Review Article

Management of status epilepticus: a narrative review

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Summary

Status epilepticus causes prolonged or repetitive seizures that, if left untreated, can lead to neuronal injury, severe disability, coma and death in paediatric and adult populations. Whilst convulsive status epilepticus can be diagnosed on clinical features alone, non-convulsive status epilepticus requires confirmation by electroencephalogram. Early seizure control remains key in preventing the complications of status epilepticus. This is especially true for convulsive status epilepticus, which has stronger evidence supporting the benefit of treatment on outcomes. When status epilepticus becomes refractory, often due to gamma-aminobutyric acid and N-methyl-D-aspartate receptor modulation, anaesthetic drugs are needed to suppress seizure activity, of which there is limited evidence regarding the selection, dose or duration of their use. Seizure monitoring with electroencephalogram is often needed when patients do not return to baseline or during anaesthetic wean; however, it is resource-intensive, costly, only available in highly specialised centres and has not been shown to improve functional outcomes. Thus, the treatment goals and aggressiveness of therapy remain under debate, especially for non-convulsive status epilepticus, where prolonged therapeutic coma can lead to severe complications. This review presents an evidence-based, clinically-oriented and comprehensive review of status epilepticus and its definitions, aetiologies, treatments, outcomes and prognosis at different stages of the patient's journey.

Introduction

Advances in our knowledge of the mechanisms, aetiologies, treatment options, monitoring and clinical outcomes of status epilepticus have led to important changes in the definitions and treatment of this condition. Several challenges and uncertainties remain, especially regarding monitoring and treatment of patients with status epilepticus beyond second-line therapy given the limited evidence guiding different treatment regimens. Patients with convulsive status epilepticus that is resistant to first- and second-line therapy are often admitted to ICU to allow administration of anaesthetic drugs in conjunction with mechanical ventilation. In this narrative review, we discuss the definitions of status epilepticus, evidence behind treatment regimens at various stages, treatment goals, outcomes and the role for newer drugs.

Definitions of status epilepticus

Status epilepticus is defined as a condition resulting either from the failure of the mechanisms of seizure termination, or from the initiation of mechanism which lead to abnormally prolonged seizures, that can have long-term consequences, including neuronal death, injury and network alteration [1].

Operationally, the International League Against Epilepsy established two time-points of utmost clinical importance: time-point 1, at which point the seizure is considered abnormally prolonged and treatment should be started; and time-point 2, at which point ongoing seizure activity is likely to result in long-term consequences and may warrant implementation of aggressive therapy [2]. Four classification axes are recognised: semiology; aetiology; electroencephalogram (EEG) correlates; and age.

The most severe and dangerous type is convulsive status epilepticus, for which there is good evidence supporting treatment at time-point 1, and this should be initiated within 5 min, aiming for seizure control (time-point 2) by 30 min (Fig. 1). Whilst convulsive status epilepticus can be diagnosed on clinical features alone, non-convulsive status epilepticus requires EEG confirmation (Fig. 2). The Salzburg consensus criteria have high sensitivity (97.7%) and specificity (90%) based on electrographic/electroclinical features that constitute EEG evidence of rhythmic epileptiform discharges occurring at a frequency > 2.5 Hz, or rhythmic EEG discharges occurring at a frequency ≤ 2.5 Hz and with either: spatiotemporal evolution; subtle clinical changes correlating to EEG changes; or EEG and clinical improvement after intravenous (i.v.) anti-epileptic drug therapy [1,3]. The most recent American Clinical Neurophysiology Society standardised critical care EEG terminology incorporated the Salzburg criteria, additionally requiring EEG changes of non-convulsive status epilepticus to be present continuously for at least 10 min or 20% of any 60-min EEG recording [4].

Types of status epilepticus

All types of status epilepticus can also be characterised in terms of response to treatment. Established status epilepticus fails to respond to first-line benzodiazepine therapy and requires use of second-line anti-epileptic drugs (AEDs). Refractory status epilepticus is defined by failure of second-line AEDs to control seizures and the need for seizure control with anaesthetic drugs. Super-refractory status epilepticus refers to seizures continuing despite administration of anaesthetic drugs.

Non-convulsive status epilepticus can present with or without coma, with protean manifestations in a broad range of contexts. This includes a subset of patients presenting with convulsive status epilepticus that transforms or 'burns out' into subtle semiology [5,6], eventually becoming non-convulsive following initiation of first- or second-line AEDs. Non-convulsive status epilepticus, even if prolonged, may not require intensive care or anaesthetic management. For this review, discussion regarding management of non-convulsive status epilepticus will focus on non-convulsive status epilepticus with coma that is identified in patients who are critically ill with acute pathological conditions or occurs following convulsive status epilepticus.

Prolonged seizures are associated with irreversible neuronal injury resulting in increased morbidity and mortality [7–9]. Early seizure control, particularly in the first 1–2 h of convulsive status epilepticus, reduces mortality and improves short- and long-term outcomes including disability and coma [3,10–12]. Recognition that 'time is brain' in the definitions of status epilepticus, and a focus on early recognition and treatment for convulsive status epilepticus with standardised treatment algorithms, is well-established. However, management of non-convulsive status epilepticus has less supporting evidence from randomised trials and is thus based largely on consensus and expert opinion, with some controversy with respect to whether or not this should be treated as aggressively as convulsive status epilepticus.

The underlying aetiology of non-convulsive status epilepticus is the strongest predictor of both survival and functional outcomes. However, whilst a number of studies have shown that, for a given diagnosis or severity, non-convulsive status epilepticus is independently associated with worse outcomes [13,14], there is a lack of good quality evidence to inform best management practice. Accordingly, whilst therapeutic trials are a part of the diagnosis and initial management, practice beyond this may vary considerably depending on the individual situation. Given these factors and the risks of anaesthesia, treatment decisions

should take into account the severity of underlying brain injury, age, comorbidities and patients' overall goals of care. In a comatose patient, careful consideration of the continuum between epileptic brain dysfunction and dysfunction due to structural brain damage is also important (Fig. 3). This disparity in evidence between the management of convulsive and non-convulsive status epilepticus causes treatment course to differ in timeline and aggressiveness (Figs. 1 and 2).

Mechanisms contributing to refractory status epilepticus

Two main mechanisms contribute to seizures becoming refractory. Modification and reduction of post-synaptic type A gamma-aminobutyric acid ($GABA_A$) receptor populations and neurotransmission contribute to seizures becoming self-sustaining [15–17]. A second mechanism promoting refractory seizure activity is N-methyl-D-aspartate (NMDA) receptor-mediated, resulting in neuronal calcium inflow and enhanced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated excitatory transmission by facilitating the insertion of the GluA1 subunit into synapses and an expanded seizure network [18]. N-methyl-D-aspartate receptors are transported to the surface as status epilepticus progresses, increasing their availability over time. N-methyl-D-aspartate receptor activity also enhances $GABA_A$ receptor internalisation, promoting further disinhibition.

Early management of convulsive status epilepticus

Families of patients with epilepsy and emergency medical services are often the first to manage patients with prolonged clinically-apparent or convulsive seizures. Onset time where known should be documented to guide the treatment stages. During the first 5 min, considered the 'stabilisation phase' (Fig. 1), as for any medical emergency an ABC (airway, breathing and circulation) approach is taken, with attention to environmental safety and risk of injury [19]. In any patient who is convulsing, the possibility of psychogenic non-epileptic seizures should also be considered [20]. Concurrent evaluation for conditions that could trigger, cause or prolong seizures is also essential, along with commencement of oxygen saturation and cardiac monitoring as hypoxia and cardiac complications are common [21]. Blood glucose, toxicological screening, blood alcohol and other laboratory investigations, including serum AED levels can unmask easily reversible aetiologies of status epilepticus and should be sampled whilst securing i.v. access [22]. Patients with suspected alcohol use should be given i.v. thiamine. Subtherapeutic levels of AEDs due to non-compliance or drug-drug interactions are common triggers of seizures in people with epilepsy.

First-line therapy

If seizures continue for longer than 5 min or recur without interval recovery ('early status epilepiticus phase' (Fig. 1)), first-line treatment is indicated [19]. Several clinical trials have established the efficacy of pre-hospital administration of benzodiazepines. The choice of benzodiazepines as a first-line therapy depends on several factors, mostly importantly their availability in the field and whether i.v. access is present. Intravenous lorazepam (0.1 $mg.kg^{-1}$, maximum 4 mg), i.v. diazepam (0.15–2 $mg.kg^{-1}$, maximum 10 mg), intramuscular or buccal midazolam (10 mg, 5 mg in older patients or if weight < 40 kg) and rectal diazepam (10 mg, 5 mg in older patients or if weight < 40 kg) are established first lines of therapy [23]. Intravenous clonazepam (0.015 $mg.kg^{-1}$, maximum 1 mg) is also used in some European countries. A second dose of benzodiazepines should be given if a patient continues to seize 5 min after the first dose.

Whilst i.v. benzodiazepines have more rapid onset of action, if i.v. access is not available other routes of administration can result in a similar time to seizure cessation as speed of administration can counterbalance their slower onset of action [20]. Intranasal midazolam and lorazepam (at the same doses as i.v.) are also efficacious but less studied options [19]. Availability, adequate dosing and speed of administration are more important than which benzodiazepine is used. Despite the strong evidence base for their use, underdosing of benzodiazepines is widespread [24]. Contrary to popular belief, administration of adequate doses of first-line benzodiazepines has been shown to decrease the requirement for tracheal intubation [25]. However, continuing or recurrent seizure activity > 5 min after the maximum/last benzodiazepine dose without interval recovery, as occurs in approximately 40% of patients with convulsive status epilepticus, should prompt preparation for second-line therapy as this now represents the 'established status epilepticus' phase.

In patients with other types of status epilepticus, including non-convulsive status epilepticus, early treatment with benzodiazepines is also advised; however, data from large randomised controlled trials are lacking. An early expert neurology or epilepsy consultation is necessary for the management of non-convulsive status epilepticus (Fig. 2). These patients require EEG confirmation of the diagnosis and initial response to treatment, and a more individualised approach to treatment and establishing treatment goals. This should include careful consideration of the cause and potential outcome, particularly in the presence of acute brain injury.

Second-line therapy

Until recently, high-quality evidence to inform the choice of AED for second-line treatment of established status epilepticus phase was lacking. Options include: i.v. fosphenytoin (20 mg.kg^{-1}, maximum 1500 mg); valproate (40mg.kg^{-1}, maximum 3000 mg); and levetiracetam (60 mg.kg^{-1}, maximum 4500 mg) (Table 1) [19]. The trial by Kapur et al. was a multicentre, double-blinded randomised trial in adults and children aged > 2 y that compared the effectiveness of i.v. levetiracetam, fosphenytoin and valproate in 384 patients with convulsive status epilepticus unresponsive to benzodiazepines in the emergency department [26]. No difference in the primary outcome measure of the absence of clinically apparent seizures and improving responsiveness at 60 min after the start of the drug infusion was found. Seizure termination occurred in approximately 50% of patients in each group, with no significant differences in secondary outcomes or safety measures. Alternative second-line therapy includes i.v. phenobarbital (15–20 mg.kg^{-1}) if not previously given. Despite its effectiveness [27], phenobarbital use is limited by higher frequency of sedation, respiratory depression and hypotension. Intravenous lacosamide (400 mg) is being used increasingly in established and refractory status epilepticus and may have comparable efficacy to traditional agents, though this is not yet proven [20,27].

ICU management: refractory and super-refractory status epilepticus

If the patient is unable to maintain their airway then tracheal intubation may be required following onset of status epilepticus. This can be challenging in a convulsing patient, but it is wise to avoid the use of neuromuscular blocking drugs when intubating the trachea of patients who are seizing and during subsequent ICU management as ongoing seizure activity cannot be detected without EEG. If neuromuscular blockade is necessary, caution should be used with succinylcholine, since its use after prolonged seizures can precipitate hyperkalaemia. Rocuronium can be used instead of succinylcholine, which can be followed by the reversal drug sugammadex to unmask any ongoing convulsive seizures, although EEG is necessary to exclude persistent non-convulsive seizures.

Refractory status epilepticus (continuing seizure activity despite second-line therapy) occurs in 33% of status episodes, while super-refractory status epilepticus (continuous seizure activity 24 h after the initiation of anaesthesia) occurs in 4% [28]. Refractory status epilepticus in a patient who presented with or has ongoing convulsive status epilepticus should prompt ICU admission and consideration for tracheal intubation for induction of anaesthesia. A study from the USA showed that approximately 1 in 3 patients with status epilepticus require tracheal intubation, a proportion that has nearly doubled over the last 20 years [29]. Of note, in a follow up paper from the Kapur et al. trial team [26], tracheal intubation rates

varied greatly between centres, even when adjusted for early vital signs and post-treatment neurologic recovery [30].

As discussed previously, the rational for tracheal intubation in suspected or confirmed non-convulsive status epilepticus is less established and needs careful consideration of the clear risks of prolonged tracheal intubation and ICU stay against the questionable benefit of therapeutic coma. Trials of i.v. second-line AEDs are recommended prior to inducing anaesthesia (Fig. 2). Induction of anaesthesia with propofol, midazolam or ketamine often provides definitive seizure control.

Anaesthetic agents for refractory status epilepticus

There are currently no randomised controlled trials that guide the selection, dose or duration of anaesthetic drugs use in treatment of refractory status epilepticus. Typically, anaesthetic drugs are used in a stepwise approach to achieve seizure control, starting with midazolam and/or propofol, followed by escalation to barbiturates (pentobarbital or thiopentone). More than one anaesthetic drug is often needed to achieve seizure control. In cases when traditional anaesthetics fail to control status epilepticus, newer agents and other modalities of control have been tried with variable efficacy. Treatment is individualised, and the pros and cons of each agent are important determinants of use; these are summarised in Table 2.

Midazolam

As a benzodiazepine, midazolam exerts its antiepileptic properties via the potentiation of the inhibitory action of GABA receptors by increasing the frequency of chloride channel opening. Midazolam has been used to treat status epilepticus for decades, with several retrospective and prospective studies supporting its utility in refractory status epilepticus [23]. It remains the preferred benzodiazepine infusion for management of refractory status epilepticus (compared to diazepam or lorazepam infusion) mainly because it does not contain propylene glycol which accumulates with continuous infusions of other benzodiazepines and can result in metabolic acidaemia, cardiac toxicity and severe hypotension. Midazolam has a fast onset of action (< 5 min) and relatively short elimination half-life (average 3 h); however, prolonged infusions of midazolam can lead to an increased terminal half-life due to increased volume of distribution and accumulation of active metabolites, an effect exacerbated in those with renal failure. In addition, similar to other benzodiazepines, extended infusions result in tachyphylaxis; higher doses may be required to achieve the same level of seizure suppression [23].

Propofol

Propofol exerts its anti-epileptic activity through multiple mechanisms, primarily GABA receptor modulation and NMDA receptor blockade. Propofol has the advantage of having a fast onset of action (peak effect 90-100 s) and rapid clearance; awakening from propofol typically occurs within 10-15 min. However, due to its high lipid solubility, prolonged infusions cause propofol to accumulate in peripheral tissues. Thus, the rapid awakening is related to the short distribution half-life of propofol, rather than its elimination half-life. Hypotension and respiratory depression are seen commonly with the administration of propofol, necessitating the need for mechanical ventilation and administration of vasopressors. Cardiac suppression and conduction abnormalities also occur and can result in bradycardia and aggravation of hypotension. A feared complication is propofol infusion syndrome, which manifests as haemodynamic collapse, renal failure, severe metabolic acidaemia and rhabdomyolysis; this usually occurs after prolonged infusions or with high doses. Propofol infusions are avoided in children due to this concern. Pancreatitis is another serious complication, especially in the setting of propofol-induced hypertriglyceridemia. Routine monitoring of serum lactate, triglycerides, amylase, lipase and renal function is recommended with prolonged infusions, and such complications may warrant discontinuation of propofol and replacement with alternative drugs [31].

Barbiturates

Prior to the introduction of propofol and midazolam, barbiturates were the drugs of choice for managing refractory status epilepticus, primarily due to their ability to induce a deep coma with profound reduction in cerebral metabolism with few treatment failures. However, due to associated serious adverse events such as severe hypotension, ileus, immune suppression, hypothermia, hepatic dysfunction and cardiac suppression, their use is now limited to cases refractory to propofol and/or midazolam. Similar to benzodiazepines, barbiturates exert their anti-epileptic properties via the potentiation of $GABA_A$ receptors, but increase the duration, not frequency, of chloride channel opening. Two barbiturates are classically used in status epilepticus: pentobarbital (more common in the USA); and thiopental (mainly used in Europe). Thiopental has a faster onset of action (10-40 s) than pentobarbital (approximately 60 s). As both are highly lipophilic, their deposition in the peripheral tissues result in a varied, dose-dependent, prolonged elimination half-life (3-22 h for thiopental and 15-50 h for pentobarbital) with often sustained, complete loss of neurological function at high doses. Pentobarbital, but not thiopental, contains propylene glycol. For patients started on barbiturates, monitoring of drug levels and propylene glycol is appropriate with prolonged therapy, in addition to close monitoring of cardiac, hepatic, and renal function [31].

Ketamine

As a non-competitive NMDA receptor antagonist, the anti-epileptic activity of ketamine is thought to be related to reduction in glutaminergic neuronal transmission and excitotoxicity. Ketamine has gained recent interest as an anaesthetic drug for refractory and super-refractory status epilepticus after a multi-centre retrospective study in North America and Europe showed permanent control of refractory status epilepticus occurred in 57% of the cohort who were given i.v. ketamine [30]. In addition, ketamine was felt to 'possibly' have contributed to seizure control in 32% of patients and was 'likely' to have led to seizure control in 12% of patients [32].

In a systematic review of single-arm case series and case reports encompassing 248 patients, the efficacy rate of ketamine from seizure control ranged between 11–100%; in the vast majority of studies included ketamine was administered after traditional anaesthetic drugs (most commonly propofol and midazolam) failed to achieve seizure control [31]. This study also showed that the efficacy rate doubled when ketamine was administered early in refractory status epilepticus [33]. More importantly, this review highlighted major limitations in the literature supporting ketamine use, including: poor methodological quality; absence of control groups; absence of unified dosage regimen; varying outcome definitions; different time points of ketamine initiation; and most notably, publication bias [33].

In a recent retrospective series (not included in the above review) of 68 patients with super-refractory status epilepticus monitored with scalp EEG (11 of whom underwent multimodal monitoring), there was a 50% decrease in seizure burden in 81% of patients and complete seizure cessation in 63% of patients, within 24 h of ketamine administration. In addition, ketamine was associated with a stable haemodynamic profile and had no effect on intracranial pressure, cerebral blood flow or cerebral perfusion pressure [34]. Of interest, one preliminary report showed the pre-hospital administration of ketamine was associated with high rates of seizure termination without the need for tracheal intubation [35].

The optimal regimen and dosage of ketamine are not established and vary by institution (Table 2) [31]. However, a low-dose of 0.9 $mg.kg^{-1}.h^{-1}$ was used among those who responded in the multicentre study discussed earlier [32]. Currently, there are at least two ongoing clinical trials evaluating the use of ketamine for refractory status epilepticus which will hopefully provide further information regarding dosing strategy and efficacy (NCT02431663 and NCT03115489).

Seizure monitoring and treatment targets

The use and interpretation of EEG, requiring clinical neurophysiology and neurology expertise, is necessary when patients with convulsive status epilepticus do not return to their baseline neurological state despite cessation of convulsions. In one study, 14% of patients with convulsive status epilepticus transited to non-convulsive status epilepticus [36]. Electroencephalogram is also often used to exclude non-convulsive status epilepticus as a cause of altered consciousness. In a trial of EEG monitoring in 364 adult patients who were critically ill with altered consciousness without recent seizure, seizure detection occurred in 4.4% (using routine EEG) to 15.7% (using continuous EEG); however the use of continuous EEG is costly, and did not translate into improved functional outcomes [37].

In settings with limited access to EEG, bispectral index (BIS) is often used to provide quantitative EEG assessment, relying on frontal raw EEG data using proprietary algorithms. Bispectral index has been validated in the assessment of depth of anaesthesia during surgical procedures, and may be able to distinguish burst-suppression ratios in patients with status epilepticus. However, BIS has substantial limitations including: inability to identify spikes and periodic patterns within bursts; it can only facilitate a goal of seizure suppression rather than burst suppression; and cannot readily guide therapy as anaesthesia is weaned [38].

There is considerable regional and international variation in the use of continuous EEG monitoring. It is often used to guide one of many treatment targets: seizure suppression (absence of electrographic or electroclinical seizures with preservation of background activity); burst-suppression (a pattern of complete EEG suppression alternating with polyphasic, higher-voltage activity); or complete suppression. Although seizure suppression is the minimal goal in status epilepticus management, the use of therapeutic coma remains controversial. Controversy around instituting burst suppression vs. seizure suppression stems from the need to balance the well-established harms from ongoing status epilepticus against the risk of anaesthesia; this leads to significant variability in the use of therapeutic coma. Burst-suppression for 12–24 h is associated with a lower rate of status epilepticus relapse when compared with EEG-seizure suppression alone; however, it is not associated with reduced mortality [39,40]. On the other hand i.v. anaesthetic use is associated with an increased incidence of: requirement for vasopressors; risk of infection; duration of hospital stay; mortality; and poor functional long-term outcome [41].

Determining cause and effect is, however, challenging as anaesthesia is reserved typically for patients with more severe illness and refractory status epilepticus. The duration of therapeutic coma is also controversial; 24–48 h of therapeutic coma (commonly targeting burst-suppression) has been recommended [23] but recent observational data suggest a higher risk of seizure recurrence and longer duration of hospital stay with more prolonged durations of coma. Interestingly, higher maximal steady doses of anaesthetics during initial trials of therapeutic coma were associated with fewer in-hospital complications. Together, these findings suggest that a deeper and shorter duration of therapeutic coma may be associated with decreased risk of seizure-recurrence and in-hospital complications [42].

Weaning of anaesthesia

Anaesthetic weaning after refractory status epilepticus suppression is often a difficult task, as it can be difficult to differentiate between re-emergence of seizures and periodic, rhythmic EEG patterns on the ictal-interictal continuum. If recurrent seizures consistent with status epilepticus re-emerge during anaesthetic weaning, anaesthetic drugs are restarted while other non-anaesthetic AEDs are added or optimised to aid with better seizure control. A patient's readiness for anaesthetic weaning may be indicated by lack of high-risk features on EEG, treatment of underling aetiology and concurrent systemic complications as a result of anaesthetic coma. In certain circumstances, optimising current AEDs and the addition of adjunctive drugs (such as lacosamide, oxcarbazepine, perampanel, topiramate or brivaracetam) are necessary to prevent recurrent status epilepticus if individual or clusters of seizures occur.

Predictors of successful anaesthetic wean have been investigated. In 24 patients with refractory status epilepticus who were treated with burst-suppression, highly epileptiform burst morphology was predictive of seizure recurrence and failure of anaesthetic wean [43]. However, the presence of such patterns should not deter clinicians from attempting to wean anaesthesia after adequate suppression has been maintained for 24–48 h, because prolonged coma beyond that is unlikely to improve outcome. During anaesthetic wean, ictal-interictal patterns (such as generalised and lateralised periodic discharges) could emerge, and the management of such patterns remain controversial. However, successful anaesthetic weans (without repeated trials of burst-suppression) has been reported despite the emergence of these patterns [44]. Because such qualitative assessment of EEG features during anaesthetic wean provides incomplete and often conflicting results [44], assessment of quantitative continuous EEG parameters (such as spectral power and functional connectivity measures) has been studied and yielded high level of accuracy at predicting success [34]. The recommended modalities for discontinuation of anaesthetic drugs are based

on expert opinions; a potential regimen is 20% dose reduction in anaesthetic drug infusions every 3 h while monitoring the EEG [31]. Further studies are needed to guide duration and rate of anaesthetic wean based on EEG and clinical parameters.

Management of super-refractory status epilepticus

When status epilepticus continues despite 24 h of anaesthetic use, or when status epilepticus recurs during anaesthetic weaning, patients are considered to have super-refractory status epilepticus. This condition is associated with a high mortality rate of 32–50% [45,46]; in those patients who survive, studies have reported rates of poor neurological outcome in up to 80% of patients at 1-year follow-up [46]. This high mortality and morbidity is linked not only to ongoing brain damage resulting from status epilepticus, but also the accompanying systemic complications of anaesthetic coma [45,46]. Whether continuing aggressive treatment with more AEDs or induced coma in super-refractory status epilepticus improves outcomes remains unknown.

Numerous strategies have been reported for super-refractory status epilepticus. An initial strategy is adding non-anaesthetic AEDs while maintaining current anaesthetic drugs, including trialling alternative second-line AEDs. There are case reports of success with almost any adjunctive licensed AED in super-refractory status epilepticus, but really no evidence to support any particular sequence or preference and, just as in treating drug-resistant epilepsy, each change is really a trial of one. When adding any AED, caution should be taken regarding potential drug-drug interactions, and clinicians should be aware of the potential risks if using multiple agents with similar mechanisms of action, particularly when seeking to avoid complications such as arrhythmias. Another strategy, in addition to adjunctive AEDs, is replacing current anaesthetic drugs with others that have not been used yet, such as barbiturates or ketamine.

There are multiple options for management of super-refractory status epilepticus beyond third-line anaesthetic agents and adjunctive AEDs; however, all have a low-level evidence of efficacy due to significant publication bias and inadequate study design. Whilst there is a range of non-pharmacological interventions (Table 3), it is important to recognise their limited evidence and potential for adverse events. When any of these essentially experimental treatments in super-refractory status epilepticus are under consideration, transparency with all concerned and a multidisciplinary discussion involving a clinical ethical committee is recommended.

Volatile inhalational anaesthetics have also been utilised as other salvage therapy in super-refractory status epilepticus. Inhalational anaesthetics are thought to inhibit seizure activity via inhibition of NMDA excitotoxicity and activation of GABA receptors. Advantages of inhalational anaesthetics include the easy titration to EEG at the bedside and ultrafast onset of action. Caution should be exercised when using inhalational anaesthetic because certain agents (specifically sevoflurane) appear to be epileptogenic [47]. Isoflurane (dosed at minimum alveolar concentration 0.5–2.0%) is the main inhalational anaesthetic reported in the literature with more than 92% efficacy in achieving complete seizure resolution; electrographic response to isoflurane appeared immediately in all patients who responded [48]. The duration of therapy ranged between 5 h and 32 days. These studies suffer several limitations including their failure to report adverse events, outcome heterogeneity, absence of comparative groups and variable reporting of previous and adjunctive treatment regimens. The use of inhalational anaesthetics is also limited by their potential serious adverse events, especially with prolonged use [48].

Treatment of underlying precipitant(s)

One of the cornerstones of management is the investigation and management of the underlying precipitant of status epilepticus. The aetiology varies among different populations and includes structural, infectious, metabolic and autoimmune causes [23]. In children, febrile status epilepticus is the most common presentation, whereas in adults around 50% of cases will occur in people with known epilepsy (due to intercurrent illness, an additional brain insult or low AED levels). Acute causes of status epilepticus include stroke: traumatic brain injury; central nervous system infection; infectious or autoimmune encephalitis; hypoxic ischaemic injury; toxic exposure; and drug withdrawal. Acute causes are more likely to result in status epilepticus progression to refractory and super-refractory status epilepticus, especially viral (most commonly herpes simplex virus) and autoimmune encephalitis [49]. In one study, encephalitis was the most common aetiology of super-refractory (66.7%) compared to non-refractory status epilepticus (12.3%) [49].

The term new-onset refractory status epilepticus (NORSE) is used to define patients with refractory status epilepticus without a readily identifiable cause for the seizures within the first 48 h; this occurs in 19% of patients [41]. Febrile infection-related epilepsy syndrome (FIRES) is a subtype of NORSE preceded by a febrile infection, with fever starting between 2 weeks and 24 h prior to onset of refractory status epilepticus; this is mostly described in children but may also occur in adults [12]. Although the cause remains cryptogenic in half of those patients with NORSE, the remainder often end up with the diagnosis of

autoimmune (19%) or paraneoplastic (18%) encephalitis [41]. Thus, a lumbar puncture with cerebrospinal fluid (CSF) analysis and blood work up looking for infectious causes and autoimmune and paraneoplastic antibodies are important, as AED/anaesthetics alone are unlikely to change the disease course without treating the underlying aetiology. In those patients with suspected herpes simplex virus encephalitis, early treatment with i.v. acyclovir is recommended, and is often commenced before microbiological confirmation of infection. In those patients with possible autoimmune refractory status epilepticus, including those with unknown aetiology, an empiric course of high-dose steroids (1 g of i.v. methylprednisolone daily for 5 days) should be considered once infective and other aetiologies are excluded, while the results of CSF analysis and serum autoantibodies are awaited. Steroids are often administered concomitantly with other first-line therapies, such as i.v. immunoglobulins, and in severe cases, plasma exchange. Autoimmune encephalitis with inadequate response to first-line therapies (i.e. persistent status epilepticus, severe dysautonomia and movement disorders etc.) requires further treatment with more sustained, second-line immunomodulatory agents such as rituximab or cyclophosphamide. These drugs have been reported to halt the antibody and cell-mediated immune responses that are driving the seizures [50-52]. The timing of initiation of more aggressive, second-line therapy is under debate; early initiation (within 2 weeks of diagnosis) has been recommended by some groups in order to avoid long-term sequelae [51,52].

Patients who develop refractory and super-refractory status epilepticus originating from a structural, focal brain lesion may benefit from acute neurosurgical resection of the epileptogenic focus. In a case series of nine patients who underwent acute resective surgery for super-refractory status epilepticus, six (67%) had resolution of seizures immediately after surgery [53]. However, the benefits of surgery should be weighed the against its risks, which include loss of neurological function and even death [53].

Status epilepticus outcomes and rationality of treatment

Long-term outcomes of status epilepticus vary significantly according to the underlying aetiology, duration of seizures, age, sex, medical comorbidities, incidence of in-hospital complications and treatment location [12,54]. Reports also vary for a variety of outcomes following status epilepticus cessation at hospital discharge, including: increased risk of subsequent epilepsy (22–41%); recurrent status epilepticus (13–37%); cognitive and functional impairment (21–61%); and long-term mortality (0–57%) [12]. In addition, critical illness polyneuropathy and myopathy is a well-recognised complication of prolonged ICU stay and protracted mechanical ventilation, occurring in up to 50% of patients [55]. Because poor outcomes are possible even despite successful treatment of status epilepticus, careful consideration is warranted when

deciding on treatment aggressiveness and duration, especially in patients with poor functional capacity at baseline and those with established wishes regarding 'acceptable' recovery and level of function. Predictive scores, such as the STESS [56], END-IT [57] and EMSE [1] scores, were developed to aid clinicians in outcome prediction; however, they should be used with caution to avoid self-fulfilling prophecies. A rational, holistic approach is thus necessary when approaching patients and families regarding commencing or continuing aggressive treatments for status epilepticus.

Conclusion

Implementing early, evidence-based treatment modalities is important to prevent mortality and complications from prolonged status epilepticus. Benzodiazepines remain the most effective first-line therapy and are commonly underdosed. Second-line therapy can consist of levetiracetam, fosphenytoin or valproic acid, which have been shown to have equivalent efficacy for the management of established status epilepticus. For those patients who progress to refractory and super-refractory status epilepticus, a trial of anaesthetic coma is often needed; however, there remains limited quality of evidence to support the choice of anaesthetic drugs, depth and duration of therapeutic coma, EEG targets of treatment and weaning strategies. Recently, ketamine has been shown in several small studies to be effective in aborting status epilepticus; however, prospective comparative studies are lacking. The aetiology of status epilepticus is the strongest predictor of outcome and can help guide therapeutic options. In those with a suspected immunologic aetiology, empiric treatment with immunomodulatory agents should be considered early. In patients with super-refractory status epilepticus, several other treatment options exist such as repetitive transcranial magnetic stimulation, vagal nerve stimulator and resective surgery, but their use should only be considered in super-refractory cases with careful consideration given their limited evidence and the potential for harm.

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Figure Legends

Figure 1. Treatment timeline of convulsive status epilepticus. *intramuscular (IM) or buccal (depending on availability) preferred in patients without i.v. access. Diazepam can be used if lorazepam and midazolam are not available. ABC, airway, breathing and circulation; IV, intravenous; AED, anti-epileptic drugs; CBC, complete blood count; CMP, complete metabolic panel; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; KD, ketogenic diet, rTMS, repetitive transcranial magnetic stimulation; and VNS, vagal nerve stimulator

Figure 2. Treatment timeline of non-convulsive status epilepticus. *intramuscular (IM) or buccal (depending on availability) preferred in patients without i.v. access. Diazepam can be used if lorazepam and midazolam are not available. **Onset of non-convulsive status epilepticus is often not observed in critically ill patients. ABC, airway, breathing and circulation; IV, intravenous; AED, anti-epileptic drugs; CBC, complete blood count; CMP, complete metabolic panel; CT, computed tomography; MRI, magnetic resonance imaging; HSV, herpes simplex virus; EEG, electroencephalogram; KD, ketogenic diet, rTMS, repetitive transcranial magnetic stimulation; and VNS, vagal nerve stimulator

Figure 3. Non-convulsive status epilepticus and coma. Relationship between depth of coma (x-axis), prognosis (x-axis), degree of structural brain damage (red y-axis) and epileptic brain dysfunction (blue y-axis) due to status epilepticus. Clinical entities depicted in the upper part of the graph are arranged along the x-axis without distinct positions, in recognition that large border zones and overlaps between the conditions may exist. AS, absence status epilepticus; IGE, idiopathic generalised epilepsy; SE, status epilepticus; EPC, epilepsia partialis continua; GED, generalised epileptiform discharges; LED, lateralised epileptiform discharges; NCSE, non-convulsive status epilepticus. Reproduced with permission from [58]

Table 1. Non-anaesthetic anti-epileptic drugs used for treatment of status epilepticus

	Routes	Loading dose	Maintenance dose	Major clinical considerations
Fosphenytoin and phenytoin	Intravenous Oral Intramuscular	20 $mg.kg^{-1}$ (max 1500 mg)	4–7 $mg.kg^{-1}.day^{-1}$ divided in 2–3 doses (max 600$mg.day^{-1}$)	Strong interactions with valproate and phenobarbital Inducer of several cytochrome P450 enzymes Narrow therapeutic window due to zero-order kinetics Should be avoided in patients with cardiac conduction abnormalities Requires monitoring of free and total drug levels Contains propylene glycol which can cause metabolic acidosis
Valproate	Intravenous Oral	20–40 $mg.kg^{-1}$ (max 3000 mg)	1500–6000 $mg.day^{-1}$ divided in 3–4 doses	Strong interaction with fosphenytoin,phenytoin and phenobarbital Potent cytochrome P450 inhibitor Risk of hepatotoxicity (especially with mitochondrial diseases), pancreatitis, thrombocytopenia, platelet dysfunction and severe encephalopathy (monitor ammonia) Requires monitoring of levels (free if low albumin
Levetiracetam	Intravenous Oral	40–60 $mg.kg^{-1}$ (max 4500 mg)	1000–4000 $mg.day^{-1}$ divided in 2–3 doses	No significant drug-drug interactions Requires dose adjustment in renal impairment Avoided in patients with history of agitation or psychiatric disease
Phenobarbital	Intravenous Oral	15–20 $mg.kg^{-1}$	1–3 $mg.kg^{-1}.day^{-1}$ divided in 2–3 doses	Strong interactions with fosphenytoin/phenytoin and valproate Inducer of several cytochrome P450 enzymes Contains propylene glycol which can cause metabolic acidosis May be preferred in alcohol withdrawal seizures Requires dose adjustment in severe renal impairment
Lacosamide	Intravenous Oral	200–400 mg	200–600 $mg.day^{-1}$ divided in 2 doses	Minimal drug interactions Should be avoided in patients with conduction abnormalities (prolongs PR interval) Requires dose adjustment in renal impairment and hepatic impairment Relatively expensive
Brivaracetam	Intravenous Oral	100–400 mg	100–600 $mg.day^{-1}$ divided in 2–3 doses	Interacts with enzyme inducers/inhibitors Increases carbamazepine and phenytoin concentrations Requires dose adjustment in hepatic impairment

Table 2. Intravenous anaesthetic drugs used for treatment of status epilepticus

	Primary mechanism of action	Onset of action	Elimination half-life	Loading dose	Maintenance dose	Serious adverse events	Clinical considerations
Midazolam	↑ $GABA_A$	1–5 min	1.8–6.4 h	0.2 $mg.kg^{-1}$ followed by repeat loading doses every 3–5 min	0.05–2 $mg.kg^{-1}.h^{-1}$	Hypotension Respiratory depression	Tachyphylaxis after prolonged infusions
Propofol	↑ $GABA_A$ ↓ NMDA	15–30 s	4–7 h	1–2 $mg.kg^{-1}$ followed by repeat load of 0.5–2$mg.kg^{-1}$ every 3–5 min	20–80 $\mu.kg^{-1}.min^{-1}$	Hypotension Respiratory depression Metabolic acidosis PRIS Pancreatitis	Monitoring of serum lactate, triglycerides, amylase, lipase, and renal function if prolonged infusions
Pentobarbital	↑ $GABA_A$	< 60 s	15–50 h	5–15 $mg.kg^{-1}$ followed by a repeat load of 5–10 $mg.kg^{-1}$	0.5–5 $mg.kg^{-1}.h^{-1}$.	Hypotension Respiratory depression Decreased cardiac output Ileus Immune suppression Hypothermia Hepatic dysfunction	Contains propylene glycol Close monitoring of cardiac, hepatic and renal parameters is needed
Thiopental	↑ $GABA_A$	10–40 s	3–22 h	2–7 $mg.kg^{-1}$	0.5–5 $mg.kg^{-1}.hr^{-1}$	As per pentobarbital	Close monitoring of cardiac, hepatic, and renal parameters is needed
Ketamine	↓ NMDA	~ 30 s	~ 2.5 h	0.5–3 $mg.kg^{-1}$, followed by repeat load of 0.5$mg.kg^{-1}$ every 3–5 min	0.1–4 $mg.kg^{-1}.h^{-1}$	Cardiac arrhythmias (rare)	Earlier use in refractory status epilepticus likely to be associated with better control Optimal dosing varies by institution

GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate;

Table 3. Non-pharmacological interventions in super-refractory status epilepticus

Intervention	Rationale	Evidence
Ketogenic diet	High fat, low carbohydrate diet of proven value in drug-resistant epilepsy in children	Case reports and series reporting termination after initiation [59,60]
Repetitive transcranial magnetic stimulation	Hypothesised to reduce cortical excitability in epilepsy, usually directed to a focal brain area, so of questionable benefit where there are widespread or generalised discharges	Case reports only, high seizure recurrence rates after initial responder [48]
Vagal nerve stimulation	An established, well-tolerated treatment option in drug resistant epilepsy, but with efficacy typically emerging over weeks or months	Case series and reports only; low quality evidence [61,62]
Electroconvulsive therapy	Hypothetised that treatment leads to alterations in neurotransmitter levels and an elevation in the seizure threshold post treatment	Case reports and series; potential for harm [63]
Therapeutic hypothermia	Conflicting evidence of benefit in hypoxic brain injury	Randomised control trial (24 h at 32–24°C) reduced progression of convulsive to non-convulsive status epilepticus. No meaningful difference in any clinical outcomes [64]

Figure 1: Treatment timeline of convulsive status epilepticus

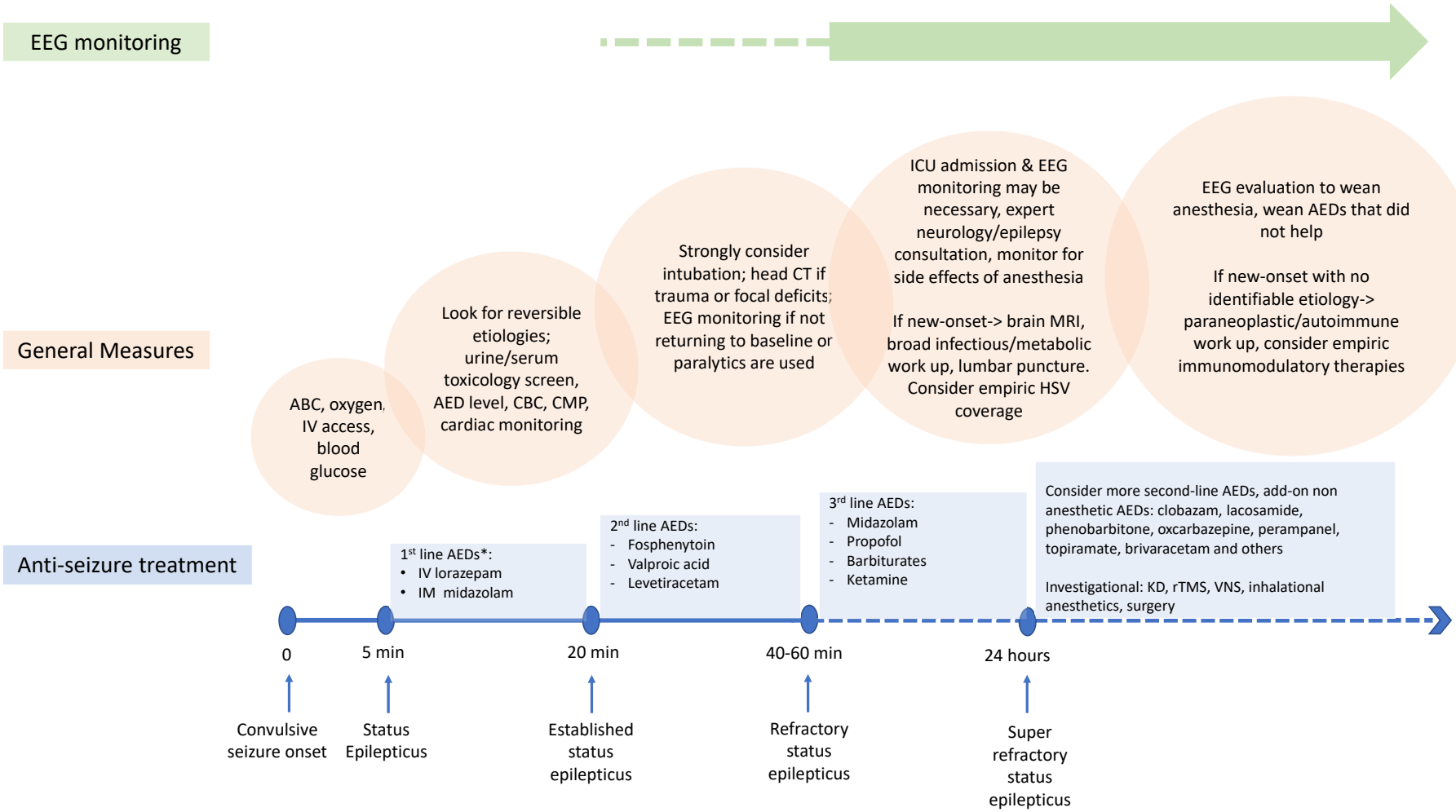
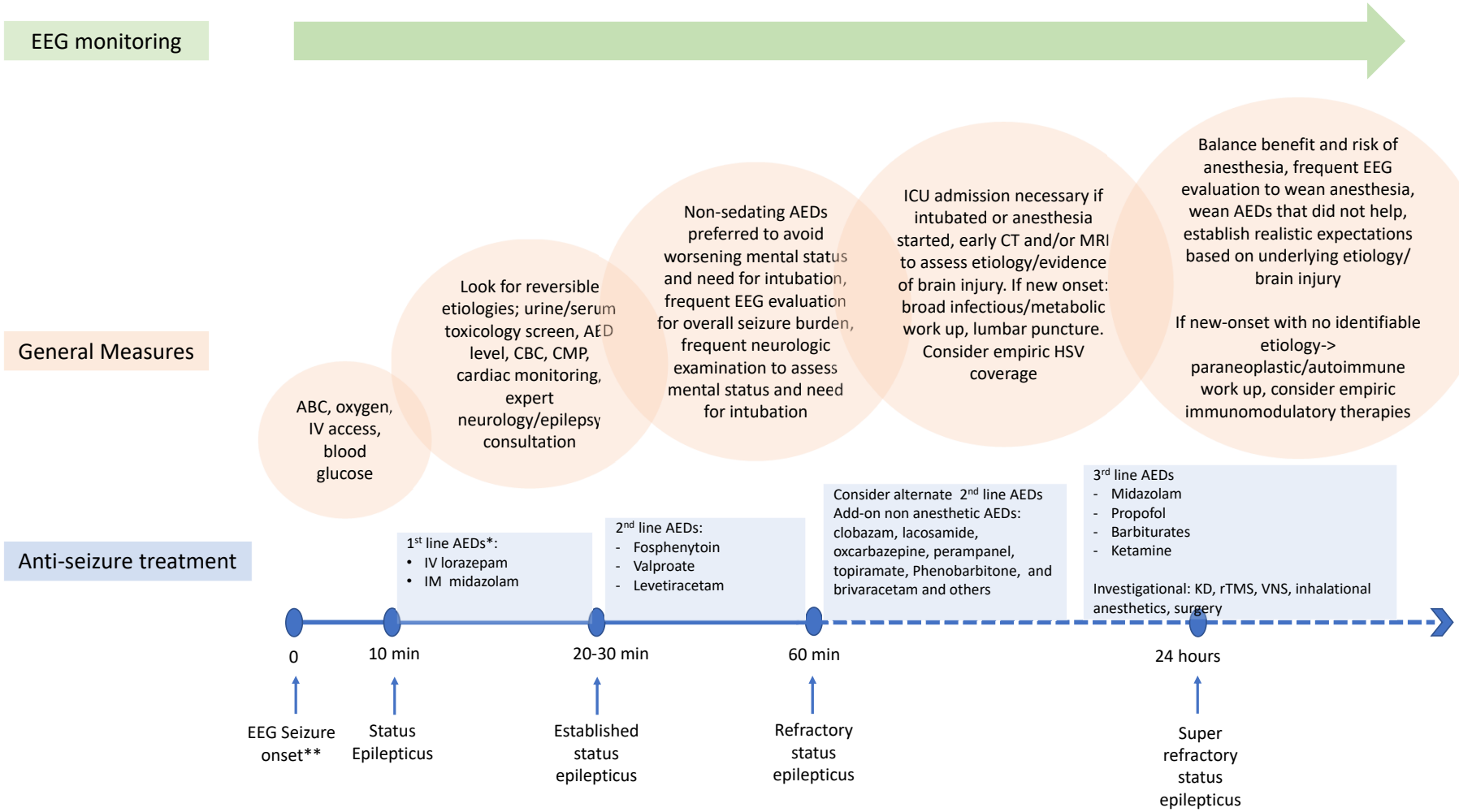
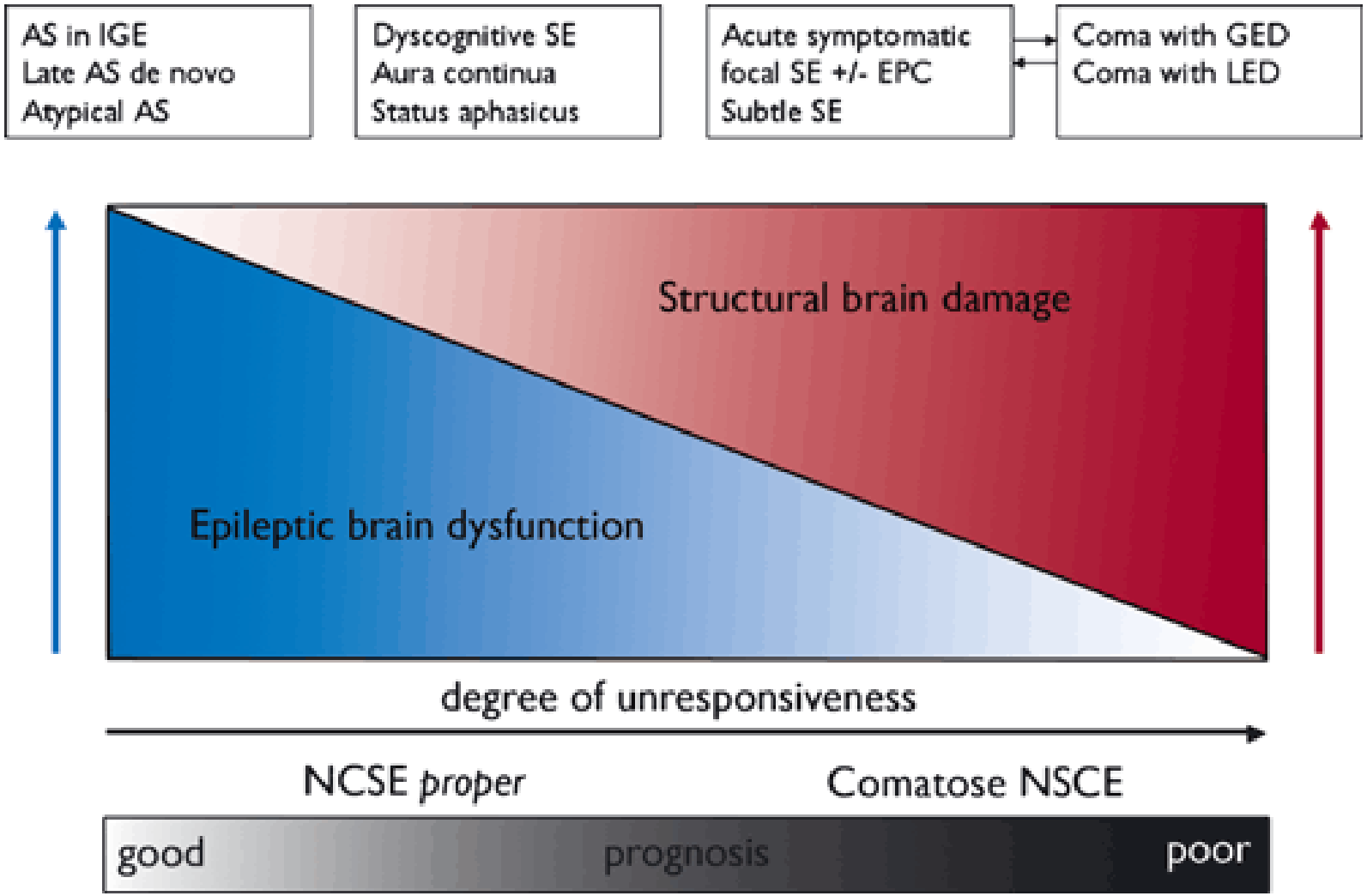


Figure 2: Treatment timeline of nonconvulsive status epilepticus




AS in IGE
Late AS de novo
Atypical AS
Dyscognitive SE
Aura continua
Status aphasicus
Acute symptomatic
focal SE +/- EPC
Subtle SE
Coma with GED
Coma with LED
Structural brain damage
Epileptic brain dysfunction
degree of unresponsiveness
NCSE proper
Comatose NSCE
good
prognosis
poor