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Refractory and Super-Refractory Status Epilepticus—an Update

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Abstract Status epilepticus is a medical emergency with a high mortality. Early recognition and initiation of treatment leads to a better response and may improve outcomes. Refractory status epilepticus is defined as recurrent seizure activity despite two appropriately selected and dosed antiepileptic drugs including a benzodiazepine. The term "super-refractory status epilepticus" was introduced during the London–Innsbruck Colloquium on status epilepticus in 2011 and refers to status epilepticus that continues or recurs 24 h or more after the initiation of treatment with anesthetic antiepileptic drugs. This includes cases in which seizure control is attained after induction of anesthesia but recurs on weaning the patient off the anesthetic agent. This article reviews the approach to refractory status epilepticus and super-refractory status epilepticus, including management as well as common pathophysiological causes of these entities.

Keywords Super refractory · Status epilepticus · EEG · Anesthesia · Critical care

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Introduction

Status epilepticus (SE) is defined as a seizure that lasts longer than 5 min or two or more seizures without return to the neurological baseline in between. Refractory SE (RSE) is defined as ongoing seizures despite two appropriately selected and dosed antiepileptic drugs (AEDs) including a benzodiazepine. In the only prospective study (of RSE) to date, approximately 23 % of patients admitted to the hospital with SE failed to respond to first-line and second-line agents and, thus, were considered to have RSE [1]. Retrospective studies suggest that 31-43 % of SE episodes become refractory [2–4]. The term "super-refractory status epilepticus" (SRSE) was first introduced during the London–Innsbruck Colloquium on SE held in Oxford in April 2011, and was defined [5] as continuous or recurrent seizures lasting 24 h or more following initiation of anesthetic medications, including cases in which seizure control is attained after induction of anesthetic drugs but recurs on weaning the patient off the anesthetic agent [6].

The true incidence of SRSE is unknown. The prospective study by Novy et al. [1] provides the closest estimate of SRSE to date, with treatment with first-line and second-line agents reported to have failed in 9 % of SE episodes (12 of 128), and these required coma induction for treatment. However, as with most studies assessing SE, persistence or recurrence of seizures beyond 24 h of anesthetic treatment is not documented. Therefore, some patients in this series may not have met the proposed criteria for SRSE.

The epidemiology of RSE and SRSE is unique in that refractory seizures are more likely to develop as a result of acute brain injury rather than as a consequence of chronic epilepsy [1, 3]. In other words, SE is more likely to become refractory in patients with a severe brain insult such as trauma, infection, or stroke. RSE may also occur in previously healthy patients in whom SE develops de novo without a clear precipitant, referred to as new-onset RSE, or NORSE [7]. The authors who proposed this term described it as a disease entity affecting a homogeneous group of patents. It is more likely that as medical knowledge advances, we will find that although the clinical presentation is similar, the underlying cause may actually be quite heterogeneous.

SE can also be described as either convulsive or nonconvulsive depending on the clinical presentation. Convulsive SE is easily recognized and typically receives early and immediate treatment. There are two general phenotypes of nonconvulsive SE (NCSE). The first is the "wandering confused" patient presenting with inattention, behavioral changes, automatisms, and abnormal involuntary movements with or without focal neurological deficits. The second is the patient with acute brain injury who has a decreased level of consciousness or coma, sometimes with a clinically subtle feature such as tonic eye deviation or rhythmic muscle twitches (subtle SE) or with no identifiable clinical correlate at all (electrographic SE). Most studies of RSE and SRSE include both convulsive SE and NCSE, and these are often variably defined. Furthermore, convulsive SE often transitions to NCSE, which clouds distinctions even further. However, the type of SE likely influences the outcome, so distinctions are important. For instance, excitotoxic damage is higher risk in convulsive SE than in some forms of NCSE. Convulsive SE also stresses other organ systems, including cardiac and pulmonary systems, from generalized convulsions potentially causing aspiration pneumonia, pulmonary edema, stress-induced cardiac injury, or myocardial ischemia, as well rhabdomyolysis and renal failure. On the other hand, NCSE, which can be detected only with electroencephalography, is often associated with considerable delay in detection and initiation of treatment, and subsequently tends to be more medically refractory.

To discuss pharmacological management of SE, it is important to understand how seizures become refractory. Although the molecular pathophysiology of SE is complex and beyond the scope of this review, several principles must be kept in mind. First, seizures are sustained by either imbalance of neuronal excitation and inhibition or failure of normal inhibitory mechanisms [8]. γ-Aminobutyric acid (GABA) is the commonest *inhibitory* neurotransmitter, preventing neurons from excess excitation by activation of the $GABA_A$ receptor, and glutamate is the commonest *excitatory* neurotransmitter, and mediates excess excitation via the *N*-methyl-D-aspartate (NMDA) receptor. Second, SE can become self-sustaining, with neuronal damage and pharmacoresistance becoming apparent after 30 min of continuous seizure activity in both experimental and clinical studies [9–13]. As SE continues, there is a progressive development of pharmacoresistance to benzodiazepines [10], and NMDA receptor blockers such as ketamine can remain effective late in the course of SE [14]. This is likely explained by intensified "receptor trafficking," in which the number of glutaminergic receptors at the cell surface increases and the number of GABA receptors decreases [15–17], leading to a reduction in GABAergic activity. There are likely many other mechanisms contributing to the development of RSE and SRSE, which may each be potential targets of therapy. Reported mechanisms include (1) mitochondrial failure or insufficiency [18], (2) inflammatory processes [19, 20] resulting in decreased integrity of the blood–brain barrier and higher potassium levels [21, 22], and (3) changes in gene expression [23].

Benzodiazepines have been well established as first-line treatment for SE [24, 25]. There has been a paucity of studies evaluating the efficacy of second-line treatments, therefore the Established Status Epilepticus Treatment Trial (ClinicalTrials.gov identifier NCT01960075) has been designed to determine the comparative efficacy of three AEDs widely used as second-line agents. The trial will compare fosphenytoin, levetiracetam, and valproic acid in benzodiazepine-refractory SE [26].

Optimum management of SE that continues despite appropriate use of first-line and second-line agents is more controversial and lacks the same strength of evidence, hence the subject of this review. We will begin with a representative case presentation, discuss the evaluation, management, and outcomes of patients with RSE and SRSE, and close with a look at treatment options currently in the pipeline.

Case Presentation

A 29-year-old woman had a brief diarrheal illness followed 1 week later by fevers, nausea, and a feeling as though her "skin was on fire." Facebook posts and texts indicated that she did not feel like herself and that "something's wrong." Several days later, she learned she was 5 weeks pregnant and then had a convulsive seizure. Within 40 min she experienced two additional convulsive seizures. She was taken to the hospital, where medical personnel observed repetitive focal seizures manifested as a fixed stare with right head turning, right gaze deviation, right facial twitching, and right arm tonic posturing for 1-2 min. The seizures were followed by brief postictal somnolence with some purposeful movements and left gaze deviation. Examination revealed no nuchal rigidity, rashes, or startle response. Neurological examination revealed no focal features. Following a bolus of midazolam, she could briefly state her name and identify her sister, but this improvement was transitory. She was given lorazepam followed by fosphenytoin load. However, focal seizures that often evolved into convulsions continued and resulted in a persistent decline

in her level of consciousness. Electroencephalography was performed, and revealed the presence of focal electrographic seizures arising independently from both the left and the right temporal regions (Fig. 1a). Because of the failure of first-line and second-line agents, she met the criteria for RSE and was intubated and propofol infusion was started. Because the patient was young, it was felt that using high-dose propofol or propofol for a long duration would put the patient in danger of propofol-infusion syndrome (PRIS). This combined with the safety of phenobarbital during pregnancy resulted in the switching from propofol to phenobarbital bolus and infusion. Recurrence of both clinical and electrographic seizures continued during attempts to wean the patient off propofol. A noncontrast CT scan of the head was unremarkable. Analysis of cerebrospinal fluid (CSF) revealed normal glucose concentration of 61 mg/dl, protein concentration of 22 mg/dl [15–45], per microliter for both whites and red blood cells, no cryptococcal antigen, a negative Venereal Disease Research Laboratory test, no anti-NMDA antibody, no histoplasma antibody, a negative Lyme disease test, and negative findings for the paraneoplastic antibodies ANNA-1, ANNA-2, ANNA-3, AGNA-1, CRMP-5, PCA-1, PCA-2, PCA-Tr, voltage-gated potassium channel (N-type, P/Q-type) antibodies, muscle acetylcholine receptor binding antibody, and ganglionic acetylcholine receptor antibody. Arbovirus panels for IgM and IgG were negative for West Nile virus, California (La Crosse) encephalitis virus, eastern equine encephalitis virus, St Louis encephalitis virus, and western equine encephalitis virus antibodies. The legionella antibody test was negative. Tests for *Brucella*, *Ehrlichia*, and Q fever antibodies were negative. Polymerase chain reaction was negative for HIV-1 RNA in serum, and negative for herpes simplex virus, cytomegalovirus, and varicella–zoster virus in CSF.

Brain magnetic resonance imaging (MRI) showed hyperintensities on fluid-attenuated inversion recovery and diffusion-weighted imaging without definite restricted diffusion in the bilateral uncus, amygdala, and hippocampus (Fig. 1b). The patient was treated with high-dose methylprednisolone owing to a clinical suspicion of autoimmune limbic encephalitis after repeated attempts to wean her off AEDs, including anesthetic agents, had failed. On day 27, anesthetic taper was successful, and she began following commands. However, on day 33 she experienced recurrent focal and convulsive seizures necessitating reinitiation of anesthesia. Ultimately, she was liberated from anesthesia and mechanical ventilation by day 48, and was ambulatory on discharge from the hospital. Extensive serum, CSF, and imaging evaluation failed to reveal a cause. Medical complications included hypotension requiring vasopressor support, ventilator-associated pneumonia, tracheostomy and percutaneous gastrostomy tube placement, drug rashes, a spontaneous abortion necessitating a dilatation and curettage procedure, and intensive-care-unit-acquired weakness.

Evaluation of the Patient with RSE and SRSE

Diagnostic evaluation should occur promptly and simultaneously with treatment. Identification and correction of the underlying precipitant may be necessary for control of SE. Investigation begins with a rapid, focused interview of any people who witnessed the onset of events (often this history is taken by emergency medical personnel). Examination is very limited in convulsive SE; however, after the convulsive phase and in cases of NCSE, nuchal rigidity or focal neurological deficits may become apparent. Patients should undergo a noncontrast CT scan, a chest X-ray to evaluate them for aspiration, and an electrocardiogram. The electrocardiogram should be obtained initially to evaluate the patient for the presence of ST-T wave changes suggestive of cardiac injury and to obtain a baseline QTc interval prior to additional drug administration. Laboratory tests including blood glucose concentration, complete blood count, basic metabolic panel, and calcium, magnesium, troponin, and AED levels are required in all patients. At this junction, the commonest causes of SE can be identified (Table 1).

When the cause of SE is not found, other laboratory investigations should be considered, including liver function tests and ammonia level, arterial blood gas level, and a toxicology screen, including a screen for alcohol. For an exhaustive list of reported causes of SE that may be used to guide evaluation, see Tan et al. [19]. A lumbar puncture for CSF analysis must be performed in immunocompromised patients, patients with a history and/or examination findings suggestive of central nervous system infection, and any patient with an unidentified cause of SE. CSF should be sent for analysis of blood cell count, glucose concentration, protein concentration, Gram staining, and select bacterial and viral cultures as well as polymerase chain reaction studies depending on the age, comorbidities, and social history of the patient. A thyroperoxidase antibody test can be performed if Hashimoto's encephalopathy is suspected, along with thyroid tests. If the initial CSF studies are not suggestive of infection and the cause has still not been identified, additional CSF analysis should be considered, including cytology and an autoimmune panel including anti-NMDA receptor antibodies and voltage-gated potassium channel antibodies. Other tests such as GAD-65 antibody and comprehensive paraneoplastic panels can be tested if there is concern about CNS involvement or limbic encephalitis respectively. In our patient case these tests were negative. Patients in whom a cause has not been identified should also undergo brain MRI including use of gadolinium contrast agent assuming there are no MRI contraindications such as a pacemaker or renal failure. In some cases a cause is not identified despite an extensive evaluation. In these patients, further testing to evaluate the patient for occult malignancy may be indicated as RSE is known to be a common presenting symptom of many paraneoplastic syndromes. Continuous

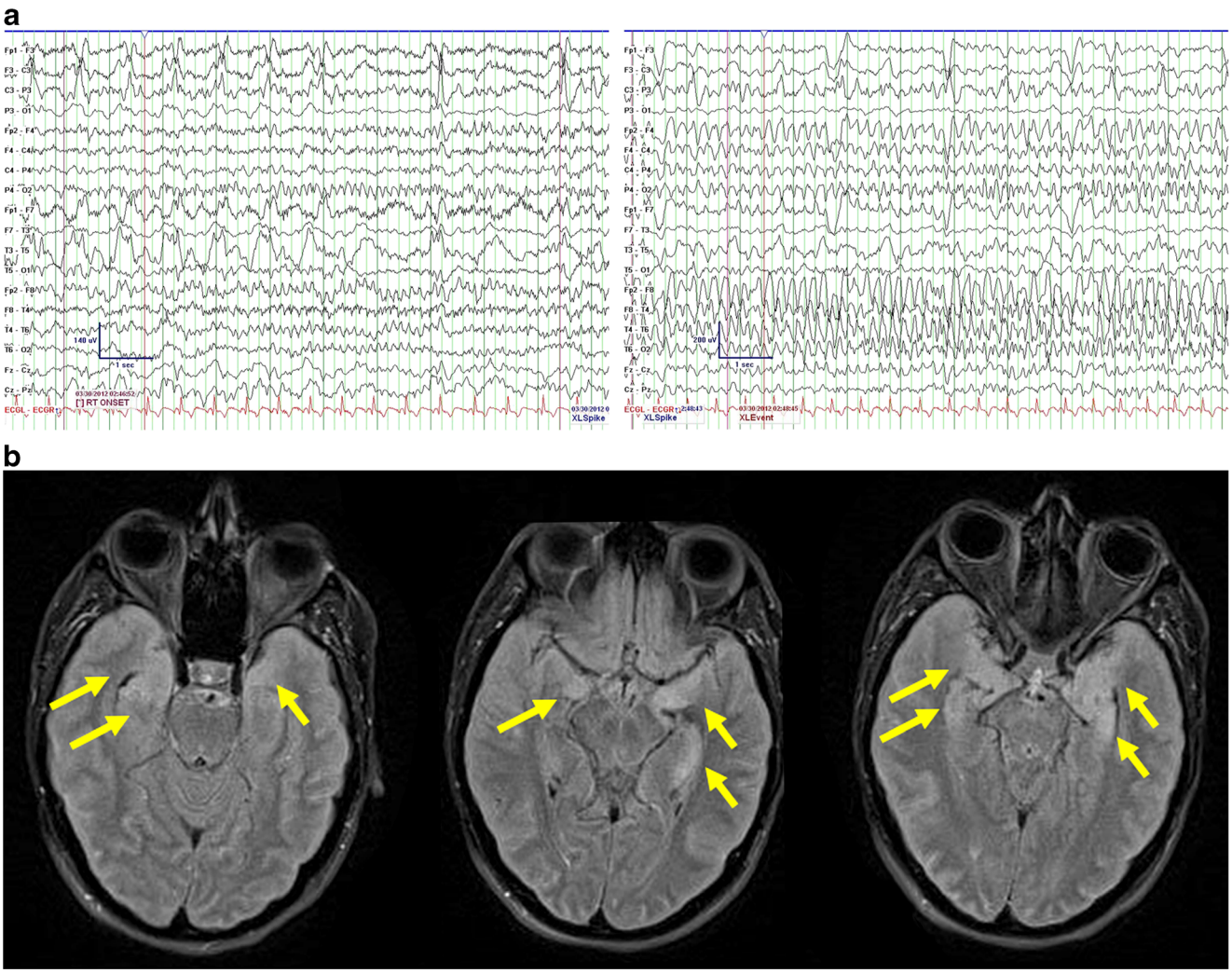

Fig. 1 **a** Evolution of fast frequencies over the right hemisphere, particularly the right temporal channels, consistent with a clear electrographic seizure. Note concurrent lateralized periodic discharges over the left hemisphere. **b** Hyperintensities of the uncus, amygdala, and hippocampus bilaterally on fluid-attenuated inversion recovery imaging

electroencephalography is generally initiated within 1 h of the onset of SE for detection of subtle clinical or subclinical electrographic seizures. In addition, there are early data suggesting that specific EEG patterns can be associated with specific causes such as the extreme delta brush seen in cases of anti-NMDA receptor encephalitis [46].

Management of the Patient with RSE and SRSE

The management of a patient with RSE requires a three-pronged approach in which the clinician simultaneously (1) achieves seizure control, (2) identifies and treats the underlying cause, and (3) prevents, identifies, and manages systemic complications [27].

Seizure control should be achieved rapidly in convulsive SE to prevent excitotoxicity-mediated cell death [28, 29], and systemic complications. Thus, when SE has been refractory to benzodiazepines and a second-line AED such as valproic acid or fosphenytoin, the patient should be considered for intubation using midazolam, propofol, or ketamine for induction and an anesthetic infusion with midazolam, propofol, or ketamine should be started. Continuous EEG monitoring is required at this point as anesthesia should be titrated until there is cessation of all electrographic seizures and/or the burst-suppression pattern. Most experts agree that aborting electrographic seizures is the primary goal in managing SE and RSE (Neur critical Care Society guidelines, class 1, level B). However, the ability of electroencephalography to clearly differentiate between ictal and interictal patterns is not always straightforward in this setting. Periodic discharges are often present (either lateralized or generalized), and can demonstrate fluctuation or subtle evolvement as well as superimposed fast or rhythmic activity, which can make the distinction between ongoing SE and the transition to the interictal or postictal state uncertain. Therefore, titration of the anesthetic agent to a

Table 1 Causes of refractory and super-refractory status epilepticus

Acute brain injury
• Cerebrovascular disease
• CNS infection
○ Bacterial meningitis
○ Viral encephalitis
○ Cerebral toxoplasmosis
○ Tuberculosis
○ Neurocysticercosis
○ Cryptococcal or other fungal meningitis
○ Abscess
• Intracranial tumor
• Traumatic brain injury
• Hypoxic–ischemic brain injury[a]
Intoxication syndromes, or withdrawal syndromes, including low levels of AEDs or withdrawal
Systemic infection or metabolic disturbance
• Sepsis
• Electrolyte imbalances, glucose imbalance, hyperammonemia
Chronic processes
• Remote brain injury (i.e., encephalomalacia due to ischemic stroke, hemorrhage, or trauma)
Uncommon causes[b]
• Autoimmune disorders
• Mitochondrial disorders
• Uncommon infectious diseases
• Uncommon genetic diseases
• Drugs and toxins
Cryptogenic (NORSE)

AEDs antiepileptic drugs, *CNS* central nervous system, *NORSE* new-onset refractory status epilepticus

[a] Hypoxic–ischemic brain injury is often excluded from studies of refractory and super-refractory status epilepticus, and aggressive treatment of status epilepticus in this setting is controversial but may be reasonable in patients undergoing therapeutic hypothermia who have preserved brainstem reflexes, a reactive EEG background, and preserved cortical N20 responses on somatosensory evoked potentials [62].

[b] See Tan et al. [19]

burst-suppression pattern should be considered when faced with these particular EEG patterns that occur in between or subsequent to periods of definite electrographic SE. Continuous EEG monitoring has also revealed that seizures may still arise from a burst-suppression pattern, so careful ongoing monitoring is required [30]. However, when rare electrographic seizures continue to recur, it is uncertain if these isolated electrographic seizures result in significant additional neuronal injury. Therefore, the risks of escalating doses of anesthesia to attain an isoelectric or flat EEG background in order to suppress rare isolated seizures may not be justified. A burst-suppression pattern is typically maintained for 24 h before initiating a slow, controlled reduction in anesthesia with concurrent EEG monitoring to detect recurrent seizures. Evidence to guide the rate at which the patient should be weaned off the anesthetic agent or the frequency of such weaning after the first weaning fails is lacking.

The risk of prolonged anesthesia is well known, but has only recently come under scrutiny, calling into question the current practice of using anesthesia for weeks or even months in some patients with SRSE. Systemic complications associated with RSE and SRSE are complex and primarily relate to prolonged immobility, anesthetic use, immunosuppression, and exposure to an intensive care unit environment [6, 31, 32]. Kowalski et al. [33] compared patients with RSE who required third-line AEDs with those who did not, and found that patients requiring third-line AEDs were at significantly higher risk of poor outcome or death. This is not surprising as it has been well documented that RSE has a higher mortality compared with SE [1–4, 13]. However, Drislane et al. [34] showed that there is a loss of prognostic utility after several hours in RSE. Kowalski et al. inferred from these findings and the results of their retrospective analysis that the use of third-line AEDs may predict outcome in RSE independently of the duration and cause of SE. More recently, Sutter et al. [35] published a retrospective review of 171 patients with RSE and showed that third-line treatment with an anesthetic agent conferred a threefold higher relative risk of death that was independent of the duration and severity of SE or underlying medical conditions compared with patients treated with a third-line nonanesthetic AED. After adjustments had been made for whether or not SE was refractory, the association of intravenous anesthesia with outcome became insignificant. These studies serve as a reminder that initiation of intravenous anesthesia for treatment of SE must not be taken lightly. Certainly, rapid seizure control must be achieved in convulsive SE. In NCSE the evidence for neuronal injury due to excitotoxicity may be less robust, and the systemic complications directly resulting from seizures are fewer [36, 37]. Thus, in these cases it is reasonable to consider further nonanesthetic AEDs prior to initiating intravenous anesthetic therapy.

There are no controlled or randomized trial data to aid in selection of the appropriate anesthetic agent, so the choice is dependent on the individual patient profile and physician preference. Single-center retrospective studies and a meta-analysis comparing midazolam, propofol, and pentobarbital [2] failed to show a short-term benefit of one anesthetic over the others. Historically, barbiturates have been favored, but currently midazolam and propofol are commonly used as the initial anesthetic agent (Table 2). In the end, the choice of the anesthetic agent is probably less important than the goal of achieving rapid seizure control.

Midazolam binds and enhances the action of the $GABA_A$ receptor. Its advantages include a rapid offset and extensive clinical experience with prolonged infusion in the setting of critical illness. Its disadvantages include tachyphylaxis and cardiovascular depression sometimes necessitating vasopressor support. Challenging the idea that anesthetics themselves contribute significantly to mortality, Fernandez et al. [38] performed a retrospective comparison of high-dose and low-

Table 2 Anesthetic doses for refractory status epilepticus

Drug	Bolus	Infusion/maintenance rates
Midazolam	0.2 mg/kg	0.1–0.4 mg/kg/h
Propofol	1-2 mg/kg	30–200 μg/kg/min
Pentobarbital/thiopental	2–5 mg/kg	1–5 mg/kg/h
Ketamine	0.5–4.5 mg/kg	Up to 5 mg/kg/h

With the exception of ketamine, other anesthetic agents are negative inotropes on cardiac function, so patients should have their blood pressure monitored frequently, including consideration of an arterial line

dose midazolam protocols used during separate periods at a single center and found high-dose midazolam to be associated with lower seizure recurrence after discontinuation of anesthesia and lower mortality at hospital discharge. There was a higher incidence of hypotension, but this did not influence outcome.

The primary antiepileptic action of propofol is unknown, but probably results from modulation of the $GABA_A$ receptor. It has rapid clearance even after extended infusion, but like all anesthetic agents, is frequently associated with hypotension. Propofol has also demonstrated relative safety with prolonged use in the setting of critical illness. However, when used for many days or weeks at the high doses often required for control of RSE, PRIS may develop. PRIS manifests itself as a severe metabolic acidosis, rhabdomyolysis, renal failure, and cardiovascular collapse that may result in death. Caution should be exercised when using propofol for treatment of RSE, and prolonged use at high doses should be avoided. Parameters including the levels of blood gases ad serum levels of lactate, creatine kinase, and lipids can be monitored. However, once the cascade of PRIS begins, it may not be successfully reversed, and is often fatal [39].

Barbiturates are almost always effective in aborting SE, but are not associated with fewer withdrawal seizures on weaning. Thiopental is the barbiturate of choice in Europe, whereas in North America, pentobarbital is the available and preferred barbiturate for treatment of SRSE. It has a theoretical neuroprotective effect and acts by enhancing the action of the $GABA_A$ receptor. It lowers core body temperature, which may improve its antiepileptic potential, but with the untoward effect of suppressing immunity. The barbiturates have a very prolonged half-life, resulting in a prolonged recovery time [40], and drug interactions are myriad. Other complications of barbiturate anesthesia include (1) profound cardiovascular depression, (2) ileus, (3) decreased clearance of bronchial secretions leading to recurrent mucous plugging and pneumonia, and less commonly, (4) pancreatic and hepatic dysfunction, (5) propylene glycol toxicity, and (6) macroglossia. Because of the prolonged recovery time and associated systemic complications, barbiturates are often used as a second-line anesthetic agent.

Although there is less experience with ketamine, it is an attractive choice mechanistically owing to antagonism of NMDA receptors rather than binding to $GABA_A$ receptors. Ketamine may also have a neuroprotective effect [41], and its use makes physiological sense given the trafficking of NMDA receptors onto the cell membrane and the internalization of $GABA_A$ receptors during RSE. Ketamine is the only anesthetic agent which is not associated with significant cardiovascular depression, which can be a significant factor with the other agents. A retrospective review of ketamine administration in 11 patients with SRSE reported that ketamine was uniformly associated with improvement in hemodynamic stability as evidenced by the ability to wean patients off vasopressor support after transitioning to ketamine from an alternative anesthetic agent [42]. A retrospective multicenter study later showed that ketamine is relatively effective and safe in RSE, as it was thought to contribute to resolution of SE in 32 % of 60 episodes of RSE [43]. Response to ketamine was more likely when the drug was used as a third-line or fourth-line agent rather than late in the course of SRSE and when maintenance dosages were greater than 0.9 mg/kg/h. In this series, the hemodynamic response to ketamine was variable, with 35 % of patients requiring an increase in vasopressor support compared with 10 % in whom vasopressor support was reduced. Data from animal models are conflicting regarding the potential neurotoxicity of ketamine. Both neuronal protection and apoptosis have been reported [44]. Data in humans are confounded by heterogeneous SE causes and patient comorbidities, so the effect of prolonged use of intravenously administered ketamine on cognitive outcomes is unknown.

If SE recurs on weaning the patient off anesthesia, other approaches may be considered as adjunctive therapies in addition to reinitiating anesthesia, including mild hypothermia, immunomodulatory therapy, surgical resection of the epileptic focus, inhalational anesthetics, ketogenic diet, and various electrical and magnetic stimulation therapies [6]. Recently, several series supporting the use of various adjunctive therapies have been published. Three cases of RSE treated with transcranial magnetic stimulation suggest safety, feasibility, and possible efficacy of this modality [45, 47]. A series of ten patients with SRSE in whom the ketogenic diet was used found that nine of the ten patients experienced resolution of SE within 3 days of diet initiation [48], providing further evidence that diet therapy may have a role in treatment of SRSE. Finally, Moseley and Degiorgio [49] reported the first case of SRSE aborted with external trigeminal nerve stimulation.

Ultimately, treatment must be tailored to the underlying cause if a cause is identified. In patients in whom no cause can be found and infection has been excluded, it is reasonable to try high-dose steroids such as 1 g of intravenously administered methylprednisolone daily for 3–5 days followed by 1 mg of orally administered prednisone per kilogram of body weight per day. This may be followed by a course of

intravenously administered immunoglobulin or plasma exchange especially if a partial response is identified. If a response is observed, then long-term treatment options include continuing use of steroids, weekly intravenous infusion of immunoglobulin or plasma exchange, and initiation of use of other immunomodulatory agents such as cyclophosphamide and rituximab. Corticosteroid administration should be accompanied by appropriate gastrointestinal prophylaxis with a proton-pump inhibitor or H2-blocking agent and glucose monitoring and treatment with insulin if needed.

Outcomes

RSE is a heterogeneous condition arising as the final common pathway from multiple causes in patients with very different comorbidities and genetic makeups. Thus, assessing the efficacy of specific therapies and determining prognosis for an individual patient is complex.

Compared with an overall mortality of 20 % in nonrefractory SE [50, 51], patients with RSE or SRSE have a mortality of 23-48 % [1–4, 31, 35, 52, 53]. The wide variation in reported mortalities for RSE and SRSE likely results from differences in inclusion criteria (whether patients with hypoxic–ischemic injury are included), the proportion of patients with generalized convulsive SE relative to NCSE, and the proportion of patients requiring prolonged anesthesia.

Most available data suggest that younger age, history of epilepsy, and presenting with a level of consciousness other than coma are favorable prognostic indicators. In particular, patients who present with NCSE and coma have a poorer prognosis for recovery. Age and cause are strongly related to outcome in nonrefractory SE [51, 54], but these relationships are less well established for RSE and SRSE [31, 52, 55, 56]. It is possible that when patients with hypoxic–ischemic injury are excluded, the cause is a less powerful predictor of outcome. A clearer relationship exists between outcome and seizure duration, with longer RSE/prolonged RSE associated with worse outcomes. However, the reason for this may be complex and might have more to do with the type of seizures themselves, complications of prolonged hospitalization, or withdrawal of care when treatment options have been exhausted [31, 35, 52, 57].

In the absence of severe systemic comorbidities, patients with RSE/SRSE can survive in an anesthetic coma for months with the chance of a good outcome if seizures are ultimately controlled [31, 53, 56, 58, 59]. In two separate studies, 28 % of survivors achieved a modified Rankin scale score of 3 or less (moderate neurological impairment or less), with some returning to their premorbid functional baseline [31, 53]. It is important to note that these numbers may also be an underestimate as the data were taken from retrospective series of primarily SRSE rather than RSE and with variable follow-up periods. Information about long-term cognitive outcomes is limited. However, a proportion of patients with SRSE may return to work [53], and improvement can occur over time [56]. Patients with SRSE may develop brain atrophy and cerebral microbleeds [53, 60], but the incidence, cause, and functional implications of these sequelae are not known. Regarding long-term seizure risk, a significant proportion of patients may develop medically refractory epilepsy after SRSE, but recurrence of SRSE is uncommon [53].

Future Directions

Much is still to be learned regarding diagnosis, treatment, and outcome of patients with RSE/SRSE. A number of studies are under way in the SRSE population, including (1) a randomized controlled double-blinded study of SGE-102, a neurosteroid metabolite of progesterone found to have anticonvulsant properties in animal seizure models [61], (2) a prospective study of the ketogenic diet as an adjunctive therapy to standard care (ClinicalTrials.gov identifier NCT01796574), and (3) studies investigating various gene therapies. There is also an international audit of RSE which aims to develop a more global perspective on the spectrum of causes, therapies and outcomes that may form the basis for future treatment trials (https://www.status-epilepticus.net/). Hopefully, these and other forthcoming studies will shed additional light on the pathological mechanisms of RSE/SRSE that will lead to better treatment and improved outcome.

Compliance with Ethics Guidelines

Conflict of Interest Sara Hocker is a member of the steering committee for the Global Audit of Treatment of Refractory and Super-Refractory Status Epilepticus (https://www.status-epilepticus.net) and serves as a member of a data safety monitoring board for SAGE Therapeutics.

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References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia. 2010;51(2):251–6.

2. Mayer SA, Classen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors and impact on outcome. Arch Neurol. 2002;59:205–10.
3. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J Neurol Neurosurg Psychiatry. 2005;76:534–9.
4. Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Arch Neurol. 2005;62:1698–702.
5. Shorvon SD, Trinka E. Proceedings of the 3rd London-Innsbruck colloquium on status epilepticus. Epilepsia. 2011;52 Suppl 8:1–85.
6.•• Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain. 2011;134(10):2802–18. *This article is an evidence-based review that screened review articles, book chapters, and 159 articles reporting therapy in RSE. The authors put forth an organized and thorough review of both pharmacological and nonpharmacological management options in RSE.*
7. Wilder-Smith EP, Lim EC, Teoh HL, Sharma VK, Tan JJ, Chan BP, et al. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. Ann Acad Med Singap. 2005;34 (7):417–20.
8. Fountain NB, Lothman EW. Pathophysiology of status epilepticus. J Clin Neurophysiol. 1995;12(4):326–42.
9. Fujikawa DG. The temporal evolution of neuronal damage from pilocarpine-induced status epilepticus. Brain Res. 1996;725:11–22.
10. Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn^{2+} sensitivity of hippocampal dentate granule cell $GABA_A$ receptors. J Neurosci. 1997;17:7532–40.
11. Mazarati AM, Wasterlain CG, Sankar R, Shin D. Self-sustaining status epilepticus after brief electrical stimulation of the perforant path. Brain Res. 1998;801:251–3.
12. Mazarati AM, Baldwin RA, Sankar R, Wasterlain CG. Time dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. Brain Res. 1998;814:179–85.
13. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus: Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339:792–8.
14. Mazarati AM, Wasterlain CG. *N*-Methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. Neurosci Lett. 1999;265:187–90.
15. Arancibia-Carcamo IL, Kittler JT. Regulation of $GABA_A$ receptor membrane trafficking and synaptic localization. Pharmacol Ther. 2009;123:17–31.
16. Smith KR, Kittler JT. The cell biology of synaptic inhibition in health and disease. Curr Opin Neurobiol. 2010;20:550–6.
17. Naylor DE, Liu H, Niquet J, Wasterlain CG. Rapid surface accumulation of NMDA receptors increases glutamatergic excitation during status epilepticus. Neurobiol Dis. 2013;54:225–38.
18. Cock HR, Tong X, Hargreaves I, Heales SJR, Clark JP, Patsalos PN, et al. Mitochondrial dysfunction associated with neuronal death following status epilepticus in rat. Epilepsy Res. 2002;48:157–68.
19. Tan RY, Neligan A, Shorvon SD. The uncommon causes of status epilepticus: a systematic review. Epilepsy Res. 2010;91:111–22.
20. Marchi N, Granata T, Freri E, Ciusani E, Ragona F, Puvenna V, et al. Efficacy of anti-inflammatory therapy in a model of acute seizures and in a population of pediatric drug resistant epileptics. PLoS One. 2011;28:e18200.
21. David Y, Cacheaux LP, Ivens S, Lapilover E, Heinemann U, Kaufer D, et al. Astrocytic dysfunction in epileptogenesis: consequence of altered potassium and glutamate homeostasis? J Neurosci. 2009;29: 10588–99.
22. Friedman A, Dingledine R. Molecular cascades that mediate the influence of inflammation on epilepsy. Epilepsia. 2011;52 Suppl 3: 33–9.
23. Henshall DC. MicroRNAs in the pathophysiology and treatment of status epilepticus. Front Mol Neurosci. 2013;6:37.
24. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345(9):631–7.
25. Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012;366(7): 591–600.
26. Bleck T, Cock H, Chamberlain J, Cloyd J, Connor J, Elm J, et al. The established status epilepticus trial 2013. Epilepsia. 2013;54 Suppl 6:89–92.
27. Hocker S, Wijdicks EF, Rabinstein AA. Refractory status epilepticus: new insights in presentation, treatment, and outcome. Neurol Res. 2013;35(2):163–8.
28. Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. Arch Neurol. 1973;28:10–7.
29. Meldrum B. Excitotoxicity and epileptic brain damage. Epilepsy Res. 1991;10:55–6.
30. Bleck TP. Electroencephalographic monitoring. In: Tobin MR, editor. Principles and practice of intensive care monitoring. New York: McGraw-Hill; 1998. p. 1035–46.
31. Hocker SE, Britton JW, Mandrekar JN, Wijdicks EF, Rabinstein AA. Predictors of outcome in refractory status epilepticus. JAMA Neurol. 2013;70(1):72–7.
32. Wijdicks EF. The multifaceted care of status epilepticus. Epilepsia. 2013;54 Suppl 6:61–3.
33. Kowalski RG, Ziai WC, Rees RN, Werner Jr JK, Kim G, Goodwin H, et al. Third-line antiepileptic therapy and outcome in status epilepticus: the impact of vasopressor use and prolonged mechanical ventilation. Crit Care Med. 2012;40(9):2677–84.
34. Drislane FW, Blum AS, Lopez MR, Gautam S, Schomer DL. Duration of refractory status epilepticus and outcome: loss of prognostic utility after several hours. Epilepsia. 2009;50(6):1566–71.
35. Sutter R, Marsch S, Fuhr P, Kaplan PW, Rüegg S. Anesthetic drugs in status epilepticus: risk or rescue?: a 6-year cohort study. Neurology. 2014;82(8):656–64.
36. Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: 'the cure may be worse than the disease'). Neurophysiol Clin. 2000;30:377–82.
37. Jordan KG, Hirsch LJ. In nonconvulsive status epilepticus (NCSE), treat to burst-suppression: pro and con. Epilepsia. 2006;47 Suppl 1: 41–5.
38. Fernandez A, Lantigua H, Lesch C, Shao B, Foreman B, Schmidt JM, et al. High-dose midazolam infusion for refractory status epilepticus. Neurology. 2014;82(4):359–65.
39. Veldhoen ES, Hartman BJ, van Gestel JP. Monitoring biochemical parameters as an early sign of propofol infusion syndrome: false feeling of security. Pediatr Crit Care Med. 2009;10(2):e19–21.
40. Lowenstein D, Aminoff S, Smon R. Barbiturate anesthesia in status epilepticus: clinical experience of 14 patients. Neurology. 1988;38: 395–400.
41. Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res. 2000;42:117–22.
42. Synowiec AS, Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM. Ketamine use in the treatment of refractory status epilepticus. Epilepsy Res. 2013;105(1–2):183–8.
43.•• Gaspard N, Foreman B, Judd LM, Brenton JN, Nathan BR, McCoy BM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia. 2013;54(8):1498–503. *Gaspard et al. reviewed the medical records and EEGs of 58 patients with 60 episodes of RSE treated with intravenously administered ketamine, and provide preliminary data on the safety and effective dose of ketamine in this setting.*

44. Green SM, Cote CJ. Ketamine and neurotoxicity: clinical perspectives and implications for emergency medicine. Ann Emerg Med. 2009;54:181–90.
45. Thordstein M, Constantinescu R. Possibly lifesaving, noninvasive, EEG-guided neuromodulation in anesthesia-refractory partial status epilepticus. Epilepsy Behav. 2012;25(3):468–72.
46. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012;79(11): 1094–100. doi:10.1212/WNL.0b013e3182698cd8.
47. Liu A, Pang T, Herman S, Pascual-Leone A, Rotenberg A. Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit. Seizure. 2013;22(10):893–6.
48. Thakur KT, Probasco JC, Hocker SE, Roehl K, Henry B, Kossoff EH, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology. 2014;82(8):665–70.
49. Moseley BD, Degiorgio CM. Refractory status epilepticus treated with trigeminal nerve stimulation. Epilepsy Res. 2014;108(3):600–3.
50. Shorvon S. Status epilepticus: its clinical features and treatment in children and adults. Cambridge: Cambridge University Press; 1994.
51. Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Short-term mortality after a first episode of status epilepticus. Epilepsia. 1997;38(12):1344–9.
52. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002;43(2):146–53.
53.•• Kilbride RD, Reynolds AS, Szaflarski JP, Hirsch LJ. Clinical outcomes following prolonged refractory status epilepticus (PRSE). Neurocrit Care. 2013;18(3):374–85. *Kilbide et al. reviewed 63 consecutive patients with prolonged (more than 1 week) RSE, finding that good outcome is not unusual in this population including some older patients, with a variety of diagnoses and despite months of coma. This study provides the best available outcome data in prolonged RSE.*
54. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia. 1994;35(1):27–34.
55. Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. Neurology. 2006;66(11): 1736–8.
56. Cooper AD, Britton JW, Rabinstein AA. Functional and cognitive outcome in prolonged refractory status epilepticus. Arch Neurol. 2009;66(12):1505–9.
57. Neligan A, Shorvon SD. Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus: a review. Epilepsy Res. 2011;93(1):1–10.
58. Bausell R, Svoronos A, Lennihan L, Hirsch LJ. Recovery after severe refractory status epilepticus and 4 months of coma. Neurology. 2011;77(15):1494–5.
59. Standley K, Abdulmassih R, Benbadis S. Good outcome is possible after months of refractory convulsive status epilepticus: lesson learned. Epilepsia. 2012;53(1):e17–20.
60. Jeon SB, Parikh G, Choi HA, Lee K, Lee JH, Schmidt JM, et al. Acute cerebral microbleeds in refractory status epilepticus. Epilepsia. 2013;54(5):e66–8.
61. Reddy K, Reife R, Cole AJ. SGE-102: a novel therapy for refractory status epilepticus. Epilepsia. 2013;54 Suppl 6:81–3.
62. Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology. 2009;72:744–9.