A B S T R A C T
Convulsive status epilepticus is the most extreme form of seizure. It is a medical and neurological emergency that requires prompt and appropriate treatment. Treatment of convulsive status epilepticus is usually divided into stages/steps. The International League Against Epilepsy has released a new definition of status epilepticus that may help to unify the definition in future studies. Over the last few years new information has become available regarding its management. The Rapid Anticonvulsant Medication Prior to Arrival Trial demonstrated non-inferiority of intramuscular midazolam in early status epilepticus compared with intravenous lorazepam. Valproate and levetiracetam have also emerged as possible alternatives to phenytoin in established status epilepticus. The potential role of lacosamide in this stage of status epilepticus remains to be defined. The ongoing Established Status Epilepticus Treatment Trial may help to determine the most effective treatment for benzodiazepine-resistant status epilepticus.

Management of refractory status epilepticus and super-refractory status epilepticus remains mostly non–evidence-based. Increasing recognition of a possible autoimmune aetiology has led to the use of immune-modulation in super-refractory status epilepticus. Ketamine is also increasingly used in this challenging condition. There are also reports of potential use of a ketogenic diet and magnesium.

Introduction
Status epilepticus (SE) is the most extreme form of a seizure. It is a medical and neurological emergency that requires prompt and appropriate treatment. Treatment of SE is divided into stages/steps. Traditionally, SE has been defined as “a seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition.” Recently the International League Against Epilepsy (ILAE) Task Force on Classification of Status Epilepticus proposed a new conceptual definition of SE based on the best-known (and yet incomplete) pathophysiology and neurobiology of SE. The Task Force proposed that SE be defined as “a condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point \(t_1\)) and can have long-term consequences (after time point \(t_2\), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type of seizures.” The definition for \(t_1\) and \(t_2\) was largely based on animal experiments and clinical research. For convulsive (tonic-clonic) seizures, 5 minutes and 30 minutes have been proposed for \(t_1\) and \(t_2\), respectively.

When SE continues despite treatment with benzodiazepines and one other antiepileptic drug (AED), it becomes “refractory” (ie refractory status epilepticus, RSE) and intensive care with anaesthetic agents should be seriously considered. Among 10% to 15% of patients with RSE, seizures may continue despite use of anaesthetic agents or may recur soon after weaning of anaesthetic agents. These patients are considered having super-refractory status epilepticus (SRSE). Since the publication of the Hong Kong Epilepsy Guideline of 2009, there have been advances in the management of convulsive status epilepticus (CSE). In this study, we review the latest evidence/clinical experience and update the management algorithm of CSE accordingly. Here we focus on management of CSE only, which is the target of most studies. Although non-CSE is common and can also have long-term consequences, the variable and subtle clinical features make diagnosis and treatment challenging. The treatment therefore remains diverse and controversial and detailed discussion is beyond the scope of this article.
Early status epilepticus

Early treatment of SE by paramedics reduces the number of patients with a persistent seizure state on arrival at the emergency department and admission to the intensive care unit. In the past decade, several studies have evaluated the efficacy of different benzodiazepines in early SE. The RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) was a randomised, double-blind, phase 3, non-inferiority clinical trial. It involved 4314 paramedics in 33 emergency medical service agencies and 79 hospitals across the United States. In this trial, a total of 893 subjects were randomised and treated. They were children with an estimated body weight of ≥13 kg and adults with >5 minutes of convulsions who were still seizing upon arrival of paramedics. A fixed dose of midazolam administered by intramuscular (IM) autoinjector was found to be at least as safe and effective as intravenous (IV) lorazepam. Patients treated with IM midazolam were more likely to have stopped seizing on arrival at the emergency department, and less likely to be hospitalised or have stopped seizing on arrival at the emergency department and admission to the intensive care unit.6 In the past decade, there have been many reports on the use of IV valproate (VPA) in treating SE following benzodiazepine failure. There are also case series that report the use of newer AEDs with IV formulations, eg LEV,15-22 despite the lack of good randomised controlled trials, in a recent meta-analysis, the uses of IV lacosamide, LEV, VPA, phenytoin, and phenobarbital were compared. It found that LEV, VPA, and phenobarbital were comparable in terms of efficacy in stopping benzodiazepine-resistant SE.23 Yet the evidence does not support the use of phenytoin despite its continued and common use. There is insufficient evidence to support the routine use of lacosamide and it was excluded from the meta-analysis. The conclusion highlighted the urgent need...
for randomised controlled trials in this scenario.23

Valproate

With an IV formulation available since 1993, VPA is a broad-spectrum AED effective against all seizure types.24,25 The exact mechanism of anticonvulsant effect has not been fully established. It may involve potentiation of GABAergic functions, N-methyl-D-aspartate (NMDA) inhibition, reduction of γ-hydroxybutyrate release, and blockade of voltage-dependent sodium currents.26 Of note, IV VPA does not require organic solvents for dissolution, thus minimising the risk of injection site reactions such as ‘purple glove’. It can be injected at a physiological pH and is not incompatible with other commonly used IV solutions. It is a broad-spectrum AED that can be used effectively in virtually all types of seizure, and safely in patients whose seizure type is poorly characterised.27 The mean efficacy of VPA has been reported to be 70% to 76% in more than 800 patients with SE.23,25 The response rate was better in children than in adults and did not differ between the SE types. The effective loading doses vary across different studies. A dose of 40 mg/kg (maximum, 3000 mg) can be given over 5 to 10 minutes.27

Safety studies have reported a <10% overall incidence of adverse events. The reported side-effects were mainly dizziness, thrombocytopenia and mild hypotension, independent of infusion rate. It was well tolerated even at high doses and fast infusion rates up to 30 mg/kg at 10 mg/kg/min with little cardiorespiratory side-effects. High doses of IV VPA, however, are more likely to cause hyperammonaemia that may be dangerous in susceptible patients, eg young children with undiagnosed underlying metabolic diseases. There is also a risk of hepatic and pancreatic toxicity, and VPA encephalopathy.23,25

Levetiracetam

The drug LEV is currently licensed as monotherapy for the treatment of partial-onset seizures with and without secondary generalisation and as add-on therapy for myoclonic and primary generalised tonic-clonic seizures. Intravenous LEV is currently approved by the United States Food and Drug Administration as an adjunctive treatment in patients aged ≥16 years as an AED when oral therapy is not tolerated.28,29

Of note is that LEV is characterised by a linear pharmacokinetic profile with less than 10% protein binding and no hepatic metabolism. With twice daily infusion, a steady state can be achieved within 48 hours. Approximately 60% of the drug is excreted unchanged by the kidneys, and its plasma half-life is reported to be between 6 and 8 hours. It has a low risk of systemic side-effects and drug-drug interactions.29 Acutely applied LEV may preferentially modulate neuronal activity by inhibition of intracellular Ca²⁺ increase, delayed rectifier K⁺ currents, Cl⁻/HCO₃⁻ exchanger, and AMPA-receptors.30

In a recent meta-analysis, the mean efficacy was 68.5% in 234 patients with SE (95% confidence interval, 56.2%-78.7%).28 A dose of LEV up to 60 mg/kg (maximum, 4500 mg) could be given over 10 minutes in established SE.27

From the available evidence and clinical experience, IV VPA or LEV can both be considered an alternative to phenytoin in benzodiazepine-resistant SE, ie established SE. Input from neurologists will be helpful in subsequent management.

The ongoing Established Status Epilepticus Treatment Trial (NCT 01960075) is an international, multicentre study that is designed to find out the most effective and/or least effective treatment of established SE among patients older than 2 years by comparing three treatment arms: fosphenytoin, LEV, and valproic acid. It is hoped that the results can provide better guidance for our management.

Refractory status epilepticus

When seizures continue despite benzodiazepine and one other AED, it becomes refractory, regardless of the elapsed time. Patients with RSE are typically comatose or have a decreased consciousness level, and have cardiopulmonary compromise. They are best managed in an intensive care facility. The most commonly used continuous infusions are midazolam, propofol, and thiopentone. Currently there is insufficient evidence to recommend any one particular agent.31 Intensive care support is preferable at this stage of management.

Midazolam has a rapid onset of action and is easily titrated. Its main disadvantage is the development of tachyphylaxis with prolonged infusion.32 A recent report suggested that use of a higher infusion rate is associated with a reduction in seizure recurrence within 48 hours of discontinuation.33

Propofol has an onset of action within 3 to 5 minutes, and its half-life is only 5 to 10 minutes. The main concern with its use is development of propofol-related infusion syndrome, a rare but potentially lethal complication with dysrhythmia, heart failure, hyperkalaemia, hypertriglyceridaemia, metabolic acidosis, and rhabdomyolysis. Propofol infusion with dose exceeding 5 mg/kg/h is not recommended for >48 hours, especially in children.24 Propofol is associated with less tachyphylaxis and less hypotension than midazolam and thiopentone, respectively.

Thiopentone infusion has been used in RSE for over 50 years and is associated with a lower frequency of treatment failure. Its side-effects, however, include significant hypotension requiring pressors, prolonged mechanical ventilation,
Electroencephalogram (EEG) is essential when monitoring the effects of anaesthetics in the treatment of RSE. Although the primary goal of treatment is seizure control, the optimal extent of EEG suppression remains controversial: seizure suppression, burst suppression, or flat recording. There is no evidence from either prospective or retrospective studies to suggest an ‘adequate’ effect.35 Critical care continuous EEG monitoring is recommended to monitor the efficacy of continuous infusions of midazolam, propofol, or thiopentone. It can confirm seizure cessation and absence of seizure recurrence. Concurrent video recording is also strongly recommended as a supplement to clinical examination. If available, the EEG recording should be initiated as soon as possible after treatment of RSE, be continued until seizures are controlled for at least 24 hours, and preferably be continued for another 24 hours after the agent is withdrawn. Nonconvulsive seizures are common after treatment of convulsive seizures, both in adults and children.36,37 Seizures may also recur despite EEG-confirmed burst suppression or complete suppression of background seizures, such that intermittent recording may not be adequate.38 Ideally the recording should also be reviewed periodically, at least twice daily. Nonetheless, such intensive EEG monitoring is currently not feasible in most settings and we should consider offering the most pragmatic level of care that resources allow.39 There are no studies to suggest the optimal duration and weaning of anaesthetic infusion although most experts would agree that continuing the infusion for approximately 24 hours after controlling the seizures and weaning over 6 to 12 hours is a reasonable regimen.39

Recently there have been reports to suggest that use of anaesthetic coma in patients might be associated with prolonged hospital stay, higher infection rates, and increased mortality. Both Sutter et al40 and Marchi et al41 reported similar findings and there was at best Class III evidence that patients treated with therapeutic coma had a poorer outcome, independent of possible confounders. Nonetheless both studies were retrospective and were performed at a single tertiary centre where subjects were non-randomised and managed according to current guidelines. There remain many unanswered questions regarding use of anaesthetic agents in SE.42 Meanwhile we should carefully and individually balance the risks and benefits of using anaesthetic agents to treat patients with RSE.

### Super-refractory status epilepticus

The term SRSE was first used in the Third London-Innsbruck Colloquium on Status Epilepticus held in Oxford on 7-9 April 2011.4 It is an uncommon but challenging condition to manage. Current management is based mainly on case series and expert opinion.39 Treatment aims in SRSE include: (1) establishing and treating underlying causes where feasible, (2) controlling the seizures, (3) neuroprotection, and (4) avoiding or treating systemic complications associated with prolonged

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**TABLE. Investigations in status epilepticus**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Descriptions</th>
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<tbody>
<tr>
<td>Basic investigations: in all patients</td>
<td>• Fingerprick glucose</td>
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<tr>
<td></td>
<td>• Vital signs (ABC: airway, breathing, circulation, etc)</td>
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<td></td>
<td>• Computed tomography of brain</td>
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<td></td>
<td>• Laboratory tests: blood glucose, renal and liver function tests, calcium, magnesium, drug levels</td>
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<td></td>
<td>(where appropriate)</td>
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<tr>
<td></td>
<td>• Electroencephalogram</td>
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<tr>
<td>Further investigations: based on clinical</td>
<td>• Cerebrospinal fluid for infection</td>
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<tr>
<td>history and examination</td>
<td>• Toxicology screen</td>
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<tr>
<td></td>
<td>• Blood gases</td>
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<tr>
<td></td>
<td>• Thyroid function/antithyroglobulin and antiperoxidase antibodies</td>
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<tr>
<td></td>
<td>• Metabolic screen</td>
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<tr>
<td></td>
<td>• Infection screen</td>
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<tr>
<td></td>
<td>• Magnetic resonance imaging (of brain) ± contrast</td>
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<tr>
<td>Other investigations to be considered (not</td>
<td>• Autoimmune encephalitis45 (blood ± cerebrospinal fluid) for NMDAR, VGKC (LGI1, Caspr2), AMPAR,</td>
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<td>exhaustive)</td>
<td>GABA-B, mGlur5, GAD65, VGCC type N or P/Q, gAChR, DPPX, etc</td>
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<td></td>
<td>• Cerebrospinal fluid for cytology</td>
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<td></td>
<td>• Vasculitis screen (ANA, dsDNA, C3/C4, ANCA, etc)</td>
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<td></td>
<td>• POLG gene ± other mitochondrial diseases</td>
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<tr>
<td></td>
<td>• Uncommon infections: scrub typhus, mycoplasma pneumonia, HIV, syphilis, etc</td>
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Abbreviations: AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; Caspr2 = contactin-associated protein-like 2; DPPX = dipeptidyl-peptidase-like protein-6; dsDNA = double-stranded DNA; GABA-B = γ-aminobutyric acid-B; gAChR = neuronal ganglionic nicotinic acetylcholine receptor; GAD65 = glutamic acid decarboxylase 65; HIV = human immunodeficiency virus; LGI1 = leucine-rich glioma inactivated protein 1; mGlur5 = metabotropic glutamate receptor 5; NMDAR = N-methyl-D-aspartate receptor; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel

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anaesthesia.

The underlying cause is by far the most significant factor in determining the outcome of SRSE. Besides basic investigations, other uncommon causes may need to be considered, especially because some may have therapeutic implications. Such causes include: (1) immune-mediated diseases, (2) mitochondrial diseases, (3) uncommon infective disorders, (4) genetic disorders, and (5) drugs and toxins. Lists of these conditions are found in other reviews.43,44 A brief summary of important investigations is shown in the Table.45 Regarding the maintenance AEDs, Shorvon and Ferlisi39 recommended: (1) polytherapy with two AEDs at high doses, (2) avoiding frequent switching of drugs, (3) preferably choosing drugs with low interaction potential and no renal/hepatic toxicity, and (4) avoiding GABAergic AEDs.

The importance of recognising the underlying aetiology in overall management cannot be over-emphasised. The prototype example is the increasing reports of autoimmune causes in de-novo–onset SRSE.45 There is increasing recognition of potential pathogenicity of various cell surface antigen autoantibodies in patients with acute onset of epilepsy. Thus, a high index of suspicion is essential for diagnosis. Many of these antibody tests are not available locally and results take weeks to return. Empirical therapy with immune-modulatory treatment (methylprednisolone, IV immunoglobulin, and/or plasma exchange) may be considered, especially if the patient has evidence of central nervous system inflammation on cerebrospinal fluid (ie elevated protein, pleocytosis and/or oligoclonal bands) or on magnetic resonance brain scan (ie mesial temporal or parenchymal fluid-attenuated inversion recovery/T2-weighted hyperintensity). Supportive clinical features include viral prodrome,
antecedent psychiatric symptoms, and a history of systemic autoimmunity.46

Treatment of SRSE remains a challenge for clinicians. Various options have been tried in case reports/case series to minimise prolonged use of anaesthetic agents. Ketamine, a non-competitive antagonist of the NMDA glutamate receptor, has demonstrated its antiepileptic properties in clinical studies and it is not associated with significant cardiovascular depression. Clinical experience in case series also supports its efficacy. Response to ketamine was shown to be better when used as a third- or fourth-line agent rather than late in the course of SRSE and when the maintenance dose was greater than 0.9 mg/kg/h.47

Intravenous magnesium has also been used in SRSE, even in the absence of evidence of hypomagnesaemia. Its antiepileptic effect, however, has not been consistently supported in an experimental setting. A recent review found reports of use in 28 non-epileptic patients in whom magnesium stopped SE in half. Adverse events of limb weakness and heart block were documented in three patients. Its possible role in SRSE, therefore, remains to be defined.48

A ketogenic diet has also been used in SRSE. It has been used in paediatric patients for many years. Its use in adult SE also appears promising. In a multicentre retrospective study of 10 adult patients, 90% of patients achieved ketosis, and SE ceased in a median of 3 days in all patients who achieved ketosis.49 Prospective trials are warranted to examine the efficacy of a ketogenic diet in adults with RSE.49 Other management modalities that include hypothermia, electroconvulsive therapy, and epilepsy surgery are still under investigation with variable success rate.50-52

An updated algorithm for the overall management of SE is summarised in the Figure.27,46,49,53

**Conclusion**

Convulsive SE—from established SE, RSE, to SRSE—remains a challenging condition to manage. The heterogeneous aetiology, presentation, natural history, and outcome increase the difficulty in performing randomised clinical trials that satisfy contemporary standards. The RAMPART study demonstrated non-inferiority of IM midazolam in early SE. In addition, VPA and LEV have also emerged as possible alternatives for phenytoin in established SE. The potential role of lacosamide in this stage of SE remains to be defined. Management of RSE and SRSE remains mostly non–evidence-based. Increasing international collaboration is important to better understand the condition. The new definition of SE from ILAE may also help to limit the methodological heterogeneity by unifying definitions and stages.

**Acknowledgement**

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**Disclaimer**

This review is designed to assist clinicians by providing an analytical framework for evaluating and treating patients with convulsive status epilepticus. It is not intended to replace a clinician’s medical judgement, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm will not apply to nor work with all patients.

**References**


