

A pragmatic approach to intravenous anaesthetics and electroencephalographic endpoints for the treatment of refractory and super-refractory status epilepticus in critical care.

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Introduction

Status epilepticus (SE) is a relative common neurological emergency, with an estimated incidence between 10-41 per 100,000 population [1]. American ethnic minorities have a higher incidence of SE compared to white Americans (57 vs 20 per 100,000 population, respectively) [2]. Despite trend studies demonstrate an increased incidence in the past few decades in the USA [3], the overall mortality of SE in adults remains around 20% [4, 5].

More than half (54%) of cases of SE present for the first time in the absence of an existing diagnosis of epilepsy [6] and epileptogenic mechanisms are likely to be specific for each condition (existing epilepsy vs non-epilepsy) [7].

In 2015 the ILAE Task Force on Classification of Status epilepticus (SE) defined SE as “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1). It is a condition that can have long-term consequences (after time point t_2), including neuronal death neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures” [8].

Based on the clinical features and severity, SE is distinguished into “convulsive” or “non-convulsive”, the former being the most common and harmful [9].

SE lasting longer than 120 minutes and not responding to first- and second-line treatments is defined as “refractory” (RSE) and requires general anaesthesia and intensive care unit admission. Frequently, RSE presents either as generalized convulsive SE (GCSE) or complex partial SE (CPSE) refractory to initial treatment, or coma following GCSE/CPSE or brain surgery or acute

brain injury. The resistance to treatment occurs in 23-43% of patients with SE [10-15] and is associated with acute, severe, and potentially fatal underlying cause such as encephalitis, massive stroke, or rapidly progressive primary brain tumours [10-13, 15-17]. The short-term mortality for RSE is threefold higher than non-Refractory SE and has been estimated to be between 16-65% [10-13, 15, 18, 19]. Age and aetiology have been consistently identified as the principal independent outcome predictors [10].

“Super-Refractory” SE (SRSE) is defined as SE that continues or recurs 24 hours or more after the onset of anaesthetic therapy [20]. Mortality of SRSE has been reported between 30 to 50%, and the survivors often demonstrate poor neurological outcome despite seizure control [21, 22].

Despite general consensus regarding the first- and second-line of treatment for SE [23], at present, there is no definitive high quality evidence or agreement to guide an optimal treatment protocol for RSE (Stage III) and SRSE (Stage IV) and a large part of the literature consists of case reports or case series (Figure 1).

There is still ongoing debate as to whether non-convulsive SE (NCSE) in critically ill patients should be treated as aggressively as GCSE. NCSE should be terminated early to reduce neurologic and systemic complications; however, it is generally accepted that a trial with a third-line non-anaesthetic anticonvulsant is completed, before administration of anesthetic agents [24].

The basis of treatment in Stage III and Stage IV consists of the administration of continuous intravenous anaesthetic agents titrated to electroencephalogram (EEG) demonstration of seizures control or burst-suppression. Rescue therapies include immunosuppression, hypothermia and rarely, neurosurgical interventions and ketogenic diet.

In this review, we pragmatically discuss the current knowledge about intravenous anaesthetics for the treatment of RSE and SRSE in adults focussing on the pathophysiology of drug resistance, progressive brain damage, and the unique pharmacokinetic and pharmacodynamic challenges that critically ill patients pose. Additionally, we summarise data on the use of continuous EEG monitoring to emphasize the importance of early termination of SE. We also propose our Institution’s intravenous anaesthetic treatment algorithm and highlight some of the practical aspects of critical care organ support required for RSE/SRSE.

Pathophysiology of refractory seizures and progressive brain damage

Epileptogenesis in SE is a process encompassing the local hypersynchronisation of excitatory or recurrent inhibitory neuronal networks [25], which could diffuse to the rest of the brain tissue generating spontaneous seizures. These paroxysmal hypersynchronous transient electrical discharges result from an imbalance between too much activation or too little inhibition in the epileptogenic focus [26].

There are several hypotheses behind the refractoriness to treatment of SE [27]. Among the biological processes underpinning this, is the internalisation of synaptic Gamma-aminobutyric acid type A (GABA_A) receptors leading to a reduction in the potency of benzodiazepines as seizures continue [28, 29]. This mechanism involves calcineurin-dependent internalisation of the GABA_A receptors and late activation of N-methyl-D-aspartic acid (NMDA) receptors (Figure 2) [30, 31].

Furthermore, the phosphorylation state of the potassium-chloride transporter KCC2 and its consequent internalisation leads to increased intracellular chloride level and decreased inhibitory effect of the GABA_A receptor activation [32].

In the acute SE phases the increased excitation and release glutamate leads to a net calcium influx, with intracellular cascade activation and osmotic swelling [33]. Neuroimaging studies have demonstrated abnormalities of both the leptomeninges and blood-brain barrier during seizures, accompanied by both cytotoxic and vasogenic oedema and hyper-perfusion of the epileptic foci [34].

In subacute phase of RSE, days and weeks after SE has commenced, many changes occur, such as gene expression, transcription factors, and mRNA expression [33]. These are often accompanied by microhaemorrhages, blood-brain barrier alteration and further seizure-induced neuronal death and reorganisation [35]. These reversible alterations are often seen in brain magnetic resonance imaging (MRI) performed to identify the aetiology of RSE/SRSE and appear as diffusion-weighted or T2-weighted cortical hyperintensities with a corresponding low apparent diffusion coefficient [36]. Furthermore, prolonged seizures and their aggressive treatment with anaesthesia lead to complex systemic physiological compromise that contribute to neuronal death; this include, but are not limited to, hypotension, hypoxia and acidosis.

In the long-term, refractory seizures lead to the development of generalised and focal atrophy [37]. Indeed, changes often seen in serial brain MRI include progressive cortical and subcortical atrophy, and the development of hippocampal signal changes or atrophy (Figure 3) [38].

Mechanisms of anaesthesia

GABA_A receptors are ubiquitous in the central nervous system, and they are situated both at the synaptic and extra-synaptic level. They are one of the main sites for the action of general anaesthetics including halogenated volatile and most intravenous anaesthetics (sodium thiopental, propofol and etomidate) [39, 40]. GABAergic anaesthetics have been shown to exert different effects on these receptors: they may increase the current elicited by small concentrations of GABA (potentiation) [41], or activate the channels in absence of GABA (direct gating) [42], and prevent the flow of current through the channels (inhibition) [43].

NMDA receptors represent another target for general anaesthetics such as ketamine, nitrous oxide and xenon as well as halogenated volatile anaesthetics to some extent [44-46]; these are glutamate activated ionotropic excitatory receptors mostly located extrasynaptically but can be found also pre-synaptically.

Although their main action is on GABA and NMDA receptors, general anaesthetics modulate a wide array of receptors. These include two-pore-domain potassium channels activated by volatile and gaseous anaesthetics, causing a reduction in excitatory currents and overall inhibitory neural effect, glycine receptors, potentiated by volatile anaesthetics and propofol, and nicotinic receptors inhibited by volatile anaesthetics. Furthermore, brainstem noradrenergic neurones and sodium channels are also modulated by anaesthetic drugs.

Although synaptic function is considered to be the major target of anaesthetic drugs, the critical mechanism which produces general anaesthesia is not yet fully understood. Anaesthetic agents enhance inhibitory or decrease excitatory transmission thus disturbing neuronal activity depending on the site of action. Despite different mechanisms and sites of action, the outwardly manifestation produced by all anaesthetic drugs is unconsciousness [47].

The central role of the thalamus and the de-activation of its nuclei is considered one of the main manifestations of anaesthetic-induced unconsciousness. It has been hypothesized that one of the mechanisms of anaesthesia entails the disruption in information integration within the corticothalamic and corticocortical networks [48].

Because of their cellular targets and the ability to suppress the EEG to partial or complete isoelectricity, anaesthetic drugs form part of the treatment of RSE and SRSE. Anaesthetic drugs that target the extra-synaptic GABA_A receptors should be more effective later on in status

epilepticus (Stage III). Indeed, propofol has been shown to be effective in benzodiazepine-resistant status epilepticus both in animal models and humans [49]. Furthermore, inhibition of NMDA receptor may increase the potency of benzodiazepines, thus providing rationale for the association of ketamine in SE refractory to benzodiazepines and GABAergic agents.

Intravenous Anaesthetic Treatment

There is an important discrepancy between the reported use of anaesthetic drugs in the treatment of RSE and the amount of published high quality research aimed at establishing their effectiveness. Reported practices indicate that a rapid administration of intravenous anesthetic agents could be adopted after a failed trial of benzodiazepines and phenytoin, but more frequently a third-line, non-anesthetic agent, is usually administered prior to induction and maintenance of general anesthesia [50].

A recent survey suggests some agreement on the first-line anaesthetic agents; however, there is less consensus on which drug and when to introduce second-line anesthetics, and even less agreement on the third-line [51]. The first-line intravenous anesthetic agents most widely used to treat RSE are propofol, midazolam, and barbiturates are often added in association or used as second-line agent [9, 51, 52]; ketamine is less frequently used as first-line agent, more often added as third-line agent in association with midazolam or propofol [51, 53].

Several authors have proposed protocols and algorithms for the treatment of RSE/SRSE [21, 54, 55] and the Neurocritical Care Society has published Guidelines for the evaluation and Management of SE in 2012 [56]; we display here the flowchart used at our institution and the doses of anaesthetic agents (Figure 4).

Propofol is widely used as the first-line intravenous anesthetic agent for RSE because it allows rapid titration, and it has a short duration of action after prolonged infusions (context-sensitive half-life). Control of clinical seizures associated with propofol alone in cohort series has been reported between 67-88.9% of cases of RSE [57, 58]. Moreover, propofol infusion has been associated with rapid termination of electrophysiologic seizures, but the achievement and maintenance of burst-suppression EEG pattern has often been achieved with incrementally higher infusion doses around 9.5 (8.2–11.0) mg/kg/h [59].

Midazolam is often used as alternative first-line agent or in association with propofol, thiopental, and ketamine for the treatment of RSE [51]. A retrospective case-control study comparing high

(0.4 mg/kg/h) vs low dose (0.2 mg/kg/h) continuous infusion of midazolam demonstrated that high dose infusions of midazolam are safe and could be associated with lower seizures rate after 48 hours after infusion discontinuation [60]. Nonetheless, midazolam infusions are reported up to 2 mg/kg/hr, and are associated with a reduced rate of infections, anaemia requiring transfusions, lymphopaenia, hyponatremia, and hypotension compared to thiopental infusions [52, 56]. To date, the only randomized clinical trial comparing thiopental sodium and propofol for the treatment of RSE was published in 2011 by Rossetti et al [61]. This small RCT demonstrated comparability of thiopental sodium vs propofol in most outcome measures considered, such as: total control of seizures, in-hospital mortality, adverse events and long-term outcome. Duration of mechanical ventilation was prolonged in patients receiving thiopental sodium, likely due to the long context-sensitive half-life of the drug with prolonged sedative effect.

A systematic review including 28 studies up to 2010 demonstrated that barbiturates are more effective than midazolam or propofol in controlling clinical and electrophysiologic seizures, and in preventing breakthrough seizures. However, this failed to demonstrate a difference in early mortality between agents [62]. Notably, the studies included in the review are hardly comparable thus leading to a severe risk of bias. Indeed, burst-suppression was more often the treatment endpoint in patients treated with barbiturates (96%), but rarely in those receiving propofol (38% and not at all in those treated with midazolam.

Anaesthetic agents with predominant GABAergic mechanism of action are limited in efficacy over time due to the progressive loss of GABA_A receptors. This phenomenon is often accompanied by overexpression of NMDA receptors as seizures continue and has been described as possible mechanisms involved both in the refractoriness to treatment with GABAergic drugs of RSE/SRSE, and in the positive response with NMDA antagonists such as ketamine. Due to its associated sympathomimetic activities, ketamine is also less often associated with hypotension compared to other anaesthetic agents [63]. The evidence available on the use of ketamine in RSE/SRSE have recently been synthesized in a systematic review; since no randomized clinical trials are available in literature, this is limited to a summary of small case series and case reports [64].

ClinicalTrials.gov Identifier: NCT03115489 Burst suppression with either traditional first-line anaesthetics (Propofol, midazolam, thiopental) vs ketamine bolus (2/5 mg/kg) followed by infusion (start at 3 mg/kg/hr + increments of 1mg/kg/hr until maximum 10 mg/kg/hr) for 48 hrs of Burst-suppression (then reduction of 2mg/kg/hr against EEG evidence of seizures).

So far, the use of early ketamine is not embedded in the routine practice due to its safety profile: it may worsen intracranial hypertension and possibly cause neurotoxic effects when used as a prolonged infusion.

Additionally, experimental and data suggest that ketamine with benzodiazepines or propofol have a strong synergistic effect in the treatment of RSE [53, 65, 66]. Following observational studies exploring the role of NMDA receptor inhibition on the spreading depolarization in acute brain injury and stroke [67, 68], a recent randomized clinical trial demonstrated that ketamine is effectively inhibiting spreading depolarization [69]; however, the association with improved outcomes has not yet been shown.

Currently, most of the data available indicate burst-suppression as the electroencephalographic endpoint of an aggressive treatment approach which is more often associated with a sustained termination of seizure activity; nonetheless, mortality and functional outcome do not differ in RSE with or without EEG suppression [62].

Current European Guidelines recommend anaesthetic drugs titration to EEG burst-suppression for propofol and thiopental sodium, whereas seizure suppression is the target endpoint when midazolam is infused. It is suggested that continuous infusions be maintained for at least 24 hours at these endpoints before weaning [24]. Generally, anesthetic infusions should be maintained for the minimum period required to achieve long-term seizure control irrespective of the agent used [11].

These findings and recommendations raise a clinical dilemma, as the potential benefits of seizure control outweigh the risks associated with increased anaesthetic drug infusions required to achieve a stable burst-suppression or seizure control pattern on EEG.

General anaesthetic drug continuous infusions for the treatment of RSE are often accompanied by severe side effects that contribute to poor outcome and death. Anaesthetic-induced hypotension often requires fluid resuscitation and pharmacological cardiovascular support (vasopressors or inotropes). Additionally, gastric dysfunction and infective complications due to immunosuppression and invasive devices are common.

In particular, barbiturates are associated with the highest incidence of complications, such as: hypotension with visceral hypoperfusion leading to splenic, gastric, hepatic and pancreatic dysfunction, and leucocyte dysfunction with increased vulnerability to infective complications [62].

High dose prolonged propofol infusions for the treatment of RSE may lead to propofol-infusion syndrome (PRIS); this is characterized by increased creatine kinase and rhabdomyolysis, diffuse electrocardiographic changes, severe metabolic acidosis and potentially cardiogenic shock. A retrospective study has shown an incidence of PRIS symptoms and signs in 45% of patients with RSE treated with Propofol infusion; two of these patients suffered cardiac arrest and 30% developed malignant arrhythmias [70]. Furthermore, another study identified systemic complications, such as pneumonia, during propofol infusion in 63% of patients [58].

Some reports have not found an association between specific coma-inducing agents or the extent of BS on outcome [Rossetti AO. Arch Neurol 2005), while others have raised concerns about the higher morbidity and mortality in BS group, mostly due to prolonged ITU stay and anaesthetic exposure [Sutter R Neurology. 2014].

Burst-suppression

EEG burst-suppression (BS) pattern usually consists of generalised intermittent sequences of slow or sharp waves (bursts) of mixed frequencies, alternating with periods of suppressed EEG to isoelectricity (amplitude of less than 10 μ V) lasting from seconds to minutes (suppression). This pattern is generally associated with a reduction in cerebral metabolic activity. This pattern was first identified during barbiturate hypnosis by Swank and Watson in 1949 [71], and it was demonstrated to persist after frontal lobe cortex isolation from the thalamus [72]. BS is usually symmetrical, but in brain injury it may also become asynchronous or focal in one brain hemisphere. Hypocapnia increases the suppression time, decreases the duration of bursts, increases the amplitude and main frequency of the bursts which could demonstrate epileptiform morphology. Both heart rate variability and alterations in the systemic and cerebral circulation (Cerebral Blood Flow, CBF) occur during BS. Researchers have hypothesized a unified subcortical mechanism underpinning both the BS cortical activity and heart rate fluctuations [73]. Characteristically, the onset of EEG suppression precedes the reduction of CBF by 5-7 seconds during inhalatory anaesthesia. This parallel shift in CBF and electrical activity suggests some degree of neurovascular coupling preservation during deep inhalatory anaesthesia.

BS is not uncommon during general anaesthesia, and it is more frequent at induction, especially if repeated boluses are used [74]. Indeed, most processed EEG depth of anaesthesia monitor devices recognise BS as one of the parameters to display with the presence of BS recognised as a definition

for deep anaesthesia. BS has also been demonstrated in coma [75], hypoxic brain injury following cardiac arrest [76], drug intoxication, encephalopathies [77] and hypothermia [78]. Specific patterns of BS with generalised bursts with stereotypical morphology have been associated with poor outcome in comatose patients after cardiac arrest [79].

Although historically BS has been recognised a very deep state of general anaesthesia, several reports demonstrated reactivity to sensory stimulation during barbiturate anaesthesia, indicating a suppression of the cortex without blockade of the sensory paths [80]. Recently, more reports have demonstrated that BS often entails a state of cortical hypersensitivity, likely due to increased extracellular calcium levels [81].

BS can be induced by several anaesthetic drugs such as inhalatory and intravenous agents, and the BS patterns characteristics of the deep stages of anaesthesia vary depending on the drug used (Figure 5). Animal research has been demonstrated the existence of distinctive BS pattern during inhalatory (isoflurane and sevoflurane) and propofol anaesthesia; these differences include higher bursts amplitude during isoflurane or sevoflurane anaesthesia and differences in bursts duration. Recently, An et al. demonstrated diverse patterns of BS in 35 patients with RSE receiving intravenous anaesthesia and observed both longitudinal intra-patient and between-patients variability in the amount of BS at constant infusion rates of anaesthesia [82].

The current literature on the use of anaesthesia in the treatment of RSE/SRSE is scanty, yet experts recommend BS with inter-burst intervals (IBI) of 10 seconds for at least 24 hours before weaning therapy [54]. Despite some studies suggesting shorter IBI (> 5 seconds) [83], their association with outcome remains uncertain [84]. Interestingly, some authors hypothesize a stronger association between successful weaning of anaesthesia and qualitative characteristics of bursts, such as monomorphic sharp morphology, bursts maximum amplitude <125 μ V, and presence of less than 50% epileptiform activity during the bursts [85].

Critical Care Continuous EEG

Monitoring the electrical activity of the brain is therefore a cornerstone of the treatment in RSE/SRSE where BS is the endpoint. This can be monitored via standard continuous electroencephalography (cEEG) or simplified EEG, such as Bispectral Index (BIS) with the possibility of measuring and recording the BS ration.

Video-cEEG refers to the simultaneous recording of EEG and clinical behavior (video) over extended time periods (hours to weeks) in critically ill patients which may include graphical displays of quantitative EEG trends (qEEG) [86]. It offers real-time, noninvasive, direct and continuous assessment of brain function and its use in critically ill patients is strongly associated with decreased in-hospital mortality [87, 88].

Compared with intermittent EEG (iEEG), which typically lasts 20–30 minutes, cEEG is more sensitive in uncovering non-convulsive seizures with a detection rate increasing from 50% after 1 hour of recording to 95% after 48 hours [89]. The detection rate of NCSE is also higher with cEEG as compared to historical controls undergoing iEEG (monthly detection rates: cEEG, 5.44 \pm 1.33; iEEG, 2.17 \pm 1.89, $P = 0.002$) [90].

Interestingly, cEEG findings strongly impact clinical care, leading to change in treatment in half of the cases, which can either be initiation, escalation, or discontinuation of AEDs [91]. Jordan reported similar results over a decade ago, suggesting that cEEG had a “decisive” impact on clinical management in 54% of patients and contributed to decisions (obtain imaging, AED prescribing, or hemodynamic manipulation for cerebral perfusion) in an additional 32% [92].

The Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society expert consensus [86] recommends the use of cEEG to identify non convulsive seizures and NCSE in critically ill patients with persistently abnormal mental status following generalized convulsive status epilepticus (GCSE) or other clinically-evident seizure, acute supratentorial brain injury with altered mental status, fluctuating mental status or unexplained alteration of mental status without known acute brain injury, generalized or lateralized periodic discharges, or bilateral independent periodic discharges on routine or emergent iEEG, requirement for pharmacological paralysis and risk for seizures and clinical paroxysmal events suspected to be seizures, to determine if they are ictal or non-ictal. cEEG is also recommended to monitor the response to treatment [86]. Other indications include: early detection of delayed cerebral ischemia associated with subarachnoid hemorrhage, evaluation the depth of sedation, and assessment of severity of encephalopathy, and prognostication after acute brain injury [93].

It is recommended that cEEG should be initiated as soon as possible when NCSE is suspected, with concurrent video recording, continued for at least 24-48 hours and reviewed as often as logistically and technically feasible, and interpreted by electroencephalographers at least twice daily (i.e. about every 12 hours).

With regard to treatment efficacy, cEEG should be continued until seizures have been controlled for at least 24 hours. cEEG should be utilized during the entire period of anesthetic treatment until at least 24 hours after anaesthesia is withdrawn [86].

Even though there has been an exponential rise in the use of cEEG in the USA [87, 94], overall only 0.3% of the critically ill patients included in several studies underwent cEEG monitoring at any point during their hospitalization. Information on cEEG in Europe is only scarcely available, but a recent Dutch survey revealed an increase in cEEG use in the Netherlands, mainly in the university and teaching hospitals, but also in general hospitals [95]. Currently, two European multicenter randomized controlled trials (TELSTAR trial—clinical trials.gov NCT02056236, CERTA trial—clinical trials.gov NCT03129438) are ongoing, aiming to relate cEEG use to patient outcome in specific patient populations.

Despite the advantages mentioned above, major barriers to more widespread use of cEEG exist. The cost of acquiring and maintaining video-cEEG equipment and providing storage servers for the captured data has financial implications, with the cEEG monitoring itself being quite labour-intensive. Real-time qEEG processing can be used to shorten cEEG review time for seizure identification, however, the prevalence of false positives supports review of raw data at the same time [96]. Patient-related issues (such as skin breakdown with electrode placements, sweat artefact, patient body movement, suction, etc.) and environmental issues (electrical noise, infusion pumps, movement, etc.) can cause difficulty in maintaining stable and low impedance for accurate interpretation of EEG information. The lack of uniform nomenclature for EEG description and of some EEG patterns of uncertain significance, which may or may not be treated, can add to the practical challenges faced by reporters. Ideally, cEEG should be reviewed continuously by qualified personnel in real time, but current staffing models rarely support this level of monitoring, and in most centers cEEG is usually reviewed intermittently (i.e. continuously recorded, but intermittently reviewed), which may result in delayed identification of malignant events [95].

In the future, newer technologies and advanced computing power may provide more affordable cEEG machines with reliable remote access, automatic seizure detection algorithms and more accurate qEEG features, paving the way for the fast assessment of large amounts of EEG data. This could lead to training of non-expert but experienced Intensive Care personnel, thus making the whole process more cost effective.

Pharmacokinetic/dynamic considerations of iv anaesthetics in the critically ill

It is well known that critically ill patients experience physiological changes which may result in altered pharmacokinetic and pharmacodynamics of medication, leading to toxicity or a subtherapeutic clinical effect (Figure 6). It is important to be aware of such alterations when initiating and reviewing medication in order to dose and monitor appropriately.

A common issue for critically ill patients is the difficult administration and absorption of medication and subsequent subtherapeutic effects [97]. Gastric absorption may be impaired due to reduced gut perfusion, delayed gastric emptying or disrupted enteral access leading to, for example, adhesion of drug to feeding tubes or nutrient interactions [98, 99]. Subcutaneous administration may also be impaired due to vasopressor usage limiting peripheral blood flow or peripheral oedema and fluid redistribution [98]. This is not usually a problem for anaesthetic medications as the majority are administered via the intravenous route, where there is no barrier to bioavailability. However, it is important to consider the reliability of the enteral route when initiating anti-epileptics and other supportive medication. These may require intravenous administration to ensure adequate therapeutic plasma concentrations, complemented by therapeutic drug monitoring if indicated (for example, phenytoin and phenobarbitone).

A significant factor which often affects the properties of anaesthetic drugs is the volume of distribution (Vd). Vd is a theoretical volume which describes the distribution of the drug throughout body compartments and is based on chemical properties such as polarity and protein binding [98]. Drugs which are highly protein bound and hydrophilic drugs tend to have a low Vd as have less capacity to disperse from the intravascular space. In critically ill patients the Vd can be altered significantly, usually due to an increase or redistribution of fluid or change in protein binding [98]. This change in Vd subsequently affects concentrations of drug in the plasma and body tissue and can lead to subtherapeutic or supratherapeutic consequences.

Hypervolemia from fluid resuscitation or capillary leakage due to sepsis and endothelial failure can cause an increase in Vd of hydrophilic medication (such as morphine and beta-lactame antibiotics) and consequently reduce both plasma concentrations and effective peripheral tissue perfusion [99].

Abnormal protein binding is commonly caused by hypoalbuminaemia and increased levels of α_1 -acid glycoprotein (AAG), an acute phase protein produced in response to stress [98, 99]. Hypoalbuminaemia has a major impact on several medications, including on anaesthetic and anti-

epileptic drugs [98]; midazolam and propofol are both lipophilic anaesthetic drugs which are highly protein bound [100], phenytoin and sodium valproate are also highly protein bound and susceptible to albumin changes [98]. A reduction in albumin causes an increase in drugs free-fraction in the plasma, causing further distribution into adipose tissue (higher Vd) and a prolonged therapeutic effect [98, 100, 101]. Higher free-fraction of several drugs used in RSE/SRSE can cause toxicity, therefore it is essential to use therapeutic drug monitoring and adjust the total drug level according to the measured albumin plasma level. For example, if the albumin concentration is not accounted for, the actual therapeutically active phenytoin concentration may be underestimated [99, 102].

Drug metabolism occurs predominantly in the liver and to a lesser extent in other organs such as the gastrointestinal tract, kidneys, lungs and the brain. Hepatic blood flow is an important factor in the liver's ability to clear drugs from the bloodstream, and the volume of blood that is completely cleared of drug by the liver per unit time (hepatic clearance) is directly proportional to both hepatic blood flow and the fraction of drug that is removed from the blood after one pass through the liver (hepatic extraction ratio). In critically ill patients, hepatic blood flow and consequently drug clearance can be affected by several factors including multi-organ failure, shock, circulatory collapse and the use of vasoactive agents, causing hepatic arterial and portal vein vasoconstriction. Hepatic clearance of drugs with high extraction ratios such as, ketamine, midazolam and propofol primarily depends on hepatic blood flow and is less sensitive to changes in liver function. Whereas clearance of drugs with low hepatic extraction ratios, such as phenobarbital and phenytoin is affected by changes in liver function but is less sensitive to changes in hepatic blood flow.

The cytochrome P450 (CYP450) enzyme system is responsible for the majority of hepatic metabolic reactions (oxidation, reduction and hydrolysis) that transform drug molecules into active or inactive metabolites. Anaesthetic agents used in the management of RSE/SRSE, ketamine and midazolam are metabolised by the CYP450 enzyme system, predominantly CYP3A4 [103]. Propofol is converted to inactive metabolites predominantly by the liver, however extra hepatic sites including kidneys and intestines account for 40% of the total clearance of propofol [104]. Critical illness can alter metabolic enzyme activity in various ways; studies suggest that pro-inflammatory cytokines released during acute inflammatory response can down regulate CYP450 enzymes leading to an increase in drug exposure [105]. Therapeutic hypothermia, which is rarely considered as a rescue treatment option in RSE/SRSE, reduces

hepatic blood flow and overall metabolism with a resulting decrease in clearance of cytochrome P450 metabolized drugs by approximately 7% to 22% per degree Celsius below 37 degrees [106, 107]. Reduced CYP3A metabolic activity resulting from renal impairment has been attributed to reduced clearance of both midazolam and its active metabolite 1 α -hydroxymidazolam [108, 109]. In addition, the renally cleared 1 α -hydroxymidazolam conjugate accumulates in renal failure and is thought to contribute to prolonged sedation in these patients.

Perhaps, the crucial aspect of renal failure/replacement in RSE is the effect of RRT on medical seizure control. Plasma levels of each drug is affected by RRT and it will be dependent on the dose of RRT. The speed of this change varies and may result in recrudescence of seizures or increased sedation requirements. Drug-specific dose corrections are available online (Epilepsy Foundation) and comprehensive guidance should be sought from the department pharmacist and RRT/Drugs correction tools [110]. For example, levetiracetam is dialysed, with removal of 51% of the dose by 4 hours of haemodialysis. Phenytoin by contrast is not dialysed and dosing should continue per normal renal function [110]. However, when prescribing and administering highly protein-bound drugs such as phenytoin, it is important to consider that RRT induced changes in plasma albumin concentration may change therapeutic effects indirectly.

Furthermore, in the phases of renal recovery or prior to RRT, therapeutic effects and plasma levels of drugs may be increased by inadequate renal clearance. Risks of this should be mitigated by clinical assessment and monitoring.

Finally, it is important to consider that anaesthetic agents used in the management of RSE/SRSE are subject to drug interactions with antiepileptic agent and other drugs commonly prescribed in intensive care both in terms of end-organ effects as well as competition for metabolic and excretion pathways.

ICU organ support

RSE is characterised by impaired consciousness and mechanical ventilation is a necessary consequence of the requirement for intravenous anaesthetic continuous infusions for long periods. From this starting point, many patients with RSE/SRSE require various level of organs support in the Intensive Care Unit (ICU). Given the duration of seizures in these patients can range up to weeks and months [111], different levels of organ support are often required at different stages of the ICU admission.

It is unusual for RSE patients to develop intracranial hypertension; as such it is usually acceptable to permit hypercapnoea in line with general principles of mechanical ventilation for critically ill patients [112]. These include minimising risk of barotrauma (limiting peak airway pressure <30cmH20) [113], reduce the risk of volutrauma (limited tidal volume ventilation, tidal volume 7 ml/kg) [114] and biotrauma (minimising shear stress by using optimal Positive End-Expiratory Pressure, PEEP) [113]. Prolonged periods of ventilation are common, both as a result of RSE duration, but also due to concurrent critical care weakness, infections and sustained decreased levels of consciousness affecting respiratory drive, adequacy of tidal volumes, and bulbar sufficiency.

Ventilation via tracheostomy may be indicated for patients with prolonged admissions. Although evidence for mortality benefit in tracheostomy is limited [115], the ability to consistently assess neurological symptoms potentially adds benefit in RSE patients.

Pulmonary complications which may develop in RSE patients are those common to all critical patients. However, aspects specific to RSE include the development of resistant organisms in the microbiome (*Pseudomonas* spp., ESBL producing Gram-negative organisms, resistant Gram-Positive organisms), related to repeated antibiotic courses and in-dwelling medical devices. Additionally, sustained periods of immunosuppression are common, whether from high-dose corticosteroid therapy, cyclophosphamide or rituximab therapy. Functional immunosuppression may also result from critical illness, barbiturate infusion, ciliary dysmotility [116] and immobility. Careful antimicrobial stewardship is required including consideration of *Pneumocystis jirovecii* prophylaxis [117].

RSE patients routinely require central venous catheters (CVC) for multiple drug administration and the concurrent use for central venous pressure monitoring and blood sampling may be needed. Consideration should be given to inserting devices with multiple lumens as it is common for multiple non-compatible infusions to be needed. Meticulous device care is essential as total duration of central venous access may require use (and re-use) of multiple central veins. Where possible femoral venous access should be avoided due to higher risks of catheter related infection [118] and risk of proximal deep venous thrombosis [119]. Daily review of need for CVC and potential for peripheral access should be routine practice. Since multiple intravenous vasoactive and/or antiarrhythmic infusions are often needed for treatment of RSE, arterial lines are usually needed for blood sampling and continuous blood pressure monitoring.

Hypotension is most commonly a result of vasodilation and decreased peripheral vascular resistance. This may occur as expected effects of drug infusion (sedatives, analgesics) or a result of evolving sepsis. The most common treatment for the management of peripheral vasodilation with hypotension includes noradrenaline infusion (with the addition of vasopressin if severe).

Cardiovascular instability may also manifest as result of RSE-induced catecholamine surges and cardiac arrhythmias are common in this group of patients and management should follow local guidance. Malignant arrhythmias may also develop either directly as a consequence of pathological involvement of the cortical regions that modulate cardiac autonomic function such as the insular and temporal lobe [120], or as result of therapy (eg, thiopental infusion). This may require cardiac electrophysiology input for percutaneous pacemaker insertion. Cardiac contractility impairment such as stress-induced cardiomyopathy (Takotsubo syndrome) are often associated with acute brain injury [121], and recently it has been reported as a manifestation resulting from RSE [122]. Management of this is principally supportive but may require interventional cardiac support if severe [123]. Use of cardiac output monitors would be dictated by usual indications and rarely as a direct result of RSE.

New-onset acute renal failure (ARF) may develop as part of multiorgan failure in RSE. This would most commonly result from sepsis and development of multiorgan failure in up to 25% of critically ill patients [124], and it is usually quantified using the RIFLE system [125]. Patients with RSE may develop acute renal failure in other specific circumstances, such as during continuous infusion of sodium thiopental or rhabdomyolysis due to prolonged convulsive status, long downtime, and compartment syndrome. If RRT is required, patients with RSE are likely to be at increased risk of dysequilibration syndrome following dialysis; the combination of rapid osmotic changes (RRT) and disruption of normal blood-brain barrier (in RSE) may increase the risk of cerebral oedema. Presence of ARF at presentation of RSE should raise the suspicion of systemic vasculitis in the differential diagnosis.

Therapeutic hypothermia can be considered as an advanced intervention for RSE [126]; however, there are no high-quality sources of evidence for duration, depth or effect of therapeutic hypothermia. The use of targeted temperature control is not routine practice and more often used as a rescue therapy for SRSE [127].

Advanced neuromonitoring

Beyond EEG and neuroimaging, ranging from serial CT to more sophisticated MRI sequences such as diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) map, susceptibility weighted images and spectroscopy, patients with SE often require additional layers of invasive and non-invasive monitoring which can help in the diagnosis, monitoring and prognostication [128]. A review of the relevant literature on this subject offers a very heterogeneous scenario where established diagnostic tools are discussed along with translational protocols. As a general rule, the ictal-interictal continuum pattern should be correlated, when available, with depth electrode recordings, intracranial pressure (ICP) fluctuations, brain oxygen measurement, data from microdialysis revolving around well-defined and experimental markers of neuronal injury [129].

Invasive CNS monitoring such as ICP monitoring may be indicated in individual cases of RSE, usually where seizure activity is related to a primary pathology causing raised ICP [130]. In these cases, control of ICP usually reflects the tenets of seizure management. Maintenance of cerebral oxygen delivery and reduction of cerebral metabolic rate, with optimisation of intracranial vascular tone, form the foundations of ICP management [131, 132]. Multimodal intracranial monitoring may be indicated in isolated cases of RSE.

Management of SE might be particularly challenging in those patients presenting with seizures that are not detected with scalp EEG (cEEG), hence potentially requiring insertion of depth electrodes for intracortical EEG. Of note, Mikell et al. recently developed a protocol for depth electrode placement in the neurocritical care patients in whom the clinical suspicion of occult seizures is high [133]. Depth EEG electrodes are typically placed as part of a so-called “bundle” of other invasive monitoring modalities including the previously mentioned ICP, but also brain-tissue oxygenation monitor, microdialysis catheter, and blood flow monitoring. Depth EEG recordings have the advantage (over scalp electrodes) of high signal-to-noise ratio and increased sensitivity to gamma band oscillations, hence offering some advantages in the early detection of early detection of secondary neurological complications commonly seen in RSE, such as ischemic events.

The interpretation of physiological signals recorded from invasive brain monitoring allows clinicians to gain timely insights into the underlying brain physiology and evolving pathophysiology, therefore providing avenues of unprecedented opportunities for optimization of medical and surgical management of this class of patients. For instance, whenever a drop in partial

brain oxygenation is noticed, hence raising suspicion of either ischemia or seizure activity, the intracortical EEG recording may show depressed or discontinuous background activity in the former and seizure activity in the later, in other words coupling data from different sources may support the interpretation of each source of invasive brain monitoring signals [133].

Conclusions: a pragmatic approach

The longer a seizure lasts, the less likely it is to stop. Early initiation of continuous intravenous anaesthetics is recommended for RSE; this inevitably requires intensive care admission and mechanical ventilation. It is recommended to titrate anaesthetic drugs infusion rates against specific EEG endpoints and use a protocolized approach for initiation, maintenance and withdrawal of anaesthesia. EEG monitoring is mandatory, and cEEG strongly recommended; however, processed EEG devices such as BIS could be used to monitor BS rate. Intravenous anaesthetic drug infusions should be maintained for the minimum period required to achieve long-term seizure control irrespective of the agent used. GABAergic and NMDA-antagonists have EEG signatures at different depths of anaesthesia that must be taken into account in the assessment of cEEG patterns. There is currently a lack of high-quality evidence to assess the effectiveness of different anaesthetic agents, and most of the existing protocols are based on expert consensus and pathophysiology rationale. Therefore, randomised, controlled trials identifying effectiveness and side effects of commonly used agents are still urgently required.

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Figure captions:

	Time	Definition	Treatment	Endpoint	Pathophysiology
Stage I	5-10 minutes	Impending SE	Benzodiazepines	Clinical resolution of SE (resolution of symptoms depending on SE type)	Protein phosphorylation Ion Channel opening and closing Neurotransmitter release Receptor trafficking: ↓ GABA _A R ↑ NMDA R ↑ AMPA R
Stage II	10-30 minutes	Established SE	Phenytoin Levetiracetam Valproate Phenobarbitone		
Stage III	30-60 minutes	Refractory SE	IV Anaesthetics (Propofol and/or Midazolam) + more AEDs	Burst-suppression and/or Seizure-free	Neuropeptide expression: ↑ Substance P ↓ Neuropeptide Y
Stage IV	> 24 hours	Super RSE	Association of IV Anaesthetics (Thiopental & Ketamine)	Burst-suppression	Genetic and epigenetic changes: Gene expression DNA methylation Regulation of mRNA

Figure 1. Schematic representation of different SE axes: Time of symptoms, Definition (terminology), Treatment, Endpoint (clinical and electroencephalographic) and Pathophysiology.

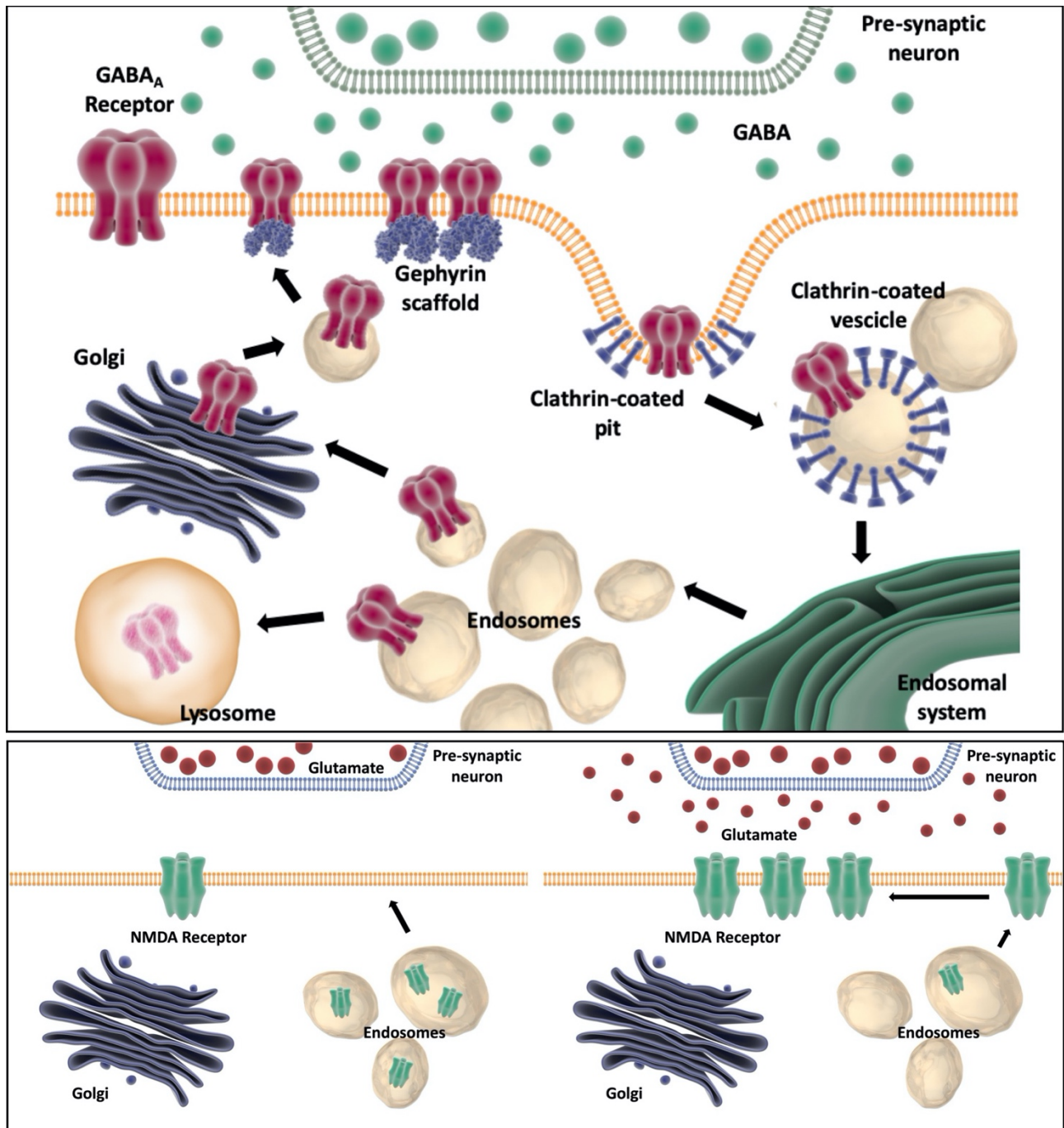


Figure 2. Cellular mechanisms underpinning the resistance to GABAergic anaesthetic drugs (top figure) and sensitivity to NMDA antagonists (bottom figure).

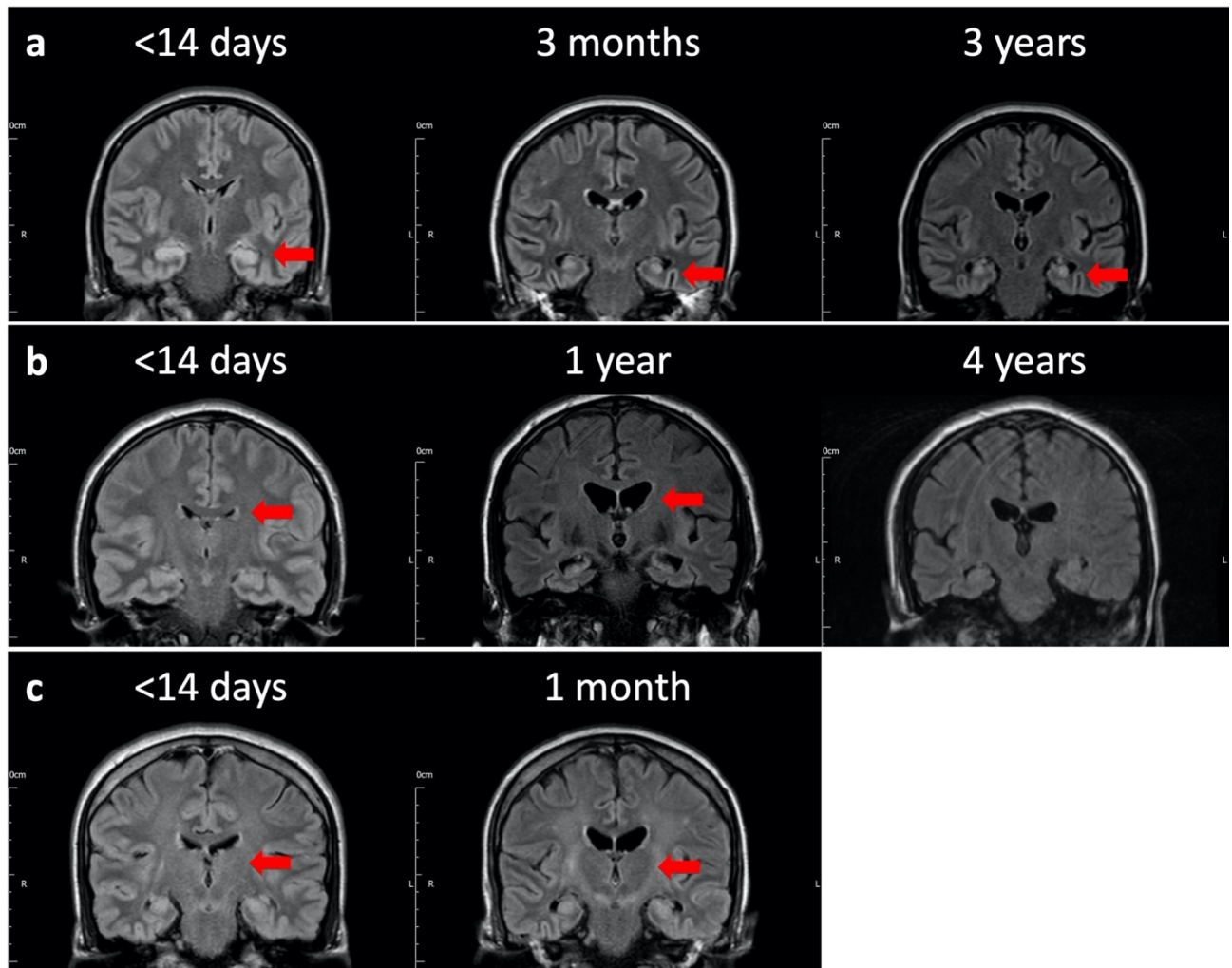


Figure 3. Coronal T2-weighted MRI images of three patients (a,b and c) at three timepoints of their disease, showing (a) acutely, bilateral hippocampal and amygdala high T2 signal, and chronic severe bilateral hippocampal and generalized atrophy, (b) chronic enlargement of the ventricles due to progressive brain atrophy, and (c) subacute basal ganglia ischaemic changes.

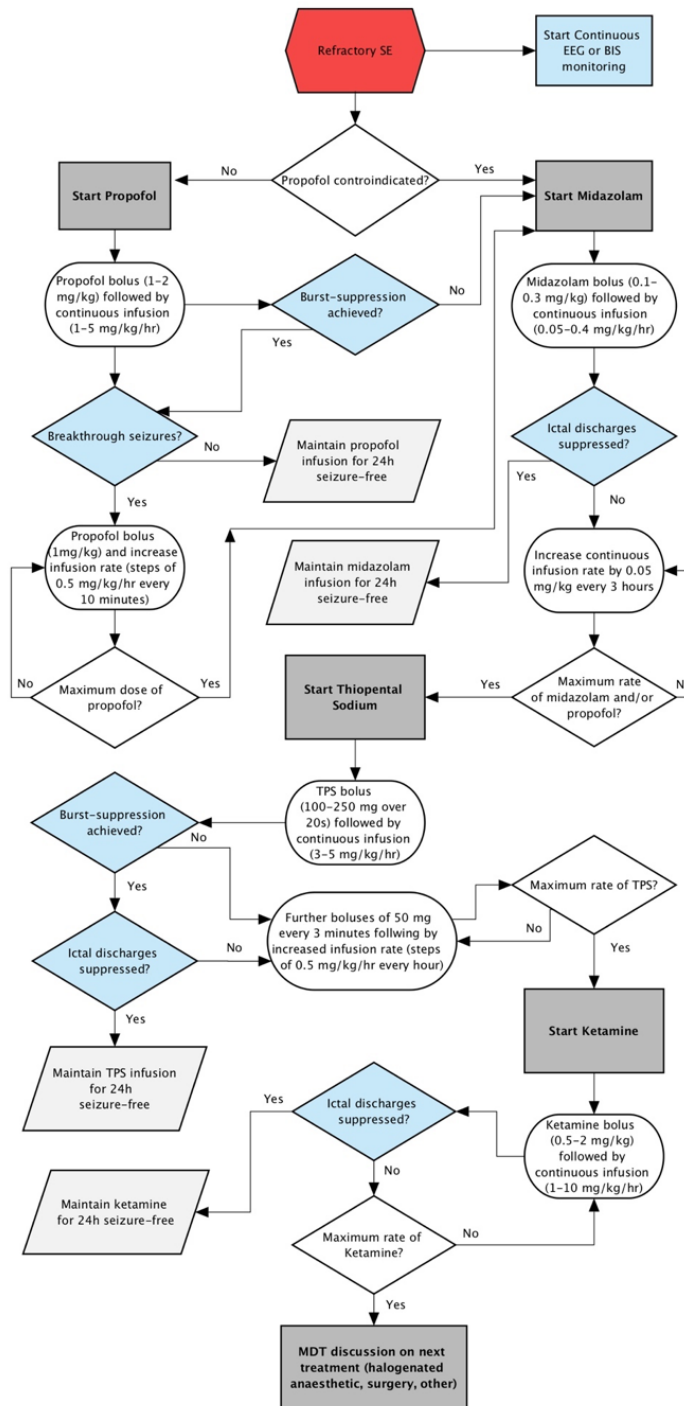


Figure 4. Flowchart of the intravenous anaesthetic protocol in use at the Neurosciences Intensive Care Unit of Oxford University Hospitals NHS Foundation Trust for the treatment of Refractory and Super-Refractory Status Epilepticus.

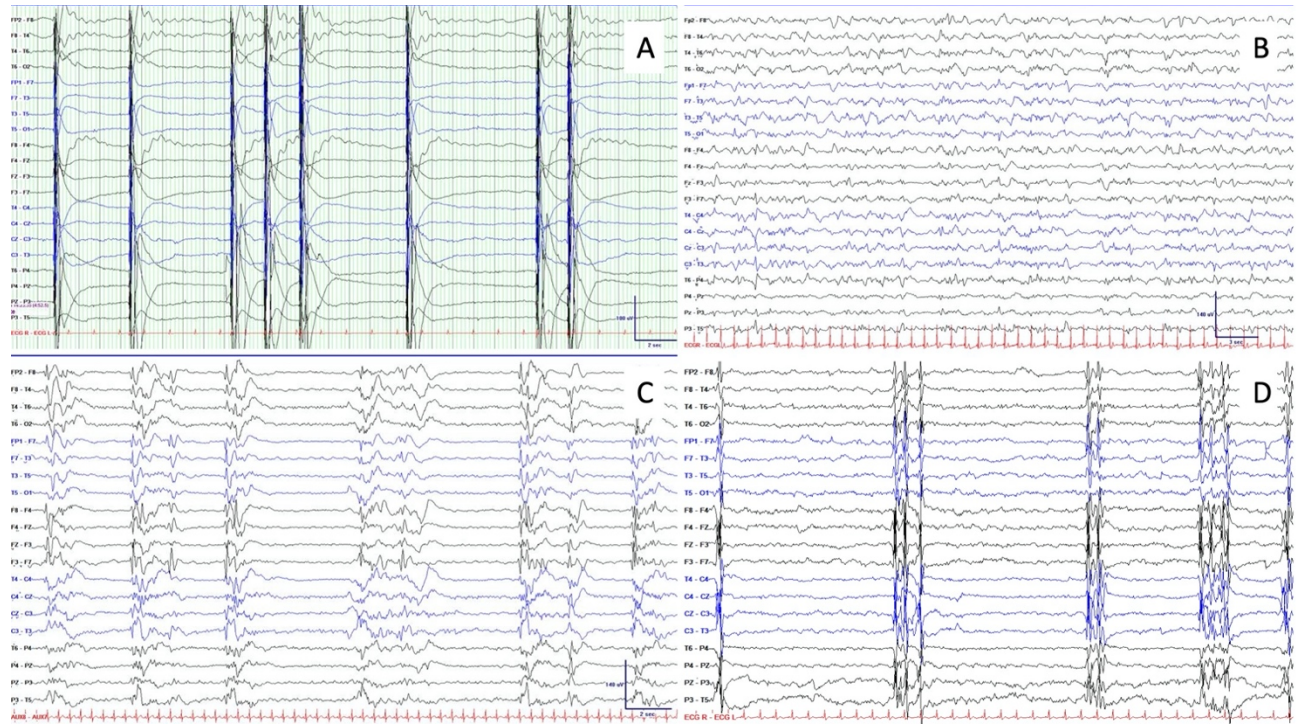


Figure 5. Burst-suppression patterns. A) EEG on ketamine and thiopental sodium showing burst suppression with intermittent bursts of high amplitude and generalized epileptic discharges (sensitivity 5 microvolts/mm, time base 15 mm/sec). B) EEG on midazolam and fentanyl showing generalized, polymorphic, irregular slow wave activity with periods of brief suppression (sensitivity 7 microvolts/mm, time base 10 mm/sec). C) EEG on propofol and fentanyl showing burst suppression (sensitivity 7 microvolts/mm, time base 15 mm/sec). D) EEG with burst suppression on thiopental sodium (sensitivity 7 microvolts/mm, time base 10 mm/sec).

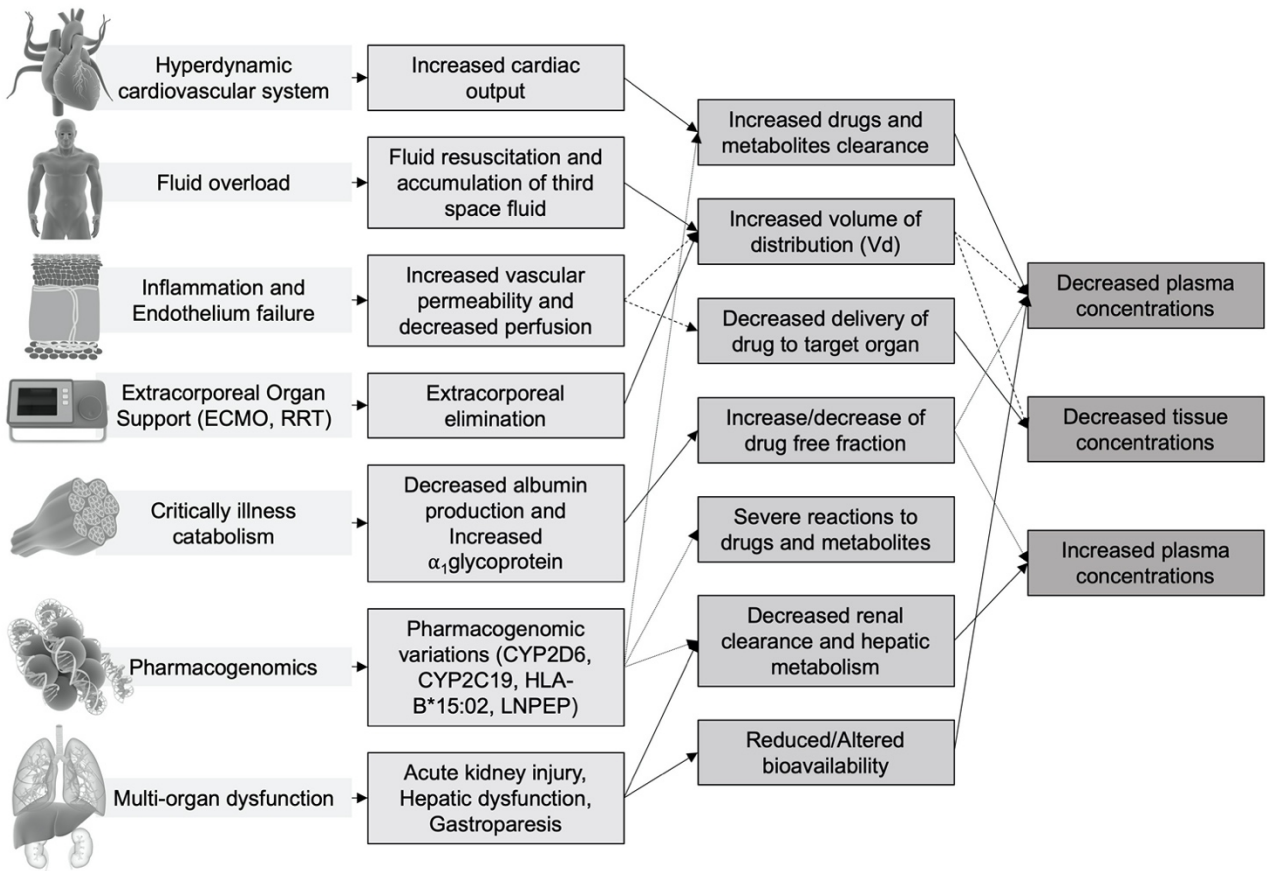


Figure 6. Summary of the pathophysiology and associated pharmacological alterations present in the critically ill patients.