



# Seizures – just the tip of the iceberg: Critical care management of super-refractory status epilepticus

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## Abstract

Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) that continues or recurs 24 h or more after the onset of anesthetic therapy, including those cases where SE recurs on the reduction or withdrawal of anesthesia. Although SRSE is a rare clinical problem, it is associated with high mortality and morbidity rates. This article reviews the treatment approaches and the systemic complications commonly encountered in patients with SRSE. As evident in our search of literature, therapy for SRSE and its complications have been based on clinical reports and expert opinions since there is a lack of controlled and randomized trials. Even though this complex condition starts as a neurological disorder, because of the associated systemic complications, it can be considered as a multisystem disorder requiring scrupulous attention and deliberate efforts to prevent, detect, and treat these systemic effects. We have critically reviewed the intensive care management for SRSE *per se* as well as its associated systemic complications. We believe that a good recovery can occur even after prolonged and severe SRSE as long as the systemic complications are detected early and managed appropriately.

**Keywords:** Critical care management, status epilepticus, super refractory

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## Introduction

Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) that persists for 24 h or more after the onset of anesthetic therapy. It also includes those scenarios wherein SE recurs on the reduction or withdrawal of anesthesia.<sup>[1]</sup> SE has an annual incidence of 10–40 per 100,000 populations.<sup>[2,3]</sup> As shown by retrospective data, SRSE occurs in 23%–43% of patients with SE resulting in high morbidity and mortality rates of up to 30%–50%.<sup>[4]</sup>

Critical care physicians are frequently exposed to the multiple challenges that present with this emerging clinical problem, and dealing with these patients proves to be a demanding task. Since there is a paucity of data attributed to the lack of controlled or

randomized studies, management has to be based on a few clinical reports and expert opinions. Practical clinical management involves a variety of scenarios which include antiepileptic drug (AED) therapy, application of hypothermia, induction and maintenance of anesthesia, and immunological and physical therapies as well.<sup>[1]</sup> SRSE is consistently attributed to a major insult to the brain most commonly in the form of a stroke, central nervous system (CNS) infection, or trauma.<sup>[5,6]</sup> The genesis can be identified with ease usually from an excellent clinical history, detailed examination, and imaging of the CNS.

The pathophysiology responsible for the persistence of seizures is attributed to the receptors on the axon surface

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which are in a dynamic state. During SE, there is an intensified “receptor trafficking” and a reduction in the functional gamma-aminobutyric acid (GABA) receptors in the aberrant neurons.<sup>[1,6]</sup> This loss of GABA receptors makes therapy more challenging as GABAergic drugs such as benzodiazepines and barbiturates fail to achieve a good control of the seizures, thereby further prolonging the seizure duration.<sup>[7,8]</sup> In addition, mitochondrial failure or insufficiency has also been postulated to be one of the causes for failure of seizure termination.<sup>[6]</sup> Damage to the blood-brain barrier in inflammatory CNS diseases has also been implicated in the persistence of seizures in SRSE. No genetic mechanism has yet been identified to explain the failure of seizure termination which is a characteristic of SRSE.<sup>[9]</sup>

### **Management of super-refractory status epilepticus**

Treating clinicians and intensivists must be aware of the fact that recovery of patients with SRSE even with a duration of up to a few weeks is not uncommon. Premature withdrawal of care (supportive or therapeutic) should not be done merely because of the protracted treatment duration. Studies by Cooper *et al.* concluded that although the mortality rate in SRSE is high, survival with significant functional and cognitive recovery is feasible.<sup>[8]</sup> The protracted course of this illness alone is not an indication to consider discontinuing treatment. Similarly, Drislane *et al.* commented that unless SRSE follows anoxia, it should not be considered a hopeless condition.<sup>[10]</sup>

Treatment strategy in SRSE is a three-pronged approach.<sup>[1,6]</sup> The primary objective of treatment is to control seizures with the intent of preventing occurrence of the initial excitotoxicity. After 24 h of continuous or recurring seizures, excitotoxic processes attributing to cerebral damage would have been initiated. The secondary objective being neuroprotection is an endeavor to impede the progression of the secondary processes which are triggered by the initial excitotoxicity. The third and final objective is the need to avoid or treat the systemic complications caused by the prolonged unconsciousness and anesthesia.

SRSE is definitely a medical emergency. In SRSE, general anesthesia remains the basis of medical therapy.<sup>[6,7]</sup> It is interesting to note that anesthesia has been recommended since the mid-19<sup>th</sup> century. It is usual to continue anesthesia for the initial 24 h and then slowly attempts are made to reverse the same if seizures prove to be under control. Recurrence of seizures during the weaning phase warrants anesthesia to be reestablished.<sup>[1]</sup> Initiating and weaning of anesthesia are continued in

24–48 h cycles initially and then as 5–7-day cycles.<sup>[1,7]</sup> The role of anesthesia is largely to obtain a period of burst suppression which will help in receptor remodeling, thus enabling conventional antiepileptic therapy to be effective.<sup>[7,9]</sup> Anesthesia is usually administered to the level of “burst suppression.” A physiological target for the titration of anesthetic treatment is provided by burst suppression. Drug dosing is typically set at a level which intends to produce burst suppression with interburst intervals of 2–30 s. As mentioned afore, slow weaning from anesthesia is strongly recommended, with a goal to reduce the infusion rate by 25% during the first 12 h of the weaning phase.<sup>[1,7,9,10]</sup>

The most commonly used anesthetic agents are injection midazolam, injection propofol, and injection thiopental. The choice of anesthetic agent is based on the patients’ hemodynamic profile and the known side effects of the drug. In our center, anesthetic therapy is initiated with injection midazolam (bolus dose of 0.2 mg/kg followed by an infusion of up to 0.4 mg/kg/h) as it achieves good seizure control without significant hemodynamic fluctuations.<sup>[7]</sup> However, the major drawback of this drug is its tachyphylaxis which commonly develops within 24–48 h. This requires the dose to be constantly adjusted to maintain its pharmacotherapeutic action. Injection midazolam is most commonly used as a sole agent initially but can be used in combination with injection propofol as well. The availability of an appropriate antidote (injection flumazenil) provides a definite advantage over the other anesthetic drugs. Injection propofol (bolus dose: 3–5 mg/kg; infusion: 5–10 mg/kg/h) is the other option as an initial sole agent, or as mentioned earlier, it may be used in combination with injection midazolam as well.<sup>[10,11]</sup> It has the added benefit of being easy to use, due to its versatile pharmacokinetic and pharmacodynamic properties. It has a fast onset and offset making it particularly attractive in being easily titratable, thus facilitating a rapid weaning process. The risk of propofol infusion syndrome should be kept in mind, especially in the pediatric population and when used in combination with a ketogenic diet, steroids, or catecholamine infusions which is common in this scenario.<sup>[12]</sup> It offers a better hemodynamic profile when compared to the conventional pentothal/thiopental infusions. Injection thiopental (bolus: 2–3 mg/kg; infusion: 3–5 mg/kg/h) apart from having a strong antiepileptic action also has the added advantage of being neuroprotective.<sup>[13,14]</sup> The drawback of this drug is attributed to the zero-order kinetics which results in a long half-life and thus a prolonged recovery time. Its strong propensity to cause hypotension and

cardiorespiratory depression, frequently requires the use of additional pressor agents. Another notable side effect is the immunosuppression associated with a prolonged barbiturate infusion.<sup>[13,14]</sup>

Injection ketamine (bolus: 0.5–4.5 mg/kg; infusion: Up to 5 mg/kg/h) may be a useful adjuvant in the treatment of SRSE, especially in late stages when medications that rely on GABA enhancement are ineffective. Injection ketamine has a 2-fold advantage over other conventional anesthetics: Primarily, it is potentially neuroprotective through its n-methyl-d-aspartate (NMDA) antagonist action, and secondarily, it does not cause systemic hypotension attributable to the fact that it is not a cardiac depressant.<sup>[15,16]</sup>

Inhalational anesthetics such as isoflurane (0.8%–2% end-tidal concentration) and declarant (8%–10% end-tidal concentration) have also been experimented with, resulting in moderate success rates as reported in a few case reports and small case series.<sup>[17]</sup> Impediments to their usage include hypotension, atelectasis, infections, paralytic ileus, and deep venous thrombosis. The major limiting factor for the use of inhalational agents remains the need of an anesthesia workstation and vaporizer. A vaporizer that can be integrated into the respiratory circuit, between the Y-piece and the patient, known as the anesthetic conserving device (AnaConDa), has been effectively used to administer inhalational agents in the Intensive Care Unit.<sup>[18]</sup>

A wide range of AEDs have been used along with the anesthetic agents to achieve seizure control in patients with SRSE.<sup>[9,11]</sup> There is no literature on the superiority or efficacy of one over the other. A combination therapy with two or three AEDs at their maximum doses is initiated and continued through the protracted course of this illness and their therapeutic levels must be adhered to.<sup>[7,11]</sup> The allergic potential of each drug and the drug interactions of the AEDs should be envisaged and clinically correlated. Other troublesome side effects encountered are acute pancreatitis, hepatic or renal failure, especially with intravenous AEDs.<sup>[1,7]</sup> High-dose intravenous valproate can induce platelet dysfunction, clotting disorders, and severe hyperammonemia in predisposed patients.

Intravenous magnesium has its distinctive role in the management of SRSE and is commonly administered even in the absence of evidence of deficiency.<sup>[1,9]</sup> The rare and successful use of drugs such as intravenous lidocaine and intravenous paraldehyde have a role to play and have been reported in literature.<sup>[19]</sup> There has

been a single case report where verapamil has been reported to be responsible to have terminated SRSE in one patient, and this was attributed to it causing an inhibition of p-glycoprotein or other drug transporter processes.<sup>[20]</sup>

The final choice of drug depends on the clinical scenario. The most effective drug should be chosen, and as the duration of SRSE increases, it is best to avoid drugs with the GABAergic mechanism.<sup>[21]</sup> It is rational to use drugs that have a low interaction potential with predictable pharmacokinetics. It is logical to circumvent the use of drugs with probable renal or hepatic toxicity or with allergic potential.<sup>[21,22]</sup>

The introduction of immunotherapy has been an interesting development in the recent years in the therapy of SRSE. This includes scenarios where there is no evident immunologic cause for the SRSE. The rationale is that there was the possibility of an overt immunologic disease in these subjects. The discovery that anti-NMDA-receptor antibodies can lead to SRSE is a proof that antibodies may play a part in the pathogenesis of SRSE. The other alternative therapy in such scenarios is high-dose methylprednisolone (1 g/day), followed by one or two courses of intravenous immunoglobulins (IVIG). In the presence of a positive response, long-term therapy with steroids, IVIG, cyclophosphamide, or rituximab is continued.<sup>[1,7,22]</sup>

Hypothermia for SRSE has seen a resurgence of interest, especially in postanoxic SRSE. It acts by reducing cerebral metabolism, glutaminergic drive, intracellular calcium overload, and oxidative stress.<sup>[19,23]</sup> Mild to moderate hypothermia (32–35°C) is recommended for 24–48 h and only as a trial of therapy. If a positive response is found, therapeutic hypothermia is continued for the next 72 h. Varied complications associated with therapeutic hypothermia such as acid-base and electrolyte disturbances, disseminated intravascular coagulation, thrombosis, infection, cardiac arrhythmia, and paralytic ileus must be prevented and if at all they occur should be promptly recognized and managed.<sup>[23]</sup> Thus, some centers now routinely apply hypothermia to patients with SRSE. The cardiovascular system, coagulation parameters, blood gases, and lactate levels must be monitored diligently. Clearance of anesthetics and AEDs may be significantly reduced by hypothermia.<sup>[23]</sup>

Various contrasting nonpharmacological physical therapies such as electroconvulsive therapy, transcranial

magnetic stimulation, vagus nerve stimulation, and drainage of the cerebrospinal fluid have been reported with different rates of success.<sup>[7,24-26]</sup> Some have also been treated by emergency neurosurgery.<sup>[27]</sup> A ketogenic diet has also been reported to be successful.<sup>[27]</sup> The rationale for which is based on the fact that its enhanced fatty acid and restricted carbohydrate contents produce a switch in metabolism from the preferred ATP-generating pathway of glycolysis to an intermediary metabolism that results in increased production of ketone bodies, decreased glucose, and increased levels of circulating fatty acids including polyunsaturated fatty acids.<sup>[28]</sup> These have membrane-stabilizing property through a marked reduction in neuronal excitability by the opening of ATP-sensitive potassium channels to cause membrane hyperpolarization and through the acetoacetate-mediated presynaptic release of excitatory neurotransmitters.<sup>[28,29]</sup>

### **Systemic complications of super-refractory status epilepticus**

It is a demanding task for the intensivist to tackle the associated systemic derangements which ensue. A quick review of the systemic effects will reveal a plethora of events. Risk factors for these systemic complications include: (1) Prolonged immobility and risk for pulmonary emboli; (2) immunosuppression and risk for nosocomial infections; (3) adverse effects and interactions related to polypharmacy; (4) prolonged anesthetic coma causing skin breakdown, muscle atrophy, and critical illness polyneuropathy.<sup>[30]</sup> Meticulous attention to these complications is indispensable and extremely time-consuming.

Cardiac complications are common; most prominent are hypotension, arrhythmias, and systolic dysfunction. Persistent seizure activity can give rise to a "sympathetic storm" resulting in a neuroendocrine response which alters the homeostatic environment as well the hemodynamic status. Examination of vitals commonly reveals tachycardia and initially an increase in the systemic blood pressure attributed to the increase in peripheral vascular resistance.<sup>[30,31]</sup> During the protracted course of this illness, the blood pressure will normalize, and after a while, there usually results in a systemic hypotension often requiring the use of vasopressors. Hypotension may result from the cardiovascular depressant effects of the anesthetic agent and is particularly problematic with the inhaled anesthetics, barbiturates, and propanol. It may also occur from hypovolemia, sepsis, or less commonly result from adrenergically driven systolic dysfunction. The QTc is often prolonged predisposing patients to ventricular

arrhythmias.<sup>[30,32]</sup> Rarely, these patients can present with low ejection states due to the neurogenic stunned myocardium or Takotsubo cardiomyopathy, both being reversible, but requiring meticulous supportive management.<sup>[33]</sup>

The respiratory system can be deleteriously affected due to multiple reasons. The most notorious is neurogenic pulmonary edema which results due to the sympathetic surge of catecholamines. The picture is that similar to adult respiratory distress syndrome (ARDS) with reduced lung compliance and difficulty in maintaining oxygenation and ventilation.<sup>[34]</sup> A pulmonary edema may be further worsened by the elevated pulmonary vascular pressure. The other commonly encountered problems are aspiration pneumonia and ventilator-associated pneumonia. All these result in reduced oxygenation which contributes to further deterioration of an already at risk brain. Other frequently encountered complications are ARDS, atelectasis, and mucus plugging resulting in respiratory acidosis and hypoxemia. A coexisting metabolic acidosis is also found associated with the rhabdomyolysis seen in SRSE. 85%–100% incidence of tracheostomy is reported in SRSE due to the need for prolonged mechanical ventilation.<sup>[30,32]</sup>

Hematological complications noted in this population include deep venous thrombosis, pulmonary embolism, drug-induced thrombocytopenia, and anemia secondary to malnutrition as well as drug-induced bone marrow suppression. Gastrointestinal complications include adynamic ileus, especially in patients receiving pentobarbital. Ileus may be severe, and in some cases, it is refractory to medical measures, necessitating a colostomy.<sup>[30,32]</sup> There have also been reports of drug-induced hepatitis and pseudomembranous colitis as well. Malabsorption and the ensuing malnutrition lead to hypoalbuminemia and anasarca.

In spite of the best preventive efforts, such as a good glycemic control and appropriate management of hypoalbuminemia, it is reported that 10%–20% of patients may develop critical illness polyneuropathy and critical illness myopathy.<sup>[32]</sup> Furthermore, as a result of continued seizure activity, the musculoskeletal system is affected resulting in conversion to anaerobic metabolism contributing to lactic acidosis and in rare scenarios, rhabdomyolysis. Renal failure is another dreaded complication secondary to rhabdomyolysis or acute tubular necrosis.<sup>[35]</sup> The immune system is also compromised due to multiple factors such as malnutrition, bone marrow suppression, drug-induced

leukopenia, and hypothermia. This presents commonly as urinary tract infections (most commonly candiduria), pneumonia, sepsis, and septic shock. Last but not the least of our concerns are the skin changes which range from decubitus ulcers to drug-induced rashes and even more serious complications such as Steven-Johnson Syndrome.<sup>[30]</sup>

Temperature monitoring too plays a vital role in the intensive care of these patients. As the seizure progresses, the body's core temperature also increases contributing to the ongoing neurological insult.<sup>[30,32]</sup> Aggressive management of temperature to maintain normothermia is beneficial. The association of systemic injury is an independent predictor of mortality in SE. Routine screening of patients for precursors of injury such as serum lactate, creatine kinase, and cardiac troponin is warranted. Routine arterial blood gas and chest X-ray will also help the intensivist in early detection and management of complications.<sup>[30]</sup> Meticulous attention to the medical complications of SE is indispensable and may lead to improved outcomes.

Thus, even though this complex condition starts as a neurological disorder, because of the associated systemic complications, it can be considered as a multisystem disorder requiring scrupulous attention and deliberate efforts to prevent, detect, and treat these systemic effects. A good recovery can occur even after prolonged and severe SRSE, and the intensivist has to ensure that premature withdrawal of care is not deliberated. Therapy should simultaneously also focus on the appropriate management of the underlying cause of the SRSE as well. We emphasize that a good outcome is highly dependent on the accurate and prompt treatment of the SRSE as well as the associated aforementioned systemic complications.

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#### Conflicts of interest

There are no conflicts of interest.

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