiagnosed neurologic disease, which may require further diagnostic and therapeutic interventions. Even in cases where no curative therapy can be provided, timely diagnosis provides opportunities for patient counseling and care planning.

Almost any neurologic disorder that implicates cerebral cortex can be the cause of seizures and SE. In fact, reports in the literature have revealed more than 180 causes of SE, both common and uncommon.[45] One approach is to divide these etiologies into 4 major categories (table 1): (1) inflammatory and autoimmune encephalitis, (2) uncommon infectious encephalitis, (3) genetic and congenital disorders, and (4) toxin, drug, and intervention-related disorders. Diagnostic algorithms have been proposed and may vary by geographic region and season (table 1).

Immunotherapies for autoimmune encephalitis and NORSE

If seizures and SE are the results of an autoimmune encephalitis, specific treatment of the underlying cause by immunotherapy in addition to antiseizure medications is often required. There is currently no evidence-based immunotherapy guideline for autoimmune encephalitis, but there are potential approaches based on personal experience and published observational evidence.[46] IV steroids, IV immunoglobulin (IVIg), and plasma exchange are common first-line options, most commonly steroids. By contrast with patients with peripheral autoimmune neurologic disorders, such as myasthenia gravis or Lambert-Eaton myasthenic syndrome, those with autoimmune encephalitis associated with autoantibodies often do not respond quickly to treatment,[47] and approaches that aim to decrease serum antibody levels (such as plasma exchange and IVIg) seem less effective. This might be explained by the intrathecal synthesis of antibodies that occurs in several types of autoimmune encephalitis, by the presence of an associated cellular immune response, or by delayed recovery of the more complex CNS. For instance, patients with LGI1 encephalitis[47] (characterized by infrequent intrathecal antibody synthesis) respond faster than patients with NMDA receptor encephalitis (characterized by very frequent intrathecal antibody synthesis).[46] Further, autoimmune encephalitides affecting the cell surface antigens, rather than extracellular antigens, are associated with better responses to immunotherapy.[46]

Rituximab, a B-cell-depleting humanized antibody, and cyclophosphamide, an alkylating agent with cytotoxic properties against T cells, are also used commonly. Rituximab and cyclophosphamide are often effective in patients who do not respond to first-line medications, at least in uncontrolled series.[45] Although rituximab and cyclophosphamide are increasingly being used in other types of autoimmune encephalitis, the available evidence is more limited.

A few case series suggest that immunotherapy might be efficacious in NORSE and its subtypes of FIRES, even when no identifiable inflammatory etiology has been identified. Indeed, retrospective data of patients with NORSE of unclear etiology despite exhaustive investigations show that this population is

Table 1 New-onset refractory status epilepticus (NORSE) etiologies and diagnostic checklist[a]

Within first 24 hours	
Initiate institution status epilepticus protocol (see below)	
Evaluate time to treatment and determine related prognostic risks	
Obtain thorough history, especially regarding immunosuppression, medications and supplements, recent travel to endemic areas, accidental or occupational exposure to animals, insects, pathogens, drugs, or toxins	
Consider treatment for possible HSV encephalitis	
Triage for appropriate cardiopulmonary support	
MRI brain with and without contrast, with MR angiogram and MR venogram head	
Initiate continuous EEG, regardless of cessation of convulsive activity	
Serologic/imaging tests for patients with NORSE (see below)	
Screen	**Disease/agent tested**
Infectious	Recommended in most or all patients
	Serologic: CBC, bacterial and fungal cultures, PPD placement, syphilis, HIV-1/2 immunoassay with confirmatory viral load if appropriate
	Serum and CSF: IgG and IgM testing for *Chlamydia pneumoniae*, *Bartonella henselae*, *Mycoplasma* pneumonia, *Coxiella burnetii*, *Shigella* species, and *Chlamydia psittaci*
	Nares: Respiratory viral DFA panel
	CSF: Cell counts, protein, and glucose, bacterial and fungal stains and cultures, PCR for HSV1, HSV2, VZV, EBV, HIV, Syphilis testing, PCR for tuberculosis
	Recommended in immunocompromised patients
	Serologic: IgG *Cryptococcus* species, IgM and IgG *Histoplasma capsulatum*, IgG *Toxoplasma gondii*
	Sputum: Molecular test for tuberculosis
	Serum and CSF: Toxoplasma IgG
	CSF: Eosinophils, silver stain for CNS fungi, PCR for JC virus, CMV, EBV, HHV6, EEE, enterovirus, influenza A/B, HIV, WNV, parvovirus, Listeria antibody, measles (rubeola)
	Stool: Adenovirus PCR, enterovirus PCR
	Recommended if geographic/seasonal/occupational risk of exposure
	Serum buffy coat and peripheral smear
	Lyme EIA with IgM and IgG reflex
	Send further serum and CSF samples to CDC Arbovirus Diagnostic Laboratory, CSF and serum *Rickettsial* disease panel, *Flavivirus* panel, *Bunyavirus* panel
	Serum testing for *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Baylisascaris procyonis*
	Other
Autoimmune/ paraneoplastic	Recommended
	Serum and CSF paraneoplastic and autoimmune epilepsy antibody panel, to include antibodies to LGI-1, CASPR2, Ma2/TaDPPX, GAD65, NMDA, AMPA, GABA-B, GABA-A, glycine receptor, anti-Tr, amphiphysin, CV-2/CRMP-5, neurexin-3α, adenylate kinase, anti-neuronal nuclear antibody types 1/2/3 (Hu, Yo, and Ri), Purkinje cell cytoplasmic antibody types 1, 2
	Serologic: Also send ANA, ANCA, antithyroid antibodies, anti-dsDNA, ESR, CRP, ENA, SPEP, IFE, antibodies for Jo-1, Ro, La, Scl-70; check RF, ACE, anti-tTG, anti-endomysium antibodies, cold and warm agglutinins
	Optional: Consider storing extra frozen CSF and serum for possible further autoimmune testing in a research laboratory
Neoplastic	Recommended: CT chest/abdomen/pelvis, scrotal ultrasound, mammogram, CSF cytology, flow cytometry, pelvic MRI
	Optional: Bone marrow biopsy, whole body PET-CT, cancer serum markers

Continued

Table 1 New-onset refractory status epilepticus (NORSE) etiologies and diagnostic checklist[a] *(continued)*

Screen	Disease/agent tested
Metabolic	Recommended: Urea/creatinine, LDH, urinalysis with microscopic urinalysis, liver function tests, electrolytes, calcium/magnesium/phosphate, ammonia, porphyria screen (spot urine)
	Consider: Vitamin B_1 level, B_{12} level, folate, lactate, pyruvate, creatine phosphokinase, troponin; tests for mitochondrial disorder (lactate, pyruvate, MR spectroscopy, muscle biopsy), tests for macrophage activation syndrome/hemophagocytic lymphohistiocytosis (serum triglycerides and sIL2-r)
Toxicologic	Recommended: benzodiazepines, amphetamines, cocaine, fentanyl, alcohol, ecstasy, heavy metals, synthetic cannabinoids, bath salts
	Consider: Extended opiate and overdose panel, lysergic acid diethylamide, heroin, phencyclidine, marijuana
Genetic	Consider: Obtain genetics consult, if possible; genetic screens for myoclonic epilepsy with ragged red fibers, mitochondrial encephalomyopathy lactic-acidosis and stroke-like episodes, POLG1, and very long chain fatty acid screen; consider ceruloplasmin and 24-hour urine copper
At 48 hours	
Assess returned testing, initiate appropriate treatments	
If patient continues to have refractory status epilepticus or coma, transfer to higher level of care for appropriate further treatment of NORSE at a center with experience in these cases, including continuous video/EEG monitoring.	
At 72 hours	
Consider initiation of 5-day course of high-dose parental corticosteroids. Transfer to higher level of care for consideration of IV immunoglobulin, plasmapheresis, or further immunomodulatory therapy if no clear diagnosis, if still having seizures, if no continuous EEG monitoring available, or if still comatose.	

Abbreviations: ACE = angiotensin-converting enzyme; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; CASPR2 = contactin-associated protein-like 2; CBC = complete blood count; CMV = cytomegalovirus; CRMP = collapsing-response mediator protein; CRP = C-reactive protein; DFA = direct fluorescent-antibody assay; EBV = Epstein-Barr virus; EEE = Eastern equine encephalitis; EIA = enzyme immunoassay; ENA = extractable nuclear antigen; ESR = erythrocyte sedimentation rate; GABA = gamma-aminobutyric acid; GAD = glutamic acid decarboxylase; HHV = human herpesvirus; HSV = herpes simplex virus; IFE = immunofixation electrophoresis; Ig = immunoglobulin; LGI-1 = leucine-rich, glioma-inactivated 1; MR = magnetic resonance; PPD = purified protein derivative; RF = rheumatoid factor; SPEP = serum protein electrophoresis; TG = transglutaminase; VZV = varicella-zoster virus; WNV = West Nile virus.
[a] Adapted from norseinstitute.org/, with permission. Please see that website for the full table, as well as other helpful tables including zoonotic/geographic tips, diagnostic clues to specific organisms or syndromes, and list of medications, drugs, and toxins that can cause status epilepticus. Table 1 was developed by the NORSE Institute Medical Advisory Board in collaboration with Dr. Shivani Goshal.

less likely to receive immunotherapy and have the poorest outcomes.[13] It is unclear whether poor outcome is related to lack of identified etiology vs a lack of timely therapy. Anakinra is an interleukin-1 receptor antagonist that has been reported to reduce the levels of inflammatory cytokines in the CSF of children with FIRES, thereby helping to terminate SE.[48] Limited data to support the use of anakinra currently exist and future studies will help shed light on the safety and efficacy of this agent in NORSE and FIRES.

Infectious causes of new-onset SE are varied and may depend on the pathogenic agents endemic to the region. Infectious causes should be sought early in the treatment course since delays to treatment may lead to worse outcomes, as in herpes simplex encephalitis, and identification of a particular pathogen will help target appropriate therapies. Genetic and congenital causes of NORSE are uncommon, but should also be sought. Identification of a genetic cause may or may not change acute therapies, but when it does not it will still allow for appropriate discussions regarding prognosis and counseling of other family members. Identification of a causative toxic or drug exposure will also guide acute therapies and may suggest that alternative therapies not frequently used in the management of SE, such as acute hemodialysis, are necessary.

Communication with decision-makers and family

Outcomes in NORSE and SRSE are variable. While reports of very good clinical outcomes after prolonged SRSE exist,[43] many cases result in severe morbidity and mortality. Given that clinical outcomes are often very poor, it is important to share this information with the patient's substitute decision-maker and family. It is crucial to attempt to balance hope and realistic outcome information while conveying updates to family members and caregivers; however, the decision-makers need to be aware of all possible outcomes. The timing of prognostic discussions is unclear and has not been studied. The timing is particularly challenging in NORSE because no clear etiology for RSE has been identified, investigations may still be underway many weeks into patient management, and as of yet there are no robust prospective NORSE-specific data to guide the health care team regarding the appropriate duration of care and likely outcomes. The latter is particularly challenging among care providers within the health care team since the lack of evidence-based prognostic information can lead to vastly different points of view regarding the appropriateness of prolonged aggressive medical care vs medical futility. Such disagreements among health care providers can lead to discord within the health care team that requires skillful management in

order to maintain a professional relationship with the patient's family. Several case reports have now shown survival and resolution of SRSE after 6 months of treatment or longer.[43]

A referral to palliative care services may be also considered. Palliative care teams lend support, not only to the substitute decision-maker and family, but also to the health care team.[49] The skill set of palliative care teams can be leveraged throughout the disease trajectory, alongside aggressive therapies with curative potential, and not solely when all hope for meaningful recovery has been lost. They are highly skilled at communication and may be able to facilitate discussions throughout the patient's trajectory of care. While there is no evidence to support the appropriate timing for palliative care involvement, it is likely that a consultation earlier in the hospitalization would allow for improved relationship-building between the health care team and substitute decision-makers, for enhanced assessment of the patient's values, for ongoing support of the family during difficult times, and for smoother transitions in the goals of care should the need arise.[49]

Preventative measures

Finally, preventative measures, with identification of risk factors, and more widespread use and availability of first responder rescue medication, and potentially earlier treatment and treatment escalation, may also tentatively be able to reduce morbidity and mortality.[42]

Future directions

We propose a roadmap for future collaborative research investigating NORSE in the following 4 domains: (1) clinical features, etiology, and pathophysiology; (2) treatment and patient management; (3) adult and pediatric evaluation and management approaches; and (4) public advocacy, professional education, and family support (table 2). International collaboration and multicenter research will be crucial in achieving these goals.

Clear and consistent definitions may provide a framework for future research investigating the clinical features and pathophysiology of NORSE and may help to decrease the heterogeneity of data being studied. Consensus definitions for NORSE and FIRES were recently proposed and published following a satellite symposium at the 2017 London–Innsbruck Status Epilepticus Symposium in Salzburg, Austria.[12] Early retrospective studies have attempted to describe the clinical profile of NORSE and to catalogue the most frequent etiologies. Further prospective studies are necessary in order to validate retrospective data and to eliminate the biases and other limitations inherent to retrospective research. Large multicenter prospective studies will further investigate the clinical, EEG, genetic, neuroimaging, and biological profile of NORSE. Ongoing retrospective research may be required, in addition to prospective studies, as additional etiologies for NORSE become known in order to generate testable hypothesis for further scrutiny. For example, retrospective research has identified autoimmune encephalitis, paraneoplastic encephalitis, and infection-related encephalitis as the most common etiologies that are eventually identified as causative in patients presenting with NORSE.[13] With this in mind, future research will need to investigate specific patient characteristics that may suggest one of these etiologies in the early days of hospitalization before positive diagnostic tests are available because these patients are likely to benefit from different management approaches. Studies will also need to focus on whether patients with a likely autoimmune etiology for NORSE will benefit from particular types of immunotherapy early in the disease trajectory and what treatment regimens will be most effective.

Currently, detailed prospective observational studies are underway or being launched by the Critical Care EEG Monitoring Research Consortium (acns.org) and the Pediatric Status Epilepticus Research Group (pserg.org), among others. Data sharing worldwide will enhance the understanding of NORSE on a clinical basis and development of laboratory models and detailed biomarker research will improve the pathophysiologic understanding of NORSE. More information can be found at norseinstitute.org.

The treatment strategies currently applied in the management of NORSE are based on expert opinion and are largely extrapolated from treatments used in RSE and autoimmune encephalitis. Data to support the preferred selection of antiepileptic agent and if and when immunomodulatory therapies are indicated do not exist. Comparative safety and efficacy analysis needs to be done for antiepileptic agents, anesthetic agents, and immune therapies in NORSE. While prospective controlled trials will be ideal to investigate these agents, retrospective analysis of existing databases will help to solidify the most appropriate trial designs in the future. Promising agents include further investigation of the safety and efficacy of ketamine (likely in combination with benzodiazepines), the ketogenic diet and anakinra in NORSE, among other immunomodulatory therapies.

Until recently, NORSE and FIRES were often thought of as separate entities, largely based on age of the patient (pediatric for FIRES). Based on the new definitions, there is no age cutoff for either diagnosis and either an adult or child may present with NORSE or the subcategory (with preceding fever) of FIRES. Retrospective databases of NORSE and FIRES exist. Comparing data from these databases will shed further light on similarities and differences between NORSE and FIRES in children and adults, and help guide further prospective randomized controlled studies.

Public advocacy, professional education, and family support will be necessary to raise awareness of NORSE as a rare syndrome. NORSE is now relatively well-recognized among experts in epilepsy and neurocritical care. However, the syndromes are not as well-recognized in general neurology and general critical care or within the general public. Improved awareness of NORSE will allow for early recognition and management of NORSE both within and outside

Table 2 Proposed roadmap for future collaborative research investigating new-onset refractory status epilepticus (NORSE)

	Clinical and physiopathology	Treatment	Children vs adults	Public advocacy, professional education, family support
Objectives	Describe the clinical syndrome Determine the causes of NORSE Improve diagnostic and prognostic accuracy	Determine the optimal treatment for NORSE ASMs and anesthetics Immune therapies Critical care, complications Long-term rehabilitation	Define the relationship between NORSE and FIRES	Raise awareness among physicians, families, and funding agencies Educate
2018	Prospective registry of NORSE/FIRES clinical data, database of EEG and MRI and biosamples (DNA, serum, CSF, brain tissue) Preliminary analysis of samples CSF: cytokine profiling, antibodies Serum: antibodies, cytokine and autoimmune profiling DNA: whole exome sequencing, targeted gene panel MRI: etiology and outcome	Prospective observational study of RSE (including NORSE) Analysis of retrospective data on immune therapies	Retrospective analysis of FIRES from the pSERG database and comparison with the retrospective NORSE database	Increased visibility on the Web Sessions at professional meetings Reviews and expert opinion articles
2018–2021	Analysis of the clinical data Analysis of samples: CSF: cytokine profiling, antibodies Serum: antibodies and autoimmune profiling DNA: whole exome sequencing MRI: etiology and outcome	Comparative efficacy and safety analysis of first-line anesthetic drugs Comparative efficacy and safety analysis of rescue anesthetic drugs Comparative efficacy and safety analysis of immune therapies	Comparison of children and adult cases in the prospective database	Increased visibility on the Web Sessions at professional meetings (special interest group at professional epilepsy societies) Develop patient education materials
2020+	Worldwide registry and biobank Animal model of NORSE (autoimmune/inflammatory SE) Development of biomarkers for early diagnosis and prognosis of NORSE	Prospective randomized control trials in SE of inflammatory origin (immune therapies) and in RSE (anesthetics)	Prospective randomized control studies	Increased visibility on the Web Enhanced information available for families and public

Abbreviations: ASM = antiseizure medication; FIRES = febrile infection-related epilepsy syndrome; pSERG = pediatric status epilepticus research group; RSE = refractory status epilepticus; SE = status epilepticus.

of tertiary care medical centers. Further, increased awareness of NORSE within the medical and public spheres as a condition with important neurologic sequelae in survivors will increase the urgency to support and fund further research and to create support networks for families and survivors. This type of family-driven progress has already led to creation of the Norse Institute (norseinstitute.org), the Salzburg symposium that led to consensus definitions,[12] a funded multicenter, prospective observational trial, and an international family registry (see the norseinstitute.org for details).

Discussion

Early challenges in advancing research investigating NORSE were numerous. It had been difficult to study NORSE in a systematic manner given the heterogeneity of definitions and etiologies and the relatively small number of patients seen in any single center. International collaborative research networks are necessary (and now exist) in order to advance current knowledge of the clinical features and pathophysiology and treatment of NORSE. These efforts are just beginning now. Public advocacy, professional education, and family support will be necessary to raise awareness and promote funding research for this uncommon clinical presentation; these initiatives are underway as well, though further progress is urgently needed.

Author contributions

Dr. Gofton: participated directly in the conception, drafting, and editing of the manuscript. Dr. Gaspard: participated directly in the conception, drafting, and editing of the manuscript. Dr. Hocker: participated directly in the conception and editing of the manuscript. Dr. Loddenkemper: participated directly in the conception and editing of the manuscript. Dr. Hirsch: participated directly in the conception and editing of the manuscript.

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New onset refractory status epilepticus research: What is on the horizon?

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