

Status Epilepticus: A Review, With Emphasis on Refractory Cases

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ABSTRACT: Status epilepticus is among the most dramatic of clinical presentations encountered by emergency room physicians, neurologists, neurosurgeons and intensivists. While progress in its management has been aided significantly with an increasing number of effective treatment options, improved diagnostic methods and more effective monitoring, poor outcomes and diagnostic failures are still frequently encountered. Refractory cases still carry significant morbidity and mortality rates, including poor cognitive outcomes. This review discusses basic pathophysiology and management of status epilepticus, neuroimaging findings, the role of continuous electroencephalogram monitoring and nonconvulsive status epilepticus as well as recent developments in treatment options for refractory cases.

RÉSUMÉ: Revue sur le status épileptique avec emphase sur les cas réfractaires au traitement. Le status épileptique est l'un des tableaux cliniques les plus dramatiques auxquels doivent faire face les urgentologues, les neurologues, les neurochirurgiens et les intensivistes. Bien qu'un nombre croissant d'options efficaces de traitement, de meilleures méthodes diagnostiques et de surveillance en aient amélioré significativement le traitement, les résultats médiocres et les diagnostic erronés sont encore fréquents. Chez les cas réfractaires au traitement, les taux de morbidité et de mortalité demeurent élevés, entre autres pour les conséquences sur la cognition. Cette revue discute de la physiopathologie et de la prise en charge de base du status épileptique, des observations à la neuroimagerie, du rôle de la surveillance EEG continue, du status epilepticus non convulsif et des développements récents dans les options de traitement pour les cas réfractaires.

Can J Neurol Sci. 2012; 39: 157-169

The original definition of status epilepticus was "A condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition"¹. Although this definition is imprecise, it introduces the concept that the normal inhibitory mechanisms of the brain have failed, and that epileptic activity has become self-sustaining, leading to a significantly increased risk for permanent brain injury. The duration criterion was formalized by the International League Against Epilepsy (ILAE) and the Epilepsy Foundation of America (1993), as at least 30 minutes of continuous seizures or sequential seizures without intervening recovery. This time frame is supported by studies on animals that show neuronal death occurring after 30 minutes of continuous convulsive seizure activity, even in absence of physiologic compromise (baboons were paralysed and intubated, with glycaemia normalized)². DeLorenzo and colleagues³ have shown that, among patients with prolonged seizures (more than ten minutes), 57% will progress to true status epilepticus without medication administration. In addition, mortality increases to 19% for seizures lasting more than 30 minutes, as compared to 2.6% for those lasting between 10 and 29 minutes. An even more conservative time cut-off was suggested when a video electroencephalogram (EEG) study of 120 secondarily generalized seizures recorded from 47 patients found that none lasted longer than two minutes (mean duration was 62 seconds),

suggesting that even five minutes of seizure activity represents a significant deviation from the mean and justifies aggressive treatment⁴. While 30 minutes is a useful cut-off in terms of defining physiological changes, the above points support recent trends towards more aggressive treatment of much briefer seizures.

Embedded within the definition of status epilepticus is the definition of seizure itself. Electrographically, this definition includes an evolutionary pattern of epileptiform discharges followed by post-ictal slowing or suppression, although these criteria may not always apply in prolonged seizures. Using animal models and human cases, Treiman and colleagues⁵ have defined five sequential electrographic stages when status epilepticus persists (Table 1), progressing from intermittent seizures without recovery, then becoming more continuous, and

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RECEIVED JANUARY 10, 2011. FINAL REVISIONS SUBMITTED SEPTEMBER 14, 2011.
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Table 1: Stages of status Epilepticus⁵

Stage 1	Discrete seizures
Stage 2	Merging seizures with waxing and waning amplitudes and frequencies
Stage 3	Continuous ictal activity
Stage 4	Continuous ictal activity interrupted by flat periods
Stage 5	Generalized periodic complexes on a flat background

culminating in generalized periodic epileptiform discharges (GPEDs) on a suppressed background. With protracted seizures, the variation in EEG over time may become limited, such that the usual criteria of evolution over time does not always apply in the case of status epilepticus, where self-sustaining ictal discharges may appear monotonous on the EEG with minimal variability in frequency, amplitude, or morphology. Individual stages from Treiman's classification may persist for long periods of time as periodic discharges or rhythmic slowing, blurring the distinction between ictal and interictal activity. This becomes especially problematic in comatose patients with mainly nonconvulsive seizures, where suppression of these poorly defined discharges is the only available therapeutic target⁶.

Classification of Status Epilepticus

Virtually any seizure type from the ILAE classification can be seen as status epilepticus (Table 2). Although one can broadly categorize prolonged seizures as convulsive or non-convulsive, many patients show both clinical and isolated electrographic seizure patterns as a result of status epilepticus. In fact, many "nonconvulsive" cases show subtle signs of seizure activity such as nystagmus, gaze deviation, or low amplitude twitching of the face or limbs. Rarely, autonomic dysfunction can be the primary ictal semiology of nonconvulsive seizures, including either sympathetic or parasympathetic effects, or both simultaneously^{7,8}. These changes are probably under-recognized, largely because they are difficult to prove as ictal phenomena, and are less dramatic clinical events than convulsions. The most commonly encountered autonomic manifestations are sympathetic activity such as pupillary dilation and changes in heart rate and blood pressure, whereas parasympathetic involvement can result in decreased vascular tone, sialorrhea, and increased gastrointestinal motility⁹. Stimulation studies have suggested lateralizing value for autonomic dysfunction: right insular stimulation increases sympathetic tone, whereas the stimulating the left insular region may favour parasympathetic activity¹⁰.

Refractory status epilepticus (SE) refers to continuous or recurrent seizures that do not respond to first line therapies such as lorazepam, and two second-line standard anticonvulsant agents, such as phenytoin and valproate. The exact incidence of RSE is difficult to calculate since the definition is ambiguous,

but may occur in up to 30% of cases¹¹⁻¹⁴. Refractory SE represents a distinct group of patients with regard to treatment strategies, monitoring requirements, and outcomes, and with respect to some unique clinical syndromes and etiologies.

Epidemiology and Prognosis of Status Epilepticus

The first systematic summary of status epilepticus epidemiology was made by Hauser et al¹⁵, in Rochester MN based on retrospective data and antedating studies with continuous EEG (cEEG) monitoring. Their figure of 15/100,000/year is almost certainly an underestimate given more recent findings. DeLorenzo et al¹⁶ conducted a prospective study in Richmond, VA that included cEEG monitoring and found an incidence of 41/100,000/year. There is a marked difference among age groups, with a bimodal distribution of peak incidence in the elderly and children, with young adults being affected least commonly. Mortality was highest among the elderly, which may reflect more serious underlying etiology, or the effect of comorbidities. The most common cause of status epilepticus remains sub-therapeutic drug levels in patients with pre-existing epilepsy, followed by previous structural brain injury, stroke, hypoxic ischemic encephalopathy, metabolic causes (including uremia, electrolyte derangements, and hepatic failure), and drug or alcohol withdrawal¹⁷.

Mortality in SE has been well studied with several established risk factors identified, including duration of SE, age, and underlying etiology, with hypoxic-ischemic injury portending worse outcomes, and epilepsy or drug withdrawal showing more favourable outcomes¹⁸. Overall mortality is estimated at 14% for adults younger than 60, but up to 38% for the elderly¹⁶. The impact of duration has been carefully studied by Drislane et al¹⁹, since earlier studies had dichotomized the

Table 2: Classification of status Epilepticus

Generalized Status Epilepticus	
1.	Tonic-clonic
2.	Tonic (e.g., in Lennox-Gastaut)
3.	Clonic (infants and children)
4.	Myoclonic status (bilaterally symmetrical jerks, mainly with acute/subacute brain disorders, including post-anoxic/ischemic injury)
5.	Absence
6.	Nonconvulsive generalized status (NCSE)
Partial Status Epilepticus	
1.	Simple partial (including epilepsy partialis continua)
2.	Complex partial status epilepticus
3.	NCSE with localization-related seizures, including transitional forms

duration of SE as either shorter or longer than one hour, with mortality rates of 2.7% and 32% respectively¹⁵. These authors demonstrated that although shorter duration of SE was indeed correlated with less mortality (31% for less than ten hours vs. 69% for longer), this difference was not significant once other known predictors were considered, such that even prolonged, refractory SE should not be considered a hopeless situation. These findings suggest that decisions about whether to withdraw care should probably be based on the prognosis for underlying cause and other comorbidities, as opposed to the duration of seizure activity. Focal seizures appeared to have a better prognosis in this study, although the impact of comatose patients after cardiac arrest seems to have skewed several categories of results, and a similar study excluding this population is warranted. A recent review by Neligan et al²⁰ concluded that age and depth of coma were the only factors that consistently predicted outcome with any accuracy. Periodic epileptiform discharges (PEDs) are often suggestive of poor outcome, but these authors correctly assert that this likely represents the underlying etiology, which is commonly a destructive lesion in lateralized PEDs (PLEDs), or hypoxic-ischemic in origin for generalized PEDs (GPEDs).

Pathophysiology of Status Epilepticus and Refractory Status Epilepticus

The transition from single seizures to status epilepticus is mainly a result of progressive loss of the inhibitory surround through a number of mechanisms, in a time-dependent fashion²¹. The earliest changes during status epilepticus likely relate to neurotransmitter release and ion channel modulation, whereas later changes relate more to receptor trafficking. Finally, after days-weeks of repeated seizures, even the balance of neuropeptides favors excitation, and eventually gene expression is also altered^{22,23}.

Early in the course of SE, gamma amino butyric acid-A (GABA_A) receptors are endocytosed into clathrin-coated pits, and then transported either to the soma for degradation or back to the post-synaptic neuronal membranes after modification at the Golgi apparatus²⁴. Over time, this leads to an overall down-regulation of GABA_A receptors. This likely explains the loss of efficacy of antiepileptic drugs (AEDs) whose mechanism of action is mainly related to potentiating the effects of GABA_A mediated chloride conductance and membrane hyperpolarization. The efficacy of benzodiazepines drops 20-fold during the first 30 minutes of continuous seizures, whereas phenytoin loses its effect more slowly²⁵. The mechanism triggering endocytosis of GABA_A receptors is poorly understood, but may relate to repeated and prolonged exposure to ligands acting on GABA_A receptors during SE.

Further enhancing the excitation-inhibition imbalance, there is an augmentation of excitatory (and excitotoxic) activity with an increase in N-methyl-D-aspartate (NMDA) receptor availability²¹. With increased calcium influx secondary to NMDA activation, there is activation of intracellular cascades culminating in caspase activation and apoptotic²⁶ and/or necrotic²⁷ cell death. Caspase inhibitors have been explored and have shown some success in animal models²⁸, but human data are lacking. In addition, the hippocampal damage can lead to a more persistent epileptic condition, if one was not present

beforehand²¹, although definitive evidence for this process is wanting in humans. N-methyl-D-aspartate toxicity is supported by the effects of domoic acid and its association with causing seizures and brain injury²⁹.

Based on this knowledge, a goal-directed approach to management can be defined, with the ultimate aim being prevention of secondary neuronal injury as a result of excitotoxicity during prolonged and unregulated NMDA activation. The above points also provide a framework for a rational pharmacotherapeutic approach to preventing brain injury as a result of status epilepticus, as outlined below.

Management of Status Epilepticus

The goals of management in status epilepticus are: 1) ensuring adequate vital functions (oxygenation and perfusion); 2) stopping the seizures; 3) preventing recurrent seizures; and 4) predicting and preventing systemic complications. A careful search for the underlying cause should always be pursued if this is not apparent at the outset. An overview of treatment options and corresponding clinical and physiologic changes is shown in Figure 1.

1. Stabilization: The presentation of convulsive status epilepticus is perhaps the most dramatic among emergency room patients, such that the initial focus is often on stopping the convulsions. While this is important, the usual priorities of resuscitation should remain the same, namely to ensure that the patient is oxygenated and maintaining an adequate blood pressure. The airway itself is often compromised due to sustained tonic or clonic contraction of the muscles of mastication such that placement of an endotracheal tube is not immediately possible; however, supplemental oxygen should be applied by mask, and if urgent intubation is required for severe hypoxia or systemic instability, a short-term paralytic may be employed, with the caveat that cEEG monitoring should be applied as soon as possible as paralytics will have no effect on the underlying cerebral epileptic activity despite apparent clinical improvement. Large bore IV access should be acquired, and bloodwork sent as clinically indicated, including glucose, electrolytes (including calcium, magnesium and phosphate), drug levels, toxicology, and arterial blood gas analysis. In general, it is not necessary to treat the patient with bicarbonate, even though a profound, combined metabolic (lactate) and respiratory (hypoventilation) acidosis is present. These blood gas abnormalities quickly resolve with correction of the seizures. If the patient shows a continuing anion-gap acidosis, this should raise suspicion of poisoning with a toxic agent such as ethylene glycol or methanol.

2. Stopping the seizures: At least two randomized controlled studies have demonstrated the effectiveness of lorazepam for treating status epilepticus. The San Francisco ambulance study showed that lorazepam (2 mg) IV was superior to diazepam or placebo in stopping seizures, although the difference between lorazepam and diazepam was small³⁰. An in-hospital study revealed that lorazepam was more effective than phenytoin in stopping acute seizures¹⁷, with minimal differences among the other drugs studied, including diazepam and phenobarbital. In most centers, a second-line agent such as phenytoin (PHT) is being administered simultaneously with abortive agents such as lorazepam. Due to the paucity of strong evidence favouring one

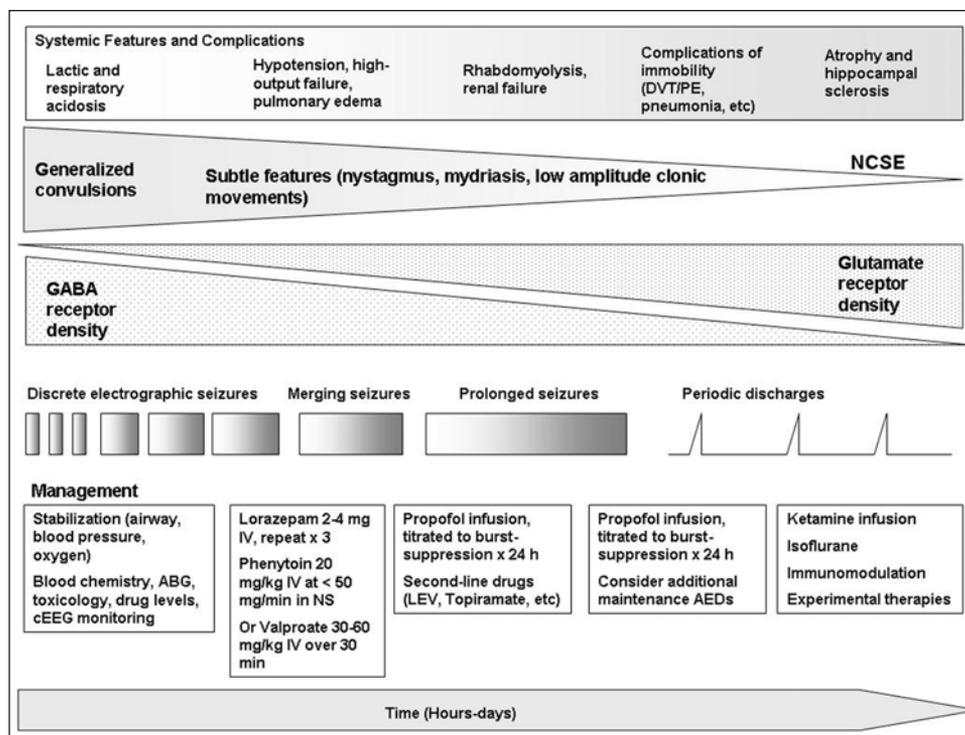


Figure 1: Clinical and physiologic changes over time in Status Epilepticus. DVT: Deep vein thrombosis; PE: Pulmonary embolus; NCSE: Nonconvulsive status epilepticus; GABA: Gamma-aminobutyric acid; ABG: Arterial blood gas; cEEG: Continuous electroencephalography; NS: Normal saline; LEV: Levetiracetam; AED: Antiepileptic drugs; IV: intravenous.

treatment protocol over another for early treatment of SE, wide variability exists in the strategies used between different centers³¹. Recent evidence suggests that valproate may also be a reasonable first-line agent for treating SE. A pilot study of 68 patients³² showed that valproate (35 mg/kg IV) successfully terminated seizures in 66% of patients, compared to a 42% success rate for phenytoin (18 mg/kg IV). As a second line agent, valproate stopped seizures in 79% of cases whereas phenytoin showed an efficacy of only 25%. A second comparative study³³ found that valproate and phenytoin had similar efficacy at 88%, although these authors included patients with 'acute repetitive seizures' in addition to those with true SE, partially explaining the high success rates with both drugs. Notably, 12% of patients treated with phenytoin experienced side effects, whereas none of those treated with valproate had adverse reactions. These results will need to be confirmed in larger studies, but do suggest that valproate may be suitable as a first-line therapy, especially for select populations who may not tolerate phenytoin. Finally, adequate doses must be used and based on body weight, rather than standard doses regardless of patient factors. One gram of phenytoin is often given as a standard dose, regardless of patient weight, which is often not enough to achieve therapeutic levels.

If seizures are ongoing after adequate repeated doses of lorazepam (i.e., 2 mg repeated every two to three minutes for four doses) and initiation of a standard maintenance drug such as phenytoin or valproate, most conventional protocols suggest

progressing to more sedating agents, such as phenobarbital. However, this necessitates definitive airway management and transfer to an ICU. In addition, phenobarbital often causes hypotension and vasopressor agents may be required.

Alternatively, and more commonly encountered in recent years, an intravenous anaesthetic such as propofol is used in this setting. Propofol also works via GABA_A receptors, requires intubation and transfer to an ICU, and frequently lowers blood pressure. However, the advantage of propofol is its short half life, such that it can be weaned and restarted in a controlled fashion. Recently, a small randomized trial demonstrated longer mechanical ventilation for barbiturates compared to propofol, although the study was significantly underpowered³⁴. Both groups demonstrated significant treatment related side-effects, and similar efficacy for terminating seizures. A single dose of propofol may rarely serve to abate the seizures and circumvent the need for transfer to ICU, but in general, use of this medication will require definitive airway management with intubation. If clinical seizures have stopped at this point and the EEG does not demonstrate ongoing ictal activity, it may suffice to monitor the patient closely and continue maintenance anticonvulsants. If either of these criteria are not met, anaesthetic drugs should be employed to achieve a burst-suppression pattern with cEEG monitoring. The optimal duration of burst-suppression, and the degree of EEG suppression (burst-suppression ratio), remain poorly defined due to a lack of trials

comparing different protocols. Guidelines have been published^{35,36}, but are often non-specific when it comes to precise targets of treatment and are based mainly on expert opinion. By convention, the anaesthetic drug of choice is titrated to achieve burst-suppression for 24-48 hours, and then slowly weaned off with careful clinical and cEEG observation, repeating the cycle if necessary until successful weaning is achieved using therapeutic levels of maintenance antiepileptic drugs.

Prolonged stays in the ICU with anaesthetic agents titrated to burst-suppression are occasionally required (in rare cases up to several months), and do not necessarily indicate irreversible brain damage³⁷. Prolonged, high dose propofol infusion in such cases has been associated with the life-threatening propofol infusion syndrome (PRIS), characterized by hypotension, acidosis, renal dysfunction, and cardiac toxicity³⁸. Occasionally, PRIS can manifest as sudden cardiovascular collapse in previously healthy patients who have been subjected to high doses of propofol³⁹. The precise incidence of PRIS remains unknown, but in one prospective study of patients treated with propofol for more than 24 hours⁴⁰, 11 of 1017 patients (1%) developed PRIS (defined in this study as metabolic acidosis and cardiac dysfunction, plus one of rhabdomyolysis, hypertriglyceridemia, or renal failure). Mortality was 18%, and most patients showed signs of PRIS within the first 24 hours in retrospective analysis. Of concern is that only 18% of patients were receiving infusions greater than 5 mg/kg/hr, suggesting that even lower doses can predispose to PRIS. Laboratory monitoring and definitive management with adequate blood levels of a standard antiepileptic medication, such that propofol can be discontinued, are the mainstays of prevention. One report described successful resuscitation after cardiocirculatory arrest from PRIS using extracorporeal membrane oxygenation (ECMO)⁴¹.

3. Preventing recurrence of seizures in the short term: The anti-epileptic effect of lorazepam is brief (probably 45 minutes maximum). To prevent recurrence of seizures, drugs with longer duration of action are used after lorazepam has provided early control. Most centres use phenytoin (PHT) given in normal saline (PHT precipitates in glucose solutions) at a rate no greater than 50 mg/minute to avoid hypotension, thought to be due to the propylene glycol diluent. However, fosphenytoin has also been reported to cause hypotension, suggesting a possible direct vasodepressor effect⁴². A loading dose of 15-20 mg/kg of PHT usually provides a serum concentration that is in the generally accepted therapeutic range of 40-80 micromol/L for 24 hours. While fosphenytoin is favoured in some centers due to its faster tolerable infusion rate, this prodrug must then be converted to PHT, such that the therapeutic effect may not actually be any faster than that of PHT⁴³. There is no good evidence that fosphenytoin is more effective or safer than regular PHT, although it may be a good option when IV access is tenuous. A third option gaining favour is valproate, which can be given IV, and is probably equally effective and less prone to cause cardiovascular side effects. A loading dose of 30-60 mg/kg is well tolerated and side effects are rare, although patients with liver disease may have impaired metabolic clearance of valproate. Idiosyncratic effects include carnitine deficiency and hyperammonemia, a syndrome which may respond to

replacement of carnitine intravenously⁴⁴. Thus, if the level of consciousness remains impaired in patients who have been loaded with valproate with EEG improvement, it is reasonable to check the ammonia level. Similarly, new signs of parkinsonism should prompt consideration of carnitine deficiency when the onset correlates with valproate administration.

Levetiracetam (LEV) is used relatively commonly in some centers due to its favourable side effect profile and lack of interaction with other drugs. There is some evidence that LEV may have neuroprotective effects as well⁴⁵. No loading dose is required, and it can be given intravenously at a dose of 500 to 1500 mg twice per day. Due to its unique mechanism of action at the synaptic vesicle 2A binding site, LEV can also be useful as adjunctive therapy by inhibiting pathologic neuronal activity in ways not addressed by other anticonvulsants. Unfortunately, an intravenous formulation is not currently available in Canada, such that effective serum levels are dependent upon the functional integrity of the gastrointestinal tract, which has often been influenced by other drugs used to treat seizures (including propofol, barbiturates, inhalational anaesthetics, and midazolam). Eue et al⁴⁶ reported on their two year experience with intravenous LEV in SE, and found that after failure of benzodiazepenes, 19 of 43 patients responded to 1000-2000 mg of LEV. No significant adverse reactions were reported. Berning et al⁴⁷ retrospectively reviewed the charts of 32 patients treated with IV LEV (median Day 1 dose, 3500 mg) and reported a success rate of 72%, including acute and remote etiologies. Topiramate has also been used with some success in generalized and complex partial SE, in doses of 300-1600 mg/day⁴⁸. Since most side effects of topiramate are cognitive in nature, titration can be achieved quickly in the ICU setting, bearing in mind the risks for acidosis and nephrolithiasis.

4. Prevention and Treatment of Systemic Complications: The systemic complications of SE can be divided into immediate and delayed categories (Figure 1). The immediate risks relate to the systemic complications of the seizures themselves and include hyperthermia, lactic acidosis, pulmonary edema and hypoxia, rhabdomyolysis and renal failure, hyperglycemia, hyperkalemia, and sudden cardiovascular collapse⁴⁹. Fever can certainly be due to the seizures themselves but should always raise the question of whether an infectious etiology is present. Hyperthermia may exacerbate systemic complications and brain injury, and there is some evidence that induced hypothermia can mitigate these effects^{50,51}. As with the acidosis that accompanies status epilepticus, most of the other immediate systemic effects are managed effectively by addressing the underlying cause and stopping the seizures. Awareness of these potential complications allows for appropriate monitoring and specific therapy when indicated.

Many patients presenting with SE will undergo diagnostic lumbar puncture to rule out infectious causes, and interpretation of the cerebrospinal fluid (CSF) parameters can be challenging, mainly with respect to the commonly encountered mild-moderate leukocytosis. Barry and Hauser⁵² studied the CSF parameters of 217 consecutive patients with SE of any cause, and found that among those with conditions usually associated with normal CSF (ie: not infectious or traumatic), the highest cell count was $28 \times 10^6 / L$. Another study of 102 patients with seizures found that up to 30% may have pleocytosis without

other explanation⁵³, with a range of 3 to 464 x 10⁶ / L and a mean of 72 x 10⁶ / L. Ultimately, one can only conclude that seizures alone can cause a modest pleocytosis, but also that this should be a diagnosis of exclusion if there are any features to suggest a possible infectious etiology.

Refractory Status Epilepticus

If two standard drugs such as phenytoin and valproate fail after lorazepam, the patient is considered to have refractory status epilepticus¹¹. All patients in this category should be intubated and transferred to an ICU for more aggressive management. Propofol and midazolam are commonly recommended at this stage⁵⁴. As mentioned, propofol acts directly on GABA_A receptors, with some modulation of calcium channels and inhibition of NMDA receptors, while midazolam acts mainly on the benzodiazepine site of GABA_A receptors. Midazolam has a higher failure rate than propofol⁵⁵ and propofol is generally preferred, although care must be taken to avoid high dose, prolonged infusions for reasons mentioned above. High dose anaesthetic barbiturates (thiopental or pentobarbital) are effective and are still used; however, with prolonged use their half-life is protracted and they can interfere with ciliary action, predisposing already susceptible patients to ventilator acquired pneumonia (VAP)⁵⁶.

Ketamine

Ketamine has the theoretical advantage of being an NMDA antagonist with reasonable experimental evidence for treatment of refractory SE^{57,58}, whereas human data is mainly limited to case reports⁵⁹. Ketamine has also been suggested as a neuroprotective agent⁶⁰. One small retrospective study showed good control with ketamine in five of seven patients with refractory status epilepticus⁶¹. Interestingly, ketamine does not seem to be as effective as conventional GABA agonist drugs early in the course of illness, but can provide ‘rescue’ therapy when these agents fail. This would appear consistent with the time-dependent down-regulation of GABA receptors and upregulation of NMDA receptors in status epilepticus. After metabolism to nor-ketamine, it binds weakly to the phencyclidine site within the NMDA channel, which can lead to symptoms of psychosis during emergence in some patients⁴⁸. Ketamine may offer hemodynamic advantages in that it generally does not cause hypotension, and may in fact support blood pressure due to catecholamine release⁶², which can also lead to tachycardia. Potential adverse effects include raising intracranial pressure⁶³, although clinically significant changes in intra-cranial pressure (ICP) are not reported in the literature. The doses used are variable, but a reasonable starting point is 1 – 1.5 mg/kg loading dose followed by an infusion at 0.5 mg/min, titrating as necessary to achieve burst-suppression on the electroencephalogram and maintaining this for at least 24 hours. There is some evidence for a synergistic effect of ketamine when administered with benzodiazepines⁶⁴. The therapeutic window for ketamine is wide, with very few side effects reported even at high doses. One case report raised concerns after a 44 year-old male with known neurosyphilis and SE was treated with ketamine at doses up to 7.5 mg/kg/hour for several days, which terminated the seizures⁶⁵. The patient was left with cognitive deficits and cerebral atrophy, which may be consistent with

toxicity related to NMDA-blockade, although this has not been reported in previously well individuals, and is difficult to distinguish from the consequences of SE itself, or from long-standing neurosyphilis. Animal models have demonstrated potential developmental toxicity related to ketamine⁶⁶. Our own experience with ketamine, while limited to a few cases, has been mixed – seizures are often suppressed temporarily, but seem to recur quickly after stopping the infusion. Furthermore, burst-suppression has been difficult to achieve unless combined with a second agent, such as midazolam.

Inhalational Anaesthesia

Inhalational anaesthetics provide another option for refractory status epilepticus, although these agents have significant practical limitations. Isoflurane and desflurane work within minutes, are easily titratable, and are remarkably effective in stopping status epilepticus^{67,68}. The safety of isoflurane has now been demonstrated (in a case report) with duration of use up to 26 days, although most patients will require vasopressor support and infection rates are probably increased⁶⁸. The mechanism of inhalational agents is not well understood, but they likely have some GABA agonist properties, and may influence thalamocortical connections as well⁶⁹⁻⁷¹. Using these agents requires an anaesthetist and vapour extraction system in the ICU. Like other agents at higher concentrations, and with prolonged use, these drugs can cause hypotension, paralytic ileus, and prolonged sedation as they redistribute from fat stores. In cases where suppression of epileptiform discharges is proving challenging, or propofol infusion syndrome is encountered, isoflurane is highly effective for suppression of the EEG and achieving a more aggressive ‘suppression-burst’ pattern.

Hypothermia

Hypothermia has gained favour as a neuroprotective strategy in recent years, largely as a result of its clear efficacy in improving outcomes after cardiac arrest^{72,73}. More recently, based on experimental evidence for an anticonvulsant effect of hypothermia⁷⁴⁻⁷⁶, Corry et al⁷⁷ treated four patients with refractory status epilepticus with therapeutic hypothermia, with successful resolution of status in all four cases, but with reported adverse effects including mild coagulopathy and one case of sepsis. Given the growing experience with therapeutic hypothermia in most centers, this seems a relatively safe option for refractory patients who have failed multiple medical treatments. Complications are rare when moderate hypothermia (32-34 degrees Celsius) is administered for less than 48 hours^{72,73}, and a neuroprotective effect is probable, even if seizures are not completely abolished.

Surgical Options

Epilepsy surgery has occasionally been employed in desperate situations to stop refractory seizures of focal origin⁷⁸⁻⁸⁰. Case reports and small series have described variable success with multiple subpial transections⁸¹⁻⁸³, focal resections⁸⁴, hemispherectomy⁸⁵ and vagal nerve stimulation^{86,87}. Surgery may be life-saving in some circumstances, and should be considered as an option for patients with status epilepticus originating from a focal lesion (or a non-lesional but well-

defined focus) after carefully weighing the expected deficits that could result from surgery and exhausting medical treatment options.

Electroconvulsive Therapy (ECT)

Electroconvulsive therapy has been discussed as a rescue therapy for refractory status epilepticus in several case reports with variable success⁸⁸⁻⁹¹. Kamel et al⁹² reported success in two of three patients treated with several days of electroconvulsive therapy after failure of multiple medications. Previous work has suggested that ECT may upregulate endogenous inhibitory mechanisms⁹³, although this has been demonstrated only in animals and in human patients without seizure disorders. Whether this rather counter-intuitive method applies to the physiology of human status epilepticus remains to be seen, and larger trials may be warranted.

Nonconvulsive Seizures and the Role of Continuous EEG (cEEG) Monitoring

In general ICUs, up to 19% of comatose patients will experience seizures, of which 90% will be nonconvulsive⁹⁴. Among patients who remain comatose after convulsive seizures, the prevalence of NCS is roughly 48%⁹⁵ and at least 20% among patients with acute structural brain lesions, including trauma. Comatose patients require at least 48 hours of continuous EEG (cEEG) recording to detect more than 90% of seizures; standard (20-30 minute) recordings are inadequate, detecting fewer than 10% of seizures found with prolonged recordings⁹⁵. It is generally acknowledged that convulsive status epilepticus leads to neuronal injury, and that absence status epilepticus does not contribute to morphological or functional changes, but the impact of other types of NCSE remains unproven⁹⁶. Although there is abundant support that neuronal death, especially in the hippocampus, does occur in animal models of NCSE⁹⁷⁻¹⁰¹, it has been difficult to establish this in human cases. Evaluating the relative contributions of the underlying etiology, convulsive seizures, and non-convulsive seizures in causing brain damage has always been problematic. The conditions causing NCSE in the ICU are the same as those causing convulsive seizures, including trauma, anoxic-ischemic encephalopathy, encephalitis, vascular lesions, neoplasms, metabolic disorders, sepsis and pre-existing epileptic conditions. Many of these are independently associated with significant cerebral injury. How can we dissociate injury due to these processes from damage attributable to the seizures themselves? This question has enormous potential clinical importance, since NCSE is common in ICU (especially neuro-ICU) patients, and may be one of very few conditions amenable to treatment that affects outcome for brain injured patients.

The ICU is riddled with barriers to EEG recording, including a multitude of unusual artifacts, although most of these can be addressed by an experienced technologist and electroencephalographers¹⁰². In addition, EEG technologists are often not available outside of usual work hours. Several approaches have been developed out of necessity to make some form of EEG monitoring available that can be set up by nurses and residents, displayed continuously at the bedside, and saved for later analysis.

The Bispectral Index (BIS)¹⁰³, which was originally developed to study ocean wave motion¹⁰⁴ and seismic activity¹⁰⁵, has been proposed as a useful measure of patient sedation, providing a number between 0 (deep sedation) and 100 (normal wakefulness). The index is calculated from a proprietary computer algorithm that incorporates EEG data, and also includes an electromyogram (EMG) monitor and a signal quality monitor. Since the EEG morphology cannot be assessed using BIS, monitoring for seizures is obviously limited. One report compared the BIS value with conventional EEG in a patient with SE and found that the BIS increased during seizures, and decreased when the seizures were controlled¹⁰⁶. The patient was unresponsive throughout, even with high BIS values, which they interpreted to mean that seizures were causing the elevated BIS values, and therefore that BIS may be useful when EEG is not available. A second report used BIS to monitor a patient with encephalitis and frequent seizures¹⁰⁷, and again found that the BIS values increased during seizure activity, correlating with EEG findings. In both cases, seizures were treated with anaesthetic agents, which would clearly affect the BIS values with or without seizures. In addition, there are multiple potential sources of artefact in the ICU, which would be impossible to exclude as contributors to the BIS value without seeing the waveform morphology. While this may be a case of “better than nothing” brain monitoring, the potential for false positives and aberrant administration of anaesthetic medications makes using BIS to monitor seizures a risky endeavour.

A subhairline EEG system was originally described by Bridgers and Ebersole¹⁰⁸. Young et al¹⁰⁹ later studied the efficiency of a subhairline EEG system with sticker electrodes in comatose ICU patients, and found a sensitivity of 70%, and specificity of greater than 90% for seizure detection as compared to simultaneous conventional EEG recordings. This sensitivity may have been limited by a relatively low sampling rate which has since been improved, but likely also reflects suboptimal spatial coverage. Nonetheless, detecting 70% of seizures (almost all of which were nonconvulsive) seems intuitively better than detecting 0%, while awaiting more formal EEG monitoring. Other temporary systems designed to provide a quick view until more complete monitoring is available have been described, including a proposed seven electrode system¹¹⁰ that could be placed by nurses or residents using surface landmarks as opposed to measurements. Using conventional EEG reformatted to this simplified montage, these authors found a sensitivity and specificity of greater than 90%; however, whether this would apply in a real-world ICU application remains to be seen. A variety of caps, nets, and other placement systems are also available, although with substantial cost, and still requiring a separate EEG machine to be available at the bedside.

An ideal quick-access EEG monitoring system will include good coverage of the head, be easily placed after minimal training, displayed on the bedside monitor and recorded for later review, and meet most of the technical standards outlined by the Canadian Society for Clinical Neurophysiology¹¹¹. Structured training should be available at a basic level such that bedside nurses, intensivists, and residents can initiate recording and interpret basic patterns. Such training would likely require participation from a neurologist/neurointensivist certified in EEG and familiar with the system, and a technician from the

manufacturing company. However, even a system meeting this description would still be regarded as a temporary tool until formal EEG assessment is available; continuous EEG with a full array of electrodes applied using the 10-20 configuration should still be considered the gold standard, if not standard of care.

The diagnosis of NCSE is problematic for several reasons, not the least of which is the lack of a gold standard by which to define the sensitivity of various criteria, perhaps with the exception of intracranial depth electrodes, although even this invasive technique has limitations in spatial coverage. It is commonplace for the same scalp EEG pattern to be interpreted differently between electroencephalographers, emphasizing the importance of considering these patterns as part of an ictal-interictal continuum. Criteria for NCSE have been developed⁸⁷ but can be cumbersome for those inexperienced in EEG (Table 3). Furthermore, the usual evolutionary pattern that defines isolated seizures may not always be appreciated in self-sustaining status epilepticus, where a more monotonous sequence of discharges, without evolutionary changes, may represent ongoing ictal activity. Again, this leaves room for subjectivity when deciding whether sequential spikes or sharp waves represent periodic interictal epileptiform discharges or ongoing seizures. In these circumstances, treatment decisions are based on input from an experienced electroencephalographer who is able to consider the possibilities in the appropriate clinical and electrophysiological context, until clear criteria can consistently distinguish between the two entities. Ideally, the neurologist or neuro-intensivist involved in the patient's care is also responsible for reviewing the EEG recordings to allow for accurate clinical correlation, and for careful weighing of pros and cons of seizure management based on comorbidities and concurrent medications. When this is not the case, video EEG is invaluable in helping the electroencephalographer correlate EEG findings with clinical information, including potential generators of artifacts, and subtle correlates of epileptiform activity.

Another common difficulty is distinguishing between triphasic waves (TWs), which usually indicate a metabolic

encephalopathy, and generalized periodic epileptiform discharges (GPEDs), which can be an ictal phenomenon. Specifically, this problem arises when there are potential clinical correlates for both patterns, such as the post cardiac-arrest patient with organ dysfunction. A study of the morphology and reactivity of these two patterns offers some useful hints with high inter-rater reliability among blinded readers, but the sensitivity and specificity of several individual criteria remain relatively low, leaving significant freedom for subjective interpretation. In the best study of this distinction so far, Boulanger et al¹¹² found that a sharp initial negative, faster repetition rate of the discharges, lack of an anterior-posterior time lag, lack of response to stimulation, and a faster background frequency all favoured nonconvulsive seizure activity over triphasic waves. While these clues are generally useful in making the distinction, the circular nature of the comparison in this study is problematic. For example, triphasic waves were considered 'correctly identified' by the blinded readers if they had met available criteria for TW's according to the authors' interpretation. The nature and biologic generator of triphasic waves has yet to be determined, as has their precise position on the ictal-interictal continuum. In general, the clinical scenario combined with the above points is usually sufficient to decide whether a patient is in generalized NCSE or suffering from a metabolic encephalopathy, but uncertainty still commonly arises.

We have seen several cases of NCSE resulting in significant brain injury not attributable to other causes, mainly with respect to hippocampal injury with severe and persistent anterograde memory impairment leading to near total dependence (Figure 2). In most cases, NCSE is undetectable without cEEG monitoring, which also provides a guide for titration of AEDs or anaesthetic

Table 3: EEG criteria for NCSE (adapted from Young et al⁹⁵)

Primary Criteria

1. Repetitive generalized or focal epileptiform discharges at >3/sec
2. Repetitive generalized or focal at <3/second *and* secondary criterion #4.
3. Sequential rhythmic waves and secondary criteria 1, 2 *and* 3 with or without 4.

Secondary criteria

1. Incrementing onset: increase in voltage and/or increase in frequency.
2. Decrementing offset: decrease in voltage or frequency.
3. Post-discharge slowing or voltage attenuation.
4. Significant improvement in clinical state or baseline EEG after anti-epileptic drug

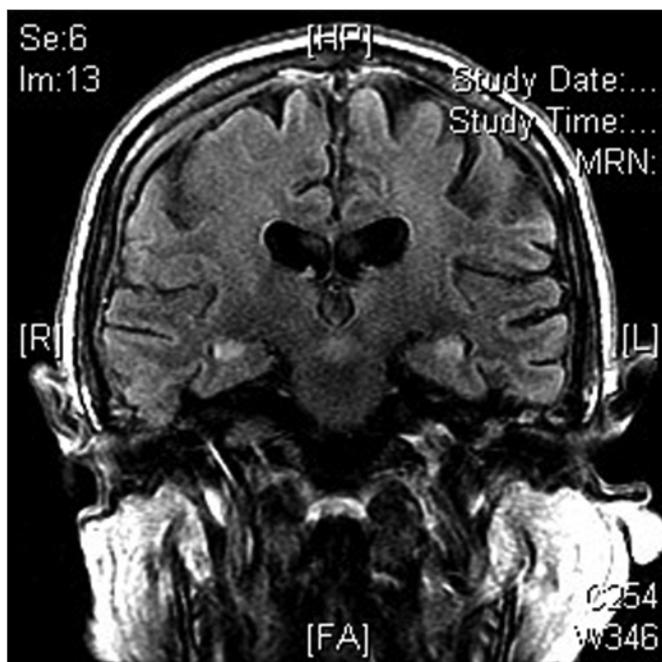


Figure 2: Bilateral increased FLAIR signal in mesial temporal structures after prolonged nonconvulsive seizures during a septic illness.

agents to achieve a burst-suppression pattern. Whether detection and treatment of nonconvulsive seizures in the ICU improves outcomes has not been systematically addressed, but it is clear that NCS are a pathological response to brain dysfunction, and treatment seems warranted.

Neuroimaging in Status Epilepticus

Imaging of the brain with magnetic resonance (MR) during status epilepticus is usually pursued for diagnostic purposes, and may disclose a number of fairly specific clues as to the underlying etiology, especially related to structural lesions. In cases not related to structural lesions, the most commonly encountered changes are focal areas of increased T2/FLAIR signal secondary to encephalitis/cerebritis, and mesial temporal signal abnormalities in limbic encephalitis (either paraneoplastic [Anti-Hu, Anti-NMDA¹¹³], infectious Herpes simplex virus [HSV] or primarily autoimmune [Anti-VGKC¹¹⁴]). In cases of unclear etiology, a multitude of other changes have been described and attributed to the seizures themselves, although the mechanism remains unclear.

Animal studies have shown that the diffusion-weighted MR (DWI) changes seen after prolonged seizures in lithium-pilocarpine models correlate well with areas of neuronal injury^{115,116}. In humans, DWI changes involving a variety of anatomical regions have been described, including the pulvinar nucleus of the thalamus^{117,118}, splenium of the corpus callosum, mesial temporal lobes, focal cortical areas in a gyral pattern, and as a crossed cerebellar diaschisis¹¹⁹. These areas of DWI abnormality are thought to represent a combination of cytotoxic

and vasogenic edema as a result of metabolic failure. For superficial areas of restricted diffusion, the MR findings seem to correlate with electrographic localization¹²⁰. In one report, MR changes were entirely restricted to the right hemisphere in a patient with callosal dysgenesis and NCSE originating from the right hemisphere¹²¹, again supporting a primary role for seizures causing the MR findings. Rarely, status epilepticus of focal origin can present with reversible tumour-like lesions involving thickened cortical areas and local enhancement with gadolinium, which later become atrophic and show local gliosis¹²². Using diffusion tensor imaging (DTI), there is now evidence that SE may also cause white matter injury, especially affecting the corpus callosum and fornices¹²³.

Another finding of uncertain significance is leptomeningeal enhancement^{119,124}, which can complicate the diagnostic process, especially if there is also a CSF pleocytosis. Exclusion of infiltrative processes such as infection, granulomatous disease, and malignancy should be pursued before attributing these changes to seizures. Finally, diffuse atrophy with preferential involvement of mesial temporal structures (Figure 3) has been described¹²⁵, although some have argued that these changes may be at least partly reversible, particularly in cases of autoimmune encephalitis.

Prognosis for Survivors

While mortality and its predictors have been relatively well described, outcomes among survivors of SE have not been thoroughly studied. Since the expected functional outcome has major implications for treatment goals, this is a significant short-

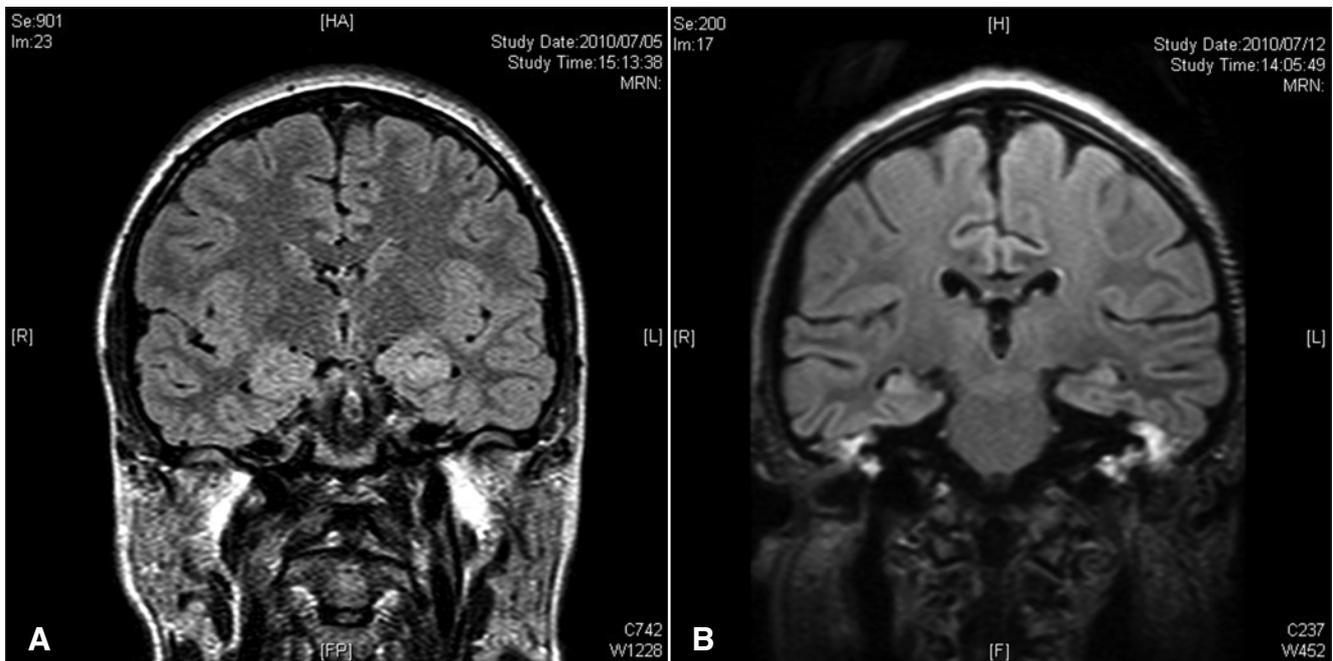


Figure 3: A) Coronal FLAIR MRI early in the course of refractory status epilepticus (New-onset refractory Status Epilepticus, or NORSE). Note the normal brain volume and increased signal in the hippocampi. B) Coronal MRI after prolonged status epilepticus in same patient as (3a), now showing diffuse atrophy and focal changes in both hippocampal regions.

coming of the existing literature. Most of the available work describes outcomes in terms of overall functional capacity as it relates to composite functional scoring systems such as the modified Rankin scale¹²⁶ or Glasgow outcome scale¹²⁷, but provides little insight into the specific types of deficits patients and their families are left to deal with. More descriptive reports of the types of deficits the patients experience are limited to case reports^{128,129}, which suggest that memory is often impaired irreversibly, as might be expected due to known hippocampal injury after prolonged seizures. This has certainly been our experience, and seems consistent with expert opinion among epileptologists and intensivists. There is some conflicting evidence, however, to suggest that status epilepticus itself may not have a direct impact on cognitive outcome, when comparing epileptic patients with SE versus those without¹³⁰. These authors found that both groups declined in subsequent cognitive assessments, but that there was no difference between the two groups with respect to incidence. The mean duration of SE in this study was 12 hours. These findings may be more supportive of cognitive decline among epileptic patients in general as opposed to showing lack of effect of SE. Neligan et al²⁰ reviewed the available literature and concluded that the evidence does not support the clinical impression that cognitive function is at risk in SE, but this conclusion may not accurately represent the data presented (which is largely retrospective). Further data from registries should provide more accurate estimates of the impact of SE on cognitive outcomes, and will likely support the consistent observation that SE does impact cognition, mainly in the memory domain. The reversibility of memory impairment after a single episode of status epilepticus is another unanswered question, and long term follow-up studies are required.

New Onset Refractory Status Epilepticus: NORSE Syndrome

Rarely, a young and previously healthy patient presents with seizures after a preceding viral prodrome, often with headache and fever, and then progresses into refractory status epilepticus¹³¹⁻¹³³. One series of well-defined NORSE syndrome patients was described by Costello et al¹³⁴. NORSE is a cryptogenic syndrome that likely encompasses infectious and non-infectious or autoimmune causes, often with equivocal or heterogeneous laboratory and imaging results and an unclear etiology. Historically these cases have been attributed to viral encephalitis, which is difficult to disprove, but as the spectrum of autoimmune encephalopathies becomes better elucidated, this pathophysiology seems a more likely candidate. Criteria have been suggested^{131,134}, and are mainly based on exclusion of a comprehensive list of known causes of new-onset seizures. Patients are generally young (mean age 29 years), more often female, and initial imaging is usually normal but may later show patchy increased T2/FLAIR signal. Cerebrospinal fluid generally shows a mild lymphocytic pleocytosis with otherwise normal parameters. The EEG may demonstrate focal, multifocal, or generalized epileptiform activity, and seizures are refractory to usual first and second-line agents. Despite a suspicion of autoimmune mechanisms, immunomodulation with steroids, plasma exchange, and IVIG has been largely ineffective in managing this group of patients. This may represent the development of self-sustaining seizures via mechanisms previously discussed, even though the original insult has

resolved. In one case of SE that fits the description of NORSE well, intrathecal synthesis of anti-GAD antibodies was discovered which prompted successful therapy with cyclophosphamide¹³⁵. Pathology specimens from four patients showed non-specific microglial activation and gliosis¹³¹. Five of six patients survived, but only one had a good outcome, while the others were severely impaired and dependent, often with difficult epilepsy. Other unusual causes of status epilepticus to be considered include undetected mitochondrial disease, atypical infections such as from *Bartonella henselae* (cat-scratch disease), and genetic disorders¹³⁶.

CONCLUSIONS

Status epilepticus is a medical emergency and should be treated with early aggressive therapy to ameliorate brain damage, systemic complications, and mortality. There is now substantial evidence that both convulsive and non-convulsive seizures are damaging to the brain and have the potential to become self-sustaining, even after the inciting cause has been addressed. Continuous EEG monitoring is strongly advised to rule out ongoing NCS, especially in obtunded patients in the ICU. Lorazepam followed by phenytoin or valproate is an appropriate initial treatment and other second line agents including topiramate and levetiracetam are gaining favour (drugs used for treatment of SE are summarized in Table 4). More consistent treatment protocols should be established using outcome data from large international registries to provide optimal evidence-based, goal-directed care. Outcome data among survivors of SE is lacking and further work in this area is needed to help guide difficult management decisions.

For refractory status epilepticus, ICU management is mandatory. Propofol is commonly employed and usually effective; ketamine and inhalational anaesthesia are useful alternatives with good safety profiles if propofol fails, while surgical options and ECT remain unproven and carry significant morbidity. Hypothermia has some evidence and is also well-tolerated, but with known risks, mainly related to infection. The role of NCSE in causing brain injury remains to be proven

Table 4: Anticonvulsant drugs in status epilepticus

Drug	Dose	Infusion Rate	Precautions and interactions
Lorazepam	2mg IV, repeat x 3-4 doses	1-2 min	Sedation Slow to clear in hepatic failure
Phenytoin	15-18 mg/kg IV load, mixed in normal saline (precipitates in glucose)	No faster than 50 mg/min	Bradycardia, hypotension, skin irritation, rash, nystagmus, elevated liver enzymes Slow to clear in hepatic failure Drug interactions
Fosphenytoin	15-20 mg/kg IV	100-150 mg/min	Similar side effects to Phenytoin with less frequency Must be metabolized to phenytoin; onset of action similar despite faster infusion rate
Valproate	30-60 mg IV	Over 30 min-1 hour, probably safe at faster rates	Caution with impaired hepatic function. Rare hyperammonemic syndrome
Levetiracetam	1500 mg po or IV (not available in Canada currently)	Undefined - rapid infusions have not shown significant adverse outcomes	Minimal No significant drug interactions
Propofol	1 mg/kg IV	1-2 mg/kg/hr, titrate to burst-suppression on EEG	Propofol infusion syndrome Hypotension, sedation Requires ICU
Clobazam	10-30 mg po bid		Sedation
Topiramate	300-1600 mg/day		Mainly cognitive side effects, may titrate quickly for SE Acidosis, nephrolithiasis

definitively, but experience and basic science data suggest that NCSE should also be aggressively treated, such that vulnerable patients should be monitored for 48 hours with cEEG to detect and treat most cases of NCSE. The NORSE syndrome continues to be defined as a cryptogenic cause of refractory SE in previously healthy young individuals, and may be due to an as yet undefined autoimmune etiology.

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