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*Editorial*

# Developments in the Treatment of Status Epilepticus in Adults: What Is Established, What Is New and What Is on the Horizon?

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## 1. Introduction

Status epilepticus (SE) is a medical emergency that accounts for 3% of medical admissions to the Emergency Department. It is associated with a mortality of approximately 30% in adults, with this being even higher in patients with refractory status epilepticus. SE is defined as continuous seizure activity or repetitive seizures that continue for more than 5 minutes without the patient recovering consciousness [1]. It can occur both in patients with and without a history of epilepsy. Morbidity and mortality are high, and they increase with the duration of uncontrolled seizures, which necessitates early active treatment. Early recognition and treatment can reduce the risk of complications and improve outcomes. Current guidance advocates the use of benzodiazepines as first-line agents, followed by levetiracetam, fosphenytoin/phenytoin, or valproate as effective second-line agents. Once seizures are refractory to these agents, management becomes more complex, involving the use of anaesthetic agents and immunotherapy (see Fig. 1) [2]. This editorial will explore the current management of status epilepticus and future therapeutic options.

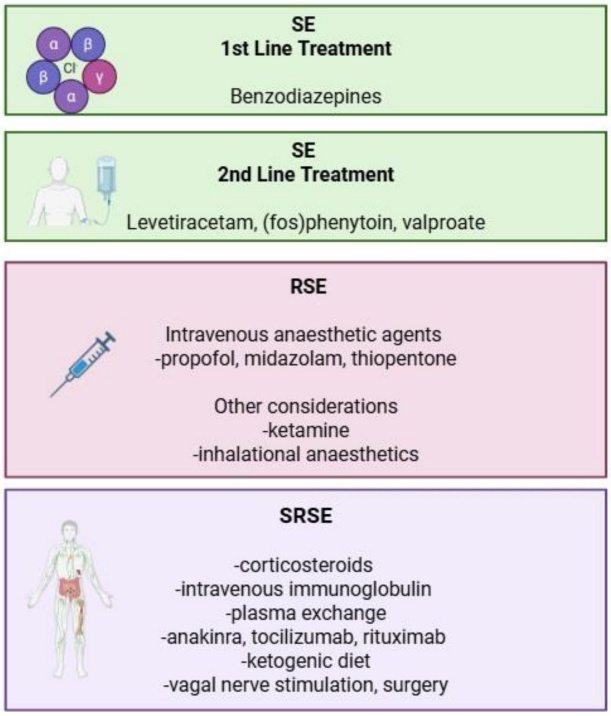


**Fig. 1. Treatment strategies for status epilepticus (SE), refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE).** The figure was produced by RM using BioRender (https://www.biorender.com/).

## 2. What Is Established in the Management of Status Epilepticus?

Treatment is based on a sequential three-step approach consisting of first-line benzodiazepines, second-line antiseizure medication (ASM) followed by the use of general anaesthesia for refractory cases. SE that persists despite the administration of first-line benzodiazepines and a suitable second-line ASM is termed refractory status epilepticus (RSE). SE that continues or recurs despite 24 hours of anaesthetic therapy or re-emerges during or after weaning from anaesthesia is termed super-refractory status epilepticus (SRSE). Mortality rates escalate from 15% in responsive cases to 25% in RSE and 40% in SRSE [3].

The Established Status Epilepticus Treatment Trial (ESETT) looked at the effectiveness of second-line ASMs, with the findings indicating that there were no significant differences in efficacy between levetiracetam, fosphenytoin (pro-drug of phenytoin), and valproate. These agents were equivalent in terminating seizures and improving the level of consciousness in approximately half of the patients [4]. While ESETT demonstrated equipoise, it clearly demonstrated that half of these patients still progressed to RSE despite the use of second-line therapy.

Interventions employed for RSE and SRSE, including anaesthetic agents and immunotherapies, are often administered based on limited evidence or on extrapolation from their use in other conditions. The lack of definitive evidence for RSE and SRSE treatments is reflected in the heterogeneity of their treatment.

## 3. Neuronal Receptor Changes During Status Epilepticus

Seizures arise following disruptions in the neuronal balance of excitatory and inhibitory pathways. Refractory seizures can occur due to changes in neurotransmitter receptor populations. Gamma aminobutyric acid-A (GABA-A) receptors, which are the target for benzodiazepines, are progressively internalized at the synaptic level, leading to reduced activity of these agents [5]. GABA-A receptors are also the primary molecular target of general anaesthetics. For this reason, *N*-methyl-$_{D}$-aspartate (NMDA) receptor antagonists such as ketamine have been suggested as an alternative approach to treating seizures that are refractory to general anaesthetics [6]. Increased expression of these excitatory NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors can, however, further compound the problem, leading to super-refractory seizures.

## 4. Neuroinflammation as a Facilitator of Seizure Activity

The role of neuroinflammation in seizure development is being increasingly understood. Disruption of the blood-brain barrier leads to the infiltration of immune cells and inflammatory mediators into the central nervous system (CNS), leading to neuronal damage. Within the CNS, support cells such as microglia and astrocytes become activated and release a cascade of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumour necrosis factor-alpha (TNF-α). These cytokines enhance neuronal excitability by their effects on ion channel function and receptor expression. This reduces the seizure threshold and promotes ongoing seizure activity. The use of anti-inflammatory and immunomodulatory agents in RSE is based upon reducing the effect of these pro-inflammatory cytokines [7]. Neuroinflammation is thought to be particularly evident in conditions such as New-Onset Refractory Status Epilepticus (NORSE), characterized by RSE occurring in a patient de novo, and Febrile Infection-Related Epilepsy Syndrome (FIRES), a subtype of NORSE seen mainly in the paediatric population.

## 5. Immunomodulatory Agents

Corticosteroids such as methylprednisolone have numerous anti-inflammatory and immunosuppressive effects. They are thought to limit the production of pro-inflammatory cytokines, regulate immune cell trafficking, and stabilise cell membranes. Corticosteroids are often used as the initial immunomodulatory treatment in RSE, especially when NORSE or FIRES are suspected.

Intravenous immunoglobulin (IVIG) is a purified solution of immunoglobulin G that is derived from human plasma. Given by infusion, it acts to neutralise the effects of destructive autoantibodies, reduces the levels of key inflammatory signalling molecules and interferes with the Fc receptor function on macrophages. It is frequently used as either first-line immunotherapy or as an adjunct to corticosteroids [8].

Plasma exchange is designed to remove pathogenic autoantibodies, immune complexes, and inflammatory mediators from the circulation. It is used in patients where there is a high suspicion of an auto-immune aetiology [9]. However, its use may be limited to centres that are able to provide renal dialysis support.

The emerging success of treatments such as anakinra (IL-1 receptor antagonist) and tocilizumab (IL-6 receptor antagonist) that block the pro-inflammatory signalling of cytokines emphasizes the importance of the cytokine system in neuroinflammation. Rituximab, a monoclonal antibody that targets the cluster of differentiation 20 (CD20) antigen on B-lymphocytes, seems to be especially effective in B-cell mediated states, such as *N*-methyl-$_{D}$-aspartate receptor (NMDAR) encephalitis [10].

## 6. Other Treatment Considerations in the Management of Status Epilepticus

The ketogenic diet is a high-fat, low-carbohydrate diet that can be used for resistant seizures. The composition of this diet causes the brain to switch from primarily using glucose to using ketones as an energy source. This is thought to help stabilize neuronal activity within the CNS [11]. It is thought that the ketogenic diet also changes the microbial flora, which subsequently plays a role in regulating seizure susceptibility.

Surgical resection techniques and neuro-stimulation therapies can be considered when medical therapies have failed. Surgery involves resection of the brain tissue that is triggering seizures. Implanted devices such as vagus nerve stimulators, responsive neurostimulators and thalamic stimulators have also been tried in resistant seizures [12].

The emerging role of genetics in both the susceptibility to seizures and resistance to anti-seizure therapies is an area of ongoing research. Mutations can be inherited or occur de novo and although genetic causes are more frequently diagnosed in young children, adults can also present with a genetic basis for their epilepsy [13]. The increasing use of whole genome sequencing (WGS) will hopefully improve our understanding of the genetic basis of epilepsy.

## 7. Conclusion

Whilst the management of SE has improved significantly, future advances in early detection, treatment of seizures, and personalized therapy are needed to reduce associated morbidity and mortality. Anti-inflammatory and immunomodulatory therapies are being increasingly used as our understanding of the role of neuroinflammation in seizure generation has evolved. A structured treatment approach should be adopted while acknowledging the need for more robust evidence to support our currently available therapeutic options.

## Key Points

• Status epilepticus is a life-threatening emergency.

• Current guidelines support the use of benzodiazepines as first-line agents with levetiracetam, (fos)phenytoin and valproate as second-line agents.

• Resistant seizures remain challenging to manage and include the use of anaesthetic agents as well as immunotherapy.

• The role of genetics in status epilepticus is an area of emerging research, and whole genome sequencing holds promise for improving our understanding of this.

## Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article.

## Author Contributions

RM conceived the idea for this article and produced the initial draft. RM, TH, SS, and TV have made substantial contributions to conception and design. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflicts of Interest

Given his role as an Editorial Board Member, Tonny Veenith had no involvement in the review of this article and has no access to information regarding its review. Full responsibility for the editorial process for this article was delegated to John Alcolado. The other authors declare no conflicts of interest.

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