

# Status epilepticus in adults

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Status epilepticus is a common neurological emergency with considerable associated health-care costs, morbidity, and mortality. The definition of status epilepticus as a prolonged seizure or a series of seizures with incomplete return to baseline is under reconsideration in an effort to establish a more practical definition to guide management. Clinical research has focused on early seizure termination in the prehospital setting. The approach of early escalation to anaesthetic agents for refractory generalised convulsive status epilepticus, rather than additional trials of second-line anti-epileptic drugs, to avoid neuronal injury and pharmaco-resistance associated with prolonged seizures is gaining momentum. Status epilepticus is also increasingly identified in the inpatient setting as the use of extended electroencephalography monitoring becomes more commonplace. Substantial further research to enable early identification of status epilepticus and efficacy of anti-epileptic drugs will be important to improve outcomes.

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## Introduction

Most seizures are brief and self-limited. Status epilepticus is broadly defined as a prolonged seizure or multiple seizures with incomplete return to baseline and remains a common neurological emergency with an annual incidence of 10–41 per 100 000 population.<sup>1–5</sup> The overall mortality associated with status epilepticus approaches 20%,<sup>6,7</sup> with generalised convulsive status epilepticus representing about 45–74% of all cases.<sup>12</sup> In view of the incidence of status epilepticus and its substantial morbidity and mortality, annual direct inpatient costs are estimated at more than €83 million in Germany<sup>8</sup> and US\$4 billion in the USA.<sup>9</sup>

Several advances in the study of status epilepticus have been made, and the increased use of extended electroencephalography (EEG) monitoring has shown a high prevalence of seizures and status epilepticus in the hospital setting. An improved understanding of the pathophysiological mechanisms underlying status epilepticus highlights the need for a more practical definition of the disorder and underscores the importance of early seizure cessation to avoid pharmaco-resistance as seizure duration increases. These concepts have contributed to the design of treatment trials in status epilepticus during the past decade.

In this Review, we discuss the current knowledge about status epilepticus and refractory status epilepticus in adults and focus mainly on the definitions, pathophysiology, epidemiology, outcomes, and treatment of generalised convulsive status epilepticus. We then summarise the data on the utility of extended EEG monitoring and emphasise the importance of early termination of status epilepticus, examine the use of new anti-epileptic rescue drugs, and review the major pre-hospital treatment trials for status epilepticus. We also propose an updated, practical treatment algorithm for generalised convulsive status epilepticus, describe plans for upcoming treatment trials, and highlight areas in need of further research.

## Definitions

The 1981 International League Against Epilepsy (ILAE) definition of status epilepticus describes a seizure that “persists for a sufficient length of time or is repeated

frequently enough that recovery between attacks does not occur”.<sup>10</sup> The absence of a definitive timeframe of seizure duration creates ambiguity, which makes it difficult to accurately define and treat status epilepticus. Accordingly, status epilepticus was redefined as a seizure lasting 60 min, then further refined by the Epilepsy Foundation to a seizure lasting 30 min on the basis of estimates of the time needed to sustain neuronal injury from a prolonged seizure.<sup>11</sup>

As understanding of seizures and status epilepticus matures, so too should the definitions thereof. Most seizures are brief and unlikely to last more than 1–2 min before spontaneously resolving.<sup>12</sup> Moreover, evidence indicates that pharmaco-resistance, especially to benzodiazepines, increases as seizure duration increases.<sup>13,14</sup> On the basis of evidence of typical seizure duration, animal data of neuronal injury, and data of pharmaco-resistance, an operational (as opposed to mechanistic) definition of status epilepticus stipulates the treatment of convulsive status epilepticus within 5 min of seizure onset.<sup>15</sup> This definition can also be extended to other forms of status epilepticus, including focal status epilepticus with dyscognitive features and absence status epilepticus. At present, the ILAE is considering a proposal of a more practical operational definition of status epilepticus that emphasises early identification and treatment. This new definition emphasises two critical timepoints; the duration of the seizure and the time at which a prolonged seizure could lead to long-term consequences, including neuronal injury and cell death.

## Epidemiology, aetiology, and outcomes

Status epilepticus is relatively common, with estimates of 50 000–60 000 new cases annually in the USA.<sup>2,16</sup> The incidence of status epilepticus in Europe is somewhat lower (10–16 per 100 000 population)<sup>4,5,17</sup> compared with the USA (18–41 per 100 000 population). Notably, American ethnic minorities have a substantially higher incidence (57 per 100 000) than whites (20 per 100 000).<sup>1</sup> Results of trend studies<sup>3,18</sup> show an increase in incidence of status epilepticus in the past few decades in the USA. Findings from a study<sup>2</sup> of first episodes of status

epilepticus showed that the majority (54%) of cases occur in the absence of a known diagnosis of epilepsy. When associated with epilepsy, status epilepticus tends to occur early in the course of epilepsy, representing the first or second unprovoked seizure 65% of the time. Status epilepticus also confers an increased risk of future seizures, with a 3.3-times higher risk of a subsequent unprovoked seizure after symptomatic status epilepticus, compared with the risk following a single, self-limited, symptomatic seizure.<sup>19</sup>

The overall mortality for status epilepticus in adults of about 20%<sup>20</sup> does not appear to be changing with time.<sup>18</sup> Outcomes are usually worse when seizures are prolonged. Evidence suggests that seizures lasting more than 30 min are less likely to terminate spontaneously and are associated with a higher mortality than seizures lasting less than 30 min.<sup>21</sup> With respect to status epilepticus-related mortality, the most important determinant remains the underlying cause of status epilepticus. The aetiologies of status epilepticus in adults are often divided into acute and chronic underlying causes to further examine their frequency and outcomes (table 1). Additional studies<sup>4,22,23</sup> have examined aetiologies and status epilepticus-related mortality, but methodological variability among studies is high and limits direct comparisons. Although the aetiology of status epilepticus varies between study populations, acute symptomatic causes of convulsive status epilepticus are generally more common and tend to be associated with higher rates of morbidity and mortality than chronic aetiologies.<sup>2,5</sup> Of the acute symptomatic aetiologies, stroke tends to be the most common.<sup>4,20</sup>

	Frequency (%)	Mortality (%)
<b>Acute</b>		
Stroke	22%	33%
Metabolic abnormalities	15%	30%
Hypoxia	13%	53%
Systemic infection	7%	10%
Anoxia	5%	71%
Trauma	3%	25%
Drug overdose	3%	25%
CNS infection	3%	0%
CNS haemorrhage	1%	0%
<b>Chronic</b>		
Low concentration of anti-epileptic drugs	34%	4%
Remote symptomatic (eg, tumour, stroke, trauma)	25%	14%
Alcohol misuse	13%	20%
Tumour	7%	30%
Idiopathic	3%	25%
Some patients had more than one aetiology.		
<b>Table 1: The frequency and mortality associated with acute and chronic causes of status epilepticus in adults<sup>20</sup></b>		

Chronic epilepsy and low anti-epileptic drug levels are the most common causes of status epilepticus among chronic or acute causes and are associated with a relatively low mortality. Other common chronic aetiologies include the delayed effects of prior lesions or injuries, such as tumours, stroke, and traumatic brain injury, which often present after a latent period of weeks to years. In some instances, the ranges for the aetiological frequencies and associated mortalities are wide, which might stem from methodological differences between studies and the inherent challenges in accurately identifying the underlying cause of status epilepticus.

In an effort to predict mortality from status epilepticus, investigators developed the Status Epilepticus Severity Score (STESS)<sup>24</sup> from four variables measured at the time of presentation: level of consciousness, seizure type, patient age, and seizure history. This score, which has subsequently undergone external validation,<sup>25</sup> has been shown to reliably predict which patients have a favourable chance of surviving an episode of status epilepticus (ie, reliable negative predictive value).<sup>26</sup> However, further study of the STESS is needed before it can be widely used to guide management of status epilepticus and aid in prognostication.

### Pathophysiology and neuronal injury

Much of the pathophysiology of status epilepticus is still poorly understood, but studies using animal models have led to substantial advances in the understanding of the basic mechanisms underlying status epilepticus. Although numerous molecular and cellular processes are almost certainly involved in the development of status epilepticus, the fundamental principle involves a failure of endogenous mechanisms to terminate a seizure. This failure can occur because of excessive abnormal excitation during a seizure or from a loss of endogenous inhibitory mechanisms. These maladaptive changes allow a single seizure to transform into status epilepticus and contribute to the self-perpetuating nature and pharmaco-resistance of the disorder. Evidence in support of these principles was seen in a classic example of status epilepticus in people after the accidental ingestion of mussels contaminated with domoic acid,<sup>27,28</sup> an analogue of the major excitatory neurotransmitter glutamate. This observation supported the notion that excess excitation can contribute to the development of seizures and status epilepticus.

Over the past two decades, research has elucidated a continuum of maladaptive changes that contribute to the transition from a single seizure to status epilepticus and to the self-sustaining nature of status epilepticus (figure 1). In the initial milliseconds to seconds after onset of a seizure, neurotransmitter release, ion channel opening and closing, and protein phosphorylation set the stage for a potentially prolonged seizure.<sup>29</sup> These molecular events are followed by alterations in receptor trafficking, including an endocytosis-mediated decrease

in inhibitory GABA<sub>A</sub>  $\beta 2/\beta 3$  and  $\gamma 2$  receptor subunits<sup>30,31</sup> and an increase in excitatory NMDA receptors.<sup>32</sup> GABA<sub>A</sub> receptor modulation is thought to also contribute to the pharmacoresistance to benzodiazepines, which becomes more prominent as the duration of status epilepticus increases.<sup>13,14</sup> Further maladaptive changes that occur within the next minutes to hours include alternations in excitatory and inhibitory neuropeptide expression, which maintains the hyperexcitable state.<sup>33,34</sup> Analysis of the genetic and epigenetic changes that occur in the days and weeks after status epilepticus has revealed both increased and decreased expression of numerous genes after status epilepticus,<sup>35,36</sup> which may contribute to the process of epileptogenesis. Epigenetic changes, including genome-wide alterations in hippocampal cell DNA methylation, have also been shown in a mouse model of status epilepticus.<sup>37</sup> Altered regulation of microRNA, which regulates post-transcriptional gene expression, is also believed to play a part in epileptogenesis and status epilepticus-induced neuronal damage.<sup>38</sup>

Convulsive status epilepticus has long been known to cause neuronal damage. In a seminal series of experiments, convulsive seizures induced in baboons led to hyperthermia, hypotension, and hypoxia, which resulted in neuronal injury in the thalamus, hippocampus, and neocortex.<sup>39</sup> Paralysis of the baboons to prevent convulsive activity yielded only partial protection against neuronal injury from induced status epilepticus, which implies that even non-convulsive electrographic seizures can result in neuronal damage and cell death.<sup>40</sup> Results of further studies<sup>41–44</sup> using various animal models of status epilepticus identified a myriad of potential mechanisms that could contribute to neuronal cell death and injury, including excitotoxicity, necrosis, apoptosis, and mitochondrial dysfunction. Evidence of neuronal injury and cell death is also increasingly recognised in human beings after status epilepticus. Serum neuron-specific enolase, a marker of neuronal injury, is elevated after both convulsive and non-convulsive status epilepticus.<sup>45–47</sup>

## Clinical presentation, diagnostic yield of extended EEG, and radiographic findings

### Diagnostic yield of extended EEG monitoring

Status epilepticus can present in several forms: convulsive, non-convulsive, and electrographic. The initial presentation of convulsive status epilepticus is typically not subtle, and is characterised by unresponsiveness and tonic, clonic, or tonic-clonic movements of the extremities. Non-convulsive status epilepticus has not been precisely defined, but is characterised by prolonged seizure activity evidenced by epileptiform discharges on EEG. There are various subtypes of non-convulsive status epilepticus, and some patients present with a change in behaviour or cognition in the absence of obvious motor manifestations. Both focal and generalised forms of non-convulsive status epilepticus exist and are reviewed

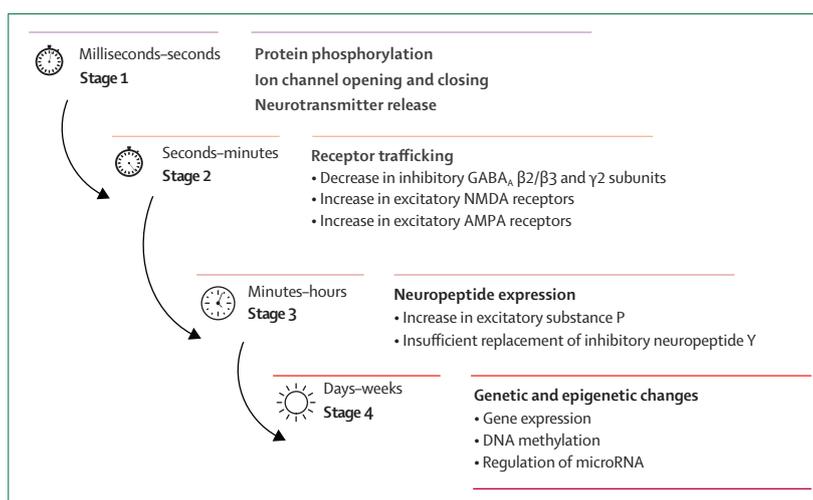


Figure 1: Cascade of selected mechanisms involved in the transition of a single seizure to status epilepticus

in detail by Meierkord and Holtkamp.<sup>48</sup> Subtle status epilepticus is a subtype of non-convulsive status epilepticus that is commonly used for comatose patients who show electrographic evidence of prolonged seizure activity. The diagnosis of subtle status epilepticus is challenging, often complicated drugs used in comatose patients (anaesthetics and paralytics), and is limited by EEG interpretation, which might vary between experts and cannot be used to diagnose status epilepticus with absolute certainty.

With time, it is common for these initially obvious clinical manifestations of convulsive status epilepticus to evolve into more subtle twitching of the extremities or face, or saccadic eye movements.<sup>49,50</sup> The clinical picture can be further complicated by the administration of drugs, particularly anaesthetics and analgesics, which can cause myoclonic jerks that can appear similar to a convulsion, but can often be differentiated from a convulsion because they do not last long. In a study of patients treated for generalised convulsive status epilepticus,<sup>51</sup> 79 (48%) of 164 patients continued to have persistent electrographic seizures on EEG and 24 (15%) of 164 patients were diagnosed as being in non-convulsive status epilepticus. Thus, a high index of suspicion for non-convulsive seizures and a low threshold to obtain extended EEG should be maintained in the setting of unexplained, persistent encephalopathy.

### Diagnostic yield of extended EEG monitoring

Numerous studies have shown high rates of seizures in patients with specific neurological injuries. Seizures occur in up to 15% of patients with subarachnoid haemorrhage,<sup>52</sup> in up to 30% of patients with intracerebral haemorrhage,<sup>53–55</sup> in up to 10% of patients with ischaemic stroke,<sup>56,57</sup> and in a wide range of patients with traumatic brain injury, depending largely on the severity of injury.<sup>58,59</sup> Non-convulsive electrographic seizures and

status epilepticus are increasingly recognised as relatively common and as potentially reversible aetiologies of encephalopathy in both critically and non-critically ill patients admitted to hospitals. Non-convulsive seizures and status epilepticus are also associated with neuronal injury and require prompt treatment. Table 2 summarises the prevalence of seizures and status epilepticus in various inpatient populations and the clinical features associated with a higher risk of seizures. Interpretation of these data warrants caution because the studies are retrospective and definitions and interpretations of electrographic seizures and interictal patterns can vary. A major conclusion drawn from these studies is that seizures and status epilepticus are relatively common in a variety of in-patient settings, and that a high index of suspicion and a low threshold for extended EEG is essential for patients with persistently unexplained or fluctuating encephalopathy. In studies where the timing of seizures was analysed,<sup>61,64</sup> 96 (87%) of 110 patients<sup>61</sup> and 69 (97%) of 71 patients,<sup>64</sup> in whom a seizure was documented, experienced their first seizure within the first 24 h of recording, although comatose patients were more likely to experience their first seizure more than 24 h after the initiation of continuous EEG.<sup>61</sup> Although studies have linked seizures and status epilepticus to poor outcomes,<sup>62,66,67</sup> the effect of EEG monitoring and the detection of electrographic seizures on patient outcomes remains unknown. Does treatment of these seizures improve outcomes in critically ill patients, or do the seizures serve as a marker for more severe brain injury, the outcome of which is more difficult to alter?

Study population	N	Prevalence of seizures or status epilepticus	Associated conditions	
Towne et al (2000) <sup>60</sup>	Mixed intensive care units, all patients comatose	236	8% non-convulsive status epilepticus	None
Claassen et al (2004) <sup>61</sup>	Mixed intensive care units	570	19% had seizures (of which 92% had exclusively non-convulsive seizures)	Coma, age <18 years, history of epilepsy, clinical seizure before EEG
Oddo et al (2009) <sup>62</sup>	Medical intensive care unit	201	10% had seizures (67% were exclusively non-convulsive)	Sepsis at time of admission
Kamel et al (2012) <sup>63</sup>	Medical intensive care unit and surgical intensive care unit	105	11%	None
Betjemann et al (2013) <sup>64</sup>	General inpatient population	1048	7%	Intracranial mass, spells (eg, shaking, staring, reduced responsiveness) as indication for EEG
Kurtz et al (2014) <sup>65</sup>	Surgical intensive care unit	154	16%	Coma, clinical seizure before EEG

EEG=electroencephalography.

**Table 2: Prevalence of seizures and status epilepticus in various inpatient populations**

### Radiographic findings

A variety of radiographic findings during and following status epilepticus have been described. Early reports described hemispheric swelling and subsequent atrophy apparent from pneumoencephalograms of children who had status epilepticus and resultant post-ictal paralysis.<sup>68</sup> CT scans after status epilepticus have shown decreased attenuation, swelling, loss of grey-white matter differentiation, sulcal effacement, and a gyriform pattern of enhancement.<sup>69,70</sup> Findings on MRI after status epilepticus often resemble a stroke (figure 2): T2 hyperintensity and restricted diffusion, with corresponding low signal on apparent diffusion coefficient.<sup>70-74</sup> These abnormalities are often seen in the cortex and hippocampi; however, other structures can be affected, including the leptomeninges (abnormal enhancement), basal ganglia, corpus callosum, and thalami, particularly the pulvinar nuclei.<sup>71,73,74</sup> Similar to reports in the stroke literature, crossed cerebellar diaschisis after status epilepticus has been reported frequently.<sup>75,76</sup> In some instances, the findings are reversible and resolve on subsequent imaging; however, persistent imaging abnormalities, such as focal atrophy and the development of hippocampal sclerosis, are common, which implies that permanent neuronal damage has occurred.<sup>74,77,78</sup>

### Pre-hospital management of status epilepticus

In a retrospective review of adults presenting with status epilepticus,<sup>79</sup> first-line therapy (typically diazepam followed by phenytoin) effectively aborted status epilepticus in 92 (60%) of 154 patients treated within 30 min of seizure onset. However, the efficacy of first-line treatment decreased as seizure duration increased. Owing to our knowledge of pharmaco-resistance and neuronal injury as status epilepticus duration increases, clinical research has focused on early treatment of status epilepticus in the pre-hospital setting. As a result of several pre-hospital drug trials,<sup>80-87</sup> status epilepticus treatment now often begins before the emergency department.

Although rectal diazepam has long been known to be effective in aborting seizures in the paediatric population,<sup>80,81</sup> the first rigorous pre-hospital study to examine the efficacy and safety of benzodiazepine use by first-responders for the treatment of status epilepticus was published in 2001.<sup>82</sup> Results of this study showed that intravenous benzodiazepines (lorazepam and diazepam) were superior to placebo in terminating status epilepticus. The patients treated with benzodiazepines also had lower rates of respiratory compromise necessitating intubation, probably due to the shorter duration of seizures in the treatment groups.

After this initial pre-hospital study,<sup>82</sup> the emphasis shifted towards an effort to improve the ease of administration of abortive anti-epileptic drugs through the study of buccal and intranasal preparations. Findings from a study of children in the pre-hospital setting showed that buccal midazolam was as safe and effective

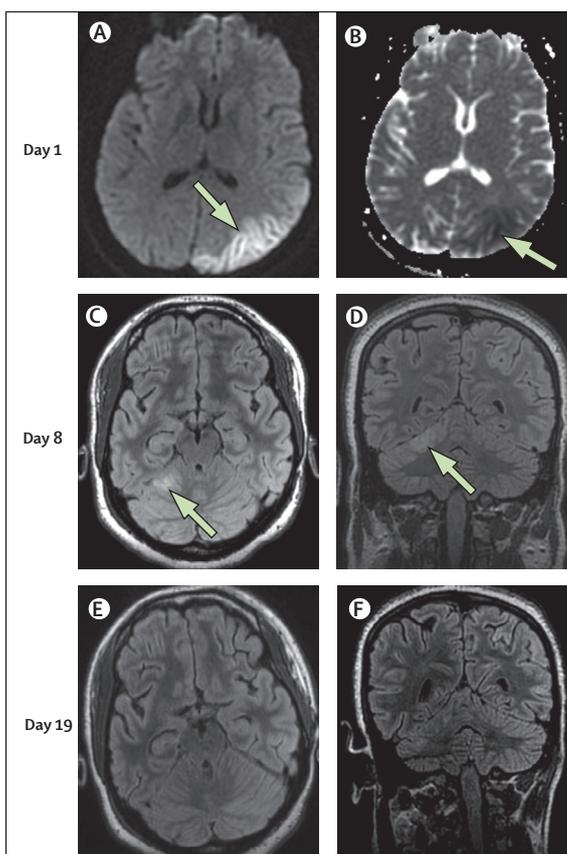
as rectal diazepam in terminating seizures.<sup>83</sup> A subsequent randomised controlled trial<sup>84</sup> showed buccal midazolam to be superior to rectal diazepam for children actively seizing at the time of presentation to the emergency room, without increasing the incidence of respiratory compromise. Results of a prospective randomised study<sup>85</sup> showed that intranasal midazolam was as effective as intravenous diazepam for the termination of paediatric febrile seizures. In a study of adults living in a residential institution,<sup>86</sup> buccal midazolam was as safe and effective as rectal diazepam in terminating status epilepticus.

The study of these alternative routes of administering abortive therapies laid the groundwork for the Rapid Anticonvulsant Medications Prior to Arrival Trial (RAMPART),<sup>87</sup> a randomised, double-blind comparison of the pre-hospital administration of intravenous lorazepam with intramuscular midazolam. The findings of this study indicated that midazolam was as effective as lorazepam in the timely termination of status epilepticus and was not associated with an increase in respiratory compromise or seizure recurrence. These trials have paved the way for the safe use of anti-epileptic rescue drugs, both in the home by family members and under the supervision of first responders.

### Hospital management of status epilepticus

Generalised convulsive status epilepticus is managed as a true medical emergency, in which the patient is stabilised, airway and vital signs are assessed and controlled, and intravenous access is obtained. Tonic-clonic seizures can be associated with periods of apnoea, cyanosis, and metabolic acidosis. The metabolic acidosis almost always self-corrects once seizures are adequately controlled. Most patients are able to breathe adequately during a seizure as long as their airway remains patent. Nonetheless, supplemental oxygen should be provided via nasal cannula or facemask, with a low threshold for endotracheal intubation if clinical signs of impending respiratory failure are observed. If intubation is necessary, use of a shortacting paralytic is preferable from a neurological standpoint to allow for assessment of ongoing clinical seizure activity. Initial management should also include a rapid assessment of blood glucose level. Patients should receive parenteral thiamine (up to 500 mg intravenous) before or concurrent with glucose to avoid depleting available thiamine stores and causing an acute Wernicke encephalopathy.<sup>88</sup>

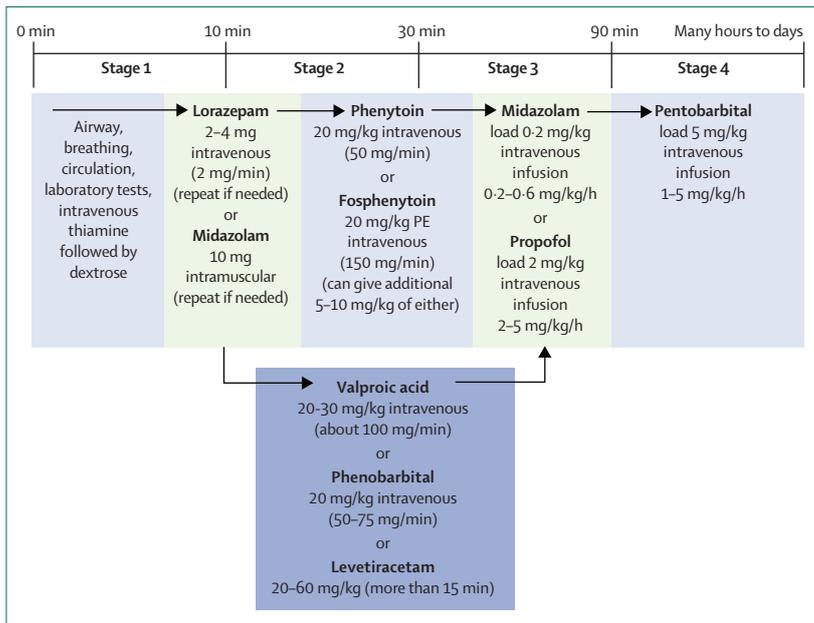
Once the patient is stabilised, the focus should shift to the rapid termination of seizure activity to minimise systemic dysfunction, neurological injury, pharmacoresistance and, ultimately, morbidity and mortality. Figure 3 provides an updated treatment algorithm for generalised convulsive status epilepticus that emphasises a more rapid progression to anaesthetic drugs to achieve early seizure termination. Intravenous lorazepam, with its rapid onset of action, has been the initial drug of choice,



**Figure 2:** MRI of a single patient with focal left hemispheric status epilepticus during a single admission to hospital

Diffusion-weighted imaging showing (A) cortically predominant restricted diffusion of the left parietal and occipital lobes with (B) low signal intensity on the corresponding apparent diffusion coefficient sequence. (C) Axial and (D) coronal T2 fluid-attenuated inversion recovery (FLAIR) sequences showing left hemispheric cortical hyperintense signal and an area of hyperintense signal in the right cerebellar hemisphere, consistent with crossed cerebellar diaschisis. (E) Axial and (F) coronal T2 FLAIR images at day 19 showing improvement from day 8 in the left hemispheric cortical hyperintense signal and resolution of the right cerebellar hyperintensity.

although intramuscular midazolam has emerged from RAMPART<sup>87</sup> as an alternative to intravenous lorazepam. The efficacy of intravenous lorazepam was shown in a randomised double-blind comparison of intravenous lorazepam with phenobarbital alone, phenytoin alone, or diazepam followed by phenytoin.<sup>89</sup> Lorazepam successfully terminated overt status epilepticus in 65% of 97 cases, similar to the results seen with phenobarbital and diazepam plus phenytoin, and superior to phenytoin alone. Although not specifically studied in this trial, convention has been to treat status epilepticus with lorazepam, which can be repeated, followed by intravenous phenytoin or fosphenytoin. Despite being more costly, preference is ideally given to fosphenytoin because it can be administered at a faster rate but with the same risk of arrhythmia and hypotension as with phenytoin and with a lower risk for local adverse reactions in case of intravenous



**Figure 3:** Updated treatment algorithm for generalised convulsive status epilepticus in adults and older children PE=phenytoin equivalents.

extravasation.<sup>90</sup> Of note, phenytoin and fosphenytoin dosing is weight-based (20 mg/kg), and a convenient dose of 1000 mg intravenously is often insufficient.<sup>91</sup> If a patient continues to seize after the initial dose, a second smaller dose of 5–10 mg/kg can be administered. Total serum phenytoin concentrations can rise to a supratherapeutic goal range (20–30 µg/mL) after correction for albumin, although treatment should not be delayed while awaiting measurements of drug concentrations.

Intravenous valproic acid, phenobarbital, and levetiracetam have emerged as alternative second-line anti-epileptic drugs for the treatment of status epilepticus. Current practice patterns surrounding the use of second-line anti-epileptic drugs are quite variable. Many clinicians, particularly outside the USA, choose these alternative drugs as a preferred second-line agent instead of phenytoin for patients with status epilepticus refractory to lorazepam. In other instances, these alternative drugs are employed as adjunct anti-epileptic drugs for status epilepticus refractory to lorazepam and phenytoin before proceeding to anaesthetics. Table 3 summarises studies comparing these anti-epileptic drugs in the treatment of status epilepticus.<sup>92–97</sup> Lacosamide has also received attention as a potential second-line anti-epileptic drug for status epilepticus. Data are limited at present, but results of recent retrospective studies<sup>98–100</sup> suggest that intravenous lacosamide at a dose of 200–400 mg is safe and can be effective in treating status epilepticus. Restrictions exist when interpreting these studies of second-line anti-epileptic drugs, most notably the small sample sizes and significant methodological variability. Importantly, there are no class 1, head-to-head, blinded comparisons of these

other anti-epileptic drugs in the treatment of status epilepticus. The Established Status Epilepticus Treatment Trial (ESETT; NCT01960075), funded by the National Institute of Neurological Disorders and Stroke and set to initiate enrolment in 2015, will address this issue by comparing fosphenytoin, valproic acid, and levetiracetam for the treatment of benzodiazepine-refractory status epilepticus in a randomised, blinded fashion.<sup>101</sup>

Previous convention for the treatment of generalised convulsive status epilepticus refractory to initial treatment with lorazepam and a second-line anti-epileptic drug typically included additional trials of second-line anti-epileptic drugs before an anaesthetic agent. The updated algorithm in figure 3 highlights an important shift in the treatment of generalised convulsive status epilepticus in adults, emphasising early escalation to anaesthetics to achieve seizure termination.<sup>102</sup> If seizures continue despite initial treatment with lorazepam and a second-line anti-epileptic drug, some investigators now advocate a more rapid progression to intravenous anaesthetics (within 30–60 min of seizure onset) rather than give another second-line anti-epileptic drug. Anaesthetic use can be associated with potentially serious complications; however, their early use for refractory generalised convulsive status epilepticus is becoming more common as the clinical emphasis shifts towards early seizure cessation to minimise neuronal injury and pharmaco-resistance, which increase with prolonged seizure duration.

The optimum treatment of non-convulsive status epilepticus is less well defined owing to a paucity of data, but some important considerations are worth highlighting. Contrary to generalised convulsive status epilepticus, most forms of non-convulsive status epilepticus are not associated with life-threatening systemic dysfunction and are therefore perceived as less of a medical emergency. The initial treatment of non-convulsive status epilepticus, including focal status epilepticus with dyscognitive features (previously known as complex partial status epilepticus), focal status epilepticus without dyscognitive features (previously known as simple partial status epilepticus), and absence status epilepticus, is similar to generalised convulsive status epilepticus and begins with benzodiazepines. If seizure activity persists, a repeat dose of benzodiazepines should be considered, followed by an anti-epileptic drug. For most forms of non-convulsive status epilepticus that persist after treatment with benzodiazepines and an anti-epileptic drug, additional trials of anti-epileptic drugs are often preferred rather than early escalation to anaesthetics.<sup>48,103</sup> This strategy is especially relevant in cases of non-convulsive status epilepticus in which consciousness is somewhat preserved and the risks of anaesthetics might outweigh the risks of continued seizure activity.<sup>104</sup>

### Refractory status epilepticus

A comprehensive review of refractory status epilepticus is beyond the scope of this Review but can be found in

	Treatment	N	Design	Results
Shaner et al (1998) <sup>92</sup>	Diazepam (2 mg/min up to 20 mg) plus phenytoin (up to 18 mg/kg) vs phenobarbital (10 mg/kg)	36	Prospective, randomised, non-blinded	Phenobarbital as effective as diazepam plus phenytoin
Misra et al (2006) <sup>93</sup>	Phenytoin (18 mg/kg) vs valproic acid (30 mg/kg)	68	Prospective, randomised pilot study, used as first-line and second-line anti-epileptic drugs	Valproic acid more effective than phenytoin
Agarwal et al (2007) <sup>94</sup>	Phenytoin (20 mg/kg) vs valproic acid (20 mg/kg)	100	Prospective, randomised, non-blinded, refractory to intravenous diazepam	Valproic acid equivalent to phenytoin
Gilad et al (2008) <sup>95</sup>	Phenytoin (18 mg/kg) vs valproic acid (30 mg/kg)	74	Prospective, randomised, without prior benzodiazepine administration	Valproic acid equivalent to phenytoin
Alvarez et al (2011) <sup>96</sup>	Phenytoin (20 mg/kg) vs valproic acid (20 mg/kg) vs levetiracetam (20 mg/kg)	187	Retrospective, non-randomised, refractory to benzodiazepines	Levetiracetam less effective than valproic acid; no significant difference between valproic acid and phenytoin
Misra et al (2012) <sup>97</sup>	Levetiracetam (20 mg/kg) vs lorazepam (0.1 mg/kg)	79	Prospective, randomised, open label pilot study	Levetiracetam equivalent to lorazepam

**Table 3: Selected studies of second-line anti-epileptic drugs for the treatment of status epilepticus**

reviews by Rossetti and Lowenstein<sup>105</sup> and Ferlisi and Shorvon.<sup>106</sup> Refractory status epilepticus is commonly defined as status epilepticus that does not terminate with a first-line agent (benzodiazepines) or a second-line anti-epileptic drug (phenytoin, valproic acid, levetiracetam, or phenobarbital).<sup>107</sup> The diagnosis of refractory status epilepticus is clinical and often involves the use of EEG to show electrographic evidence of continued seizure activity because patients are often intubated, paralysed, and sedated after benzodiazepines and an anti-epileptic drug fail to stop their seizures. Between 23% and 43% of patients in status epilepticus will progress to refractory status epilepticus.<sup>107–109</sup> Mortality rates for refractory status epilepticus range from 17% to 39%, approximately three times higher than rates for non-refractory status epilepticus.<sup>107–110</sup>

Rapid seizure control in refractory status epilepticus is crucial to avoid the development of pharmacoresistance and ongoing neurological injury, which justifies early escalation to anaesthetic agents rather than the use of additional anti-epileptic drugs used for generalised convulsive status epilepticus. The three commonly used anaesthetics in the USA, midazolam, propofol, and pentobarbital, are given as an intravenous bolus before maintenance infusion, whereas thiopental is a particularly common anaesthetic in Europe. Choice of anaesthetic depends largely on individual circumstances, such as medication interactions, comorbidities, and vital-sign instability.

Midazolam and propofol tend to be first-line anaesthetics, whereas pentobarbital is often reserved for status epilepticus refractory to these drugs. The half-life of midazolam is initially short; however, the half-life increases as the duration of treatment increases.<sup>111</sup> Prolonged administration of midazolam is often complicated by an acute decrease in drug response (tachyphylaxis), which might necessitate dose adjustments to maintain seizure suppression. Propofol also has a short half-life, which is advantageous when frequent

neurological exams are required. Propofol infusion for more than 48 h should be done with caution because of the increased risk of a life-threatening propofol infusion syndrome characterised by rhabdomyolysis, hypertriglyceridaemia, cardiac and renal failure, and metabolic acidosis.<sup>112</sup> Pentobarbital has a considerably longer half-life owing to its propensity to accumulate in adipose tissue. A review of anaesthetic use for refractory status epilepticus<sup>113</sup> reported no significant difference in short-term mortality between patients treated with these drugs; however, pentobarbital was associated with a lower frequency of breakthrough seizures but also a higher frequency of hypotension, compared with propofol and midazolam. An attempt to study the effects of anaesthetics in a prospective randomised trial was undersampled, but showed that barbiturates, such as thiopental and pentobarbital, were associated with a longer duration of mechanical ventilation compared with propofol.<sup>114</sup> Findings from other retrospective studies<sup>115,116</sup> suggested that use of an anaesthetic for treatment of status epilepticus might be associated with worse outcomes, including increased risk of infection and death; however, when weighing the adverse effects of ongoing seizure activity against the inherent risks of intravenous anaesthetics, the investigators ultimately concluded that further randomised, prospective studies were needed to inform decision making. These studies of anaesthetics should be interpreted with caution as their retrospective nature introduces bias and makes it difficult to determine causality between poor outcomes, anaesthetics, and severity of status epilepticus.

For treatment of refractory status epilepticus with anaesthetics, extended EEG monitoring should be used to guide drug titration towards a goal of electrographic seizure suppression. At present, there is no evidence to help guide the degree of electrographic suppression or optimal duration of treatment. Common practice is to achieve electrographic burst suppression, characterised by 1–2 s bursts of cerebral activity interspersed by 10 s

intervals of background suppression. Generally, this pattern is continued for 24–48 h before sedation is lightened.<sup>17</sup> During this time of electrographic suppression, maintenance anti-epileptic drugs should be increased to therapeutic or even supratherapeutic doses to further prevent seizures while anaesthetics are tapered.

### Conclusion and future directions

Substantial progress has been made in the identification and treatment of status epilepticus, yet the disorder remains a common neurological emergency with substantial morbidity and mortality. Knowledge regarding the process of epileptogenesis and the transition from a single seizure to self-sustaining status epilepticus has improved through basic research largely with animal models. This research has also led to increased recognition that persistent seizures cause further neurological injury, pharmacoresistance, and worse outcomes as seizure duration increases. These concepts have led to clinical studies of the pre-hospital management of status epilepticus to achieve early seizure termination and serve as the basis for an updated treatment algorithm emphasizing a more rapid escalation to anaesthetics for refractory status epilepticus, an important change in the approach to treating status epilepticus in hospital settings.

Still, many questions remain and further research is needed, including more rigorous studies of the anti-convulsants used at present. ESETT will address the efficacy of the second-line anticonvulsants fosphenytoin, levetiracetam, and valproic acid for the treatment of status epilepticus refractory to benzodiazepines. Treatment trials for status epilepticus also need improved outcome measures, such as electrographic evidence of seizure termination on EEG, to more accurately assess treatment efficacy. The development and validation of dry electrode EEG devices that can be easily applied without a trained EEG technologist are essential. This technology enables early and accurate identification of status epilepticus in hospitals where 24 h EEG services are not available, and could potentially improve both clinical and research outcomes.

Within the hospital setting, prospective studies are needed to establish a cost-effective approach for the early identification and treatment of seizures and status epilepticus. The effect of extended EEG monitoring on

outcomes should be investigated further. Studies are needed to better define the effect of early use of anaesthetics, associated complications, and optimal duration of treatment to burst suppression for refractory status epilepticus.

#### Contributors

JPB performed the literature search and wrote the manuscript. DHL reviewed and revised the manuscript. Both authors contributed to the creation of the figures and tables.

#### Declaration of interests

We declare no competing interests.

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#### Search strategy and selection criteria

We searched PubMed and article references for papers in English published between Jan 1, 1969, and Jan 31, 2015, with the terms "status epilepticus", "status epilepticus mortality", "refractory status epilepticus", "status epilepticus and EEG monitoring", "status epilepticus radiographic findings", "status epilepticus and MRI", and "status epilepticus treatment". The final set of publications was selected based on the quality of each study and its relevance to this Review.

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