Refractory Status Epilepticus in Adults Admitted to ITU in Glasgow 1995-2013
A retrospective case review for Provoked and Unprovoked Status Epilepticus

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Dedication

To Imran, Alishba and Humnah who constantly supported me. Finishing this is a relief for all of us I believe! At times it felt like never ending task. I also want to thank my dad for inherited strength that I have from him. I have learned over last few years that life is all about balance, persistence, and hope!

Special thanks to Professor John Paul Leach who constantly supported me during all the challenging times that I had during my journey to get to this point. It was not a straightforward or short journey I must say!

Acknowledgements

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Glossary

AED	Anti-epileptic medication
ASE	Autoimmune status epilepticus
CBZ	Carbamazepine
DNSE	De Novo Status Epilepticus
CVD	Cerebrovascular disease
CVS	Cardiovascular
EEG	Electroencephalogram
GTCS	Generalised tonic clonic seizures
GBP	Gabapentin
GEN	General
ITU	Intensive care unit
ICH	Intracerebral haemorrhage
LTG	Lamotrigine
LEV	Levetiracetam
NCSE	Non convulsive status epilepticus
N-RSEPE	Neuro ITU refractory status epilepticus with history of prior epilepsy
N-RDNSE	Neuro ITU refractory De Novo status epilepticus
PVD	Peripheral vascular disease
PHT	Phenytoin
SE	Status epilepticus
RDNSE	Refractory De Novo Status Epilepticus
SRDNSE	Supra refractory De Novo Status Epilepticus
RSE	Refractory status epilepticus
SRSE	Supra refractory status epilepticus
SEPE	Status epilepticus with Prior Epilepsy (SEPE)
SRSEPE	Supra refractory SE with Prior Epilepsy
SUDEP	Sudden unexpected death in epilepsy (SUDEP)
SIGN	Scottish Intercollegiate Guideline Network
TPM	Topiramate
PVD	Peripheral vascular disease
VPA	Valproate
VGB	Vigabatrin,

Chapter 1 - Executive Summary of Study and methods

Introduction

Status epilepticus (SE) is an emergency condition with poor outcomes. Despite the severity of this condition the information we have on risk factors and outcome is scant. The literature on this subject and identification of risk factors and outcomes are of great importance to improve the care of those with or at risk of the condition. The aims of the study are to identify risk factors, long term morbidity, mortality, and outcomes of status epilepticus in adult patients by dividing SE between status epilepticus in patients with epilepsy (SEPE) and patients with De Novo status epilepticus (DNSE). There is literature looking at the incidence of SE, but this is lacking in patients with SE severe enough to merit admission to an intensive care unit (ITU) setting, thereby fulfilling the definition of Refractory status epilepticus (RSE), and in some cases Supra-Refractory status epilepticus (SRSE). The time frame spanned the decades following the introduction of newer AEDs. Within our population, subdivision of patients cared for in neurosciences ITU settings were also studied.

Methods

Methods for main group analysis

The Research Ethics Committee for our regional Health Board (NHSGGC) was contacted and gave permission for this study to continue without a full ethics submission. Between 2013 and 2016, coding records were searched across NHS Greater Glasgow and Clyde for adults over the age of 16 years admitted to an Intensive Care Facility in any hospitals in Glasgow and patients were identified for period between January 1995 and December 2013. Local records from the ITU in the Institute of Neurological Science provided additional data. Coding for admission depended on the World Health Organisation's International Classification of Diseases in 9th and 10th Revisions (ICD 9 and ICD 10 respectively). ICD9 codes, which were used up to 31st March 1996, had no specific code for Status Epilepticus. From April 1996, ICD 10 codes were used, and to ensure we captured all settings for high intensity medical care we sought admissions to ITU, High Dependency Units and Coronary Care Units with primary diagnosis of ICD10 codes G40 ('Epilepsy'), G41 ('Status Epilepticus') & R568 ('Other & Unspecified Convulsions'). Patients with a specific diagnosis of hypoxic brain injury were not specifically excluded from analysis. Patients where duration of seizure was too short

(admission to ITU had occurred as a precaution after seizure cessation) were excluded from the study. Patients with a final diagnosis of Pseudostatus Epilepticus or prolonged dissociative attacks were excluded from this audit but will be presented separately in a later paper. Demographic information including age, gender, history of substance abuse was collected in each case. The outcome after admission was recorded, and for each case we recorded death during admission, at 1 year after admission, and - where appropriate – 5 years and 10 years after admission. Where patients had died more than 5 years before coding identification, paper records may have been destroyed, leaving only electronic records available. Where necessary, demographic and admission data were collected from the NHS GGC audit department (n = 280). We identified a total of 800 admissions to ITU with relevant diagnostic codes. We excluded 167 cases with insufficient information available, or with no supportable diagnosis of RSE, leaving 633 admissions to ITU with RSE with supporting information.

Those presenting with RSE who had no prior diagnosis of epilepsy were termed De Novo Status Epilepticus (DNSE). Those who had a prior diagnosis of epilepsy were designated SE with Prior Epilepsy (SEPE). Unfortunately, further information about classification of epilepsy was not available in majority of cases. All cases in this study fulfilled criteria of refractory status epilepticus (RSE). Patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) are be considered refractory (11). In this study all 633 cases needed ITU admission and failed 1st line treatment with Benzodiazepines and one or more anti-epileptic medication to try and control status epilepticus. Medical notes both paper form and electronic form were thoroughly reviewed in each patient and outcomes were defined according to clinical coding but for further confirmation notes were also reviewed.

The Glasgow incidence of SE-related admissions per 100,000 was calculated using population estimates for Greater Glasgow from the census nearest the midpoint of the sample incidence, being the 2011 census figure of 577,869. Statistical comparisons were carried out using Microsoft Excel 2016 and Mini Tab version 18. Comparison of mortality rates between groups was carried out using a Two Tailed Z test, producing a p value and 95% confidence intervals. The causes, treatments, and outcomes (including short-term and long-term mortality) of those with DNSE and SEPE were compared. The existence of current alcohol or drug dependency was either noted from a direct statement to that effect or inferred from other supporting information (e.g., previous admission for detoxification, deranged LFTs before admission, ongoing treatment with methadone, or treatment required for alcohol withdrawal syndrome).

We used clinical notes to ascertain whether there was any neurological deficit by the time of discharge or (where data was available) if full recovery occurred later. We looked at compliance of AEDs and recorded documented lack of compliance from review of clinical notes. We looked at type of AEDs. We collected data about patients established on newer vs old AEDs and recorded if patients were on enzyme inducing or non-enzyme inducing medication. Data was collected about poor adherence with AEDs on review of paper and electronic notes. It was also noted if patients had recurrent admission to hospital with alcohol and drugs related issues or if primary care doctor mentioned noncompliance in any prior correspondence. Mortality data was gained form the notes and timed as occurring during ITU admission or at 1, 5, or 10 years after the date of admission to ITU. The Glasgow incidence of SE-related admissions per 100,000 was calculated using population estimates for Greater Glasgow from the census nearest the midpoint of the sample incidence, being the 2011 census figure of 577,869. Statistical comparisons were carried out using Microsoft Excel 2016 and Mini Tab version 18. Comparison of mortality rates between groups was carried out using a Two Tailed Z test, producing a p value and 95% confidence intervals.

Subgroup analysis of supra refractory status epilepticus

The term supra refractory status epilepticus (SRSE) was introduced during the London-Innsbruck Colloquium on status epilepticus in 2011, the term “super-refractory status epilepticus” refers to SE of more than 24 h duration despite appropriately dosed treatment with anaesthetic agents (12). We reviewed notes and investigations and identified cases which needed ITU stay for seizure management for more than 24 hours and analysed data for these as subgroup analysis. In these SRSE cases we confirmed on going seizure activity by taking note of ongoing clinical seizures as documented in clinical notes and continues AED medications plus anaesthesia requirements from drug charts while patients were still in ITU. Unfortunately, due to lack of documentation and possibility due to lack of availability of EEG monitoring in majority cases EEG could not be used as a method of confirmation for SRSE. For this reason, we had to rely on drug charts and information documented in medical notes to confirm SRSE. Supra refractory cases were analysed separately as subgroup to identify any difference in causation, morbidity and mortality in these patients. Out of 633 cases of SE admitted to ITU 231 had SRSE. Manual review of clinical notes was made to ensure the patients had SRSE. Demographic information was collected in each case. The outcome after admission was recorded, and for each case we recorded death during admission, at 1 year after

admission, and - where appropriate - 5 years and 10 years after admission. We reviewed notes and investigations. Those presenting with SRSE who had no prior diagnosis of epilepsy were termed Supra refractory De Novo Status Epilepticus (SRDNSE). Those who had a prior diagnosis of epilepsy were designated Supra refractory SE with Prior Epilepsy (SRSEPE). The causes, treatments, and outcomes (including short-term and long-term mortality) of those with SRDNSE and SRSEPE were compared.

Subgroup analysis of neuro ITU status epilepticus

Total of 193 cases were identified to be admitted to neuro ITU as case of refractory status epilepticus (RSE). Those presenting to neuro ITU with RSE who had no prior diagnosis of epilepsy were termed De Novo Status Epilepticus (N-RDNSE). Those who had a prior diagnosis of epilepsy were designated SE with Prior Epilepsy (N-RSEPE). The causes, treatments, and outcomes (including short-term and long-term mortality) of those with N-RDNSE and N-RSEPE were compared. The existence of alcohol or drug dependency was either noted from a direct statement to that effect or inferred from other supporting information (e.g., previous admission for detoxification, deranged LFTs before admission, ongoing treatment with methadone, or treatment required for alcohol withdrawal syndrome). Clinical records were used to ascertain whether there was any neurological deficit by the time of discharge or (where data was available) if full recovery occurred later. Mortality data was gained form the notes and timed as occurring during ITU admission or at 1, 5, or 10 years after the date of admission to ITU. Comparison was made between causes, mortality and morbidity of neuro ITU and general ITU cases. In each case electronic and paper notes were reviewed by author and data was collected. Where there was any uncertainty, it was resolved by consensus review both from author and supervisor.

Results

A total of 800 admissions to ITU with relevant diagnostic codes were identified. 167 cases were excluded due to insufficient information available, or with no supportable diagnosis of Refractory status Epilepticus (RSE), leaving 633 admissions to ITU with RSE with supporting information.

All 633 cases fulfilled criteria of RSE as these cases failed 1st and second line agents and they needed ITU admission and 3rd line agents to treat SE.

Cases which stayed in ITU for more than 24 hours (2-7 days) fulfilled the criteria for super-refractory (SRSE).

193 cases out of 633 cases were admitted to neurosciences ITU.

Outcomes for refractory status epilepticus (RSE) 633 patients

1. Provocation by alcohol +/ or drug misuse was significant in 54.9% of those with RDNSE and 33.7% of those with RSEPE.

2. The admission mortality rate was higher in RDNSE than RSEPE (13.8% versus 7.5%).

3. One-year post admission, this difference in mortality rates in RDNSE and RSEPE was maintained, but expanded in subsequent years, such that 5 years after admission 41.5% of RDNSE had died compared to 27.6% of those with RSEPE.

4. On subgroup analysis, total death number was 206 over 4 years in RDNSE group. Alcohol and death related causes made 34.46% (n=71) of total deaths over 4 years in this group. 2nd most common cause was malignancy 12% (n=25), 10.67% (n=22) patients had death due to CVD coming up as 3rd most common cause.

5. In RSEPE group total death count over 4 year was 78. Most common cause of death in this group was seizure related complication 73% (n=29), 2nd most common cause was alcohol and drug related complication 12.8% (n=10) and 3rd most common cause of mortality was sepsis 10.25% (n=8).

6. At each time point, alcohol and drugs comprise the largest contributor to mortality in both groups but in those with RSEPE alcohol and drug use comprise a less striking contributor to mortality.

7. In the RDNSE group 28% of all deaths within 1 year were related to alcohol and drug-related complications, increasing to 34.4% of all deaths over 10 years. In the SEPE group, 1-year mortality was 20.2%, with 31.6% dying because of seizures over 10 years.

8. Where information was available, we looked at the discharge status, showing incidence of full recovery in those with RDNSE (19.98%) and RSEPE (50%).

Supra refractory status epilepticus (SRSE) 231 patients.

1. Demographic data shows increased rates related solely to addiction and abuse in the group with SRDNSE compared to SRSEPE (43.53% versus 33.33%).

2. Top 3 causes of SRES in De novo group were Alcohol/drugs 43.5%, HI 15.6%, and brain bleeds and metabolic 9.5% respectively.

3. Top 3 causes of SRSE in SEPE group were alcohol and drugs 33%, idiopathic 13%, poorly controlled epilepsy and issues with AED's made 12% contribution each making up to 24%.

4. The admission mortality rate was higher in SRDNSE than SRSEPE (15% versus 9.5%).

5. By one-year post-admission, mortality rates in our cohort are considerable with 24.48% of SRDNSE and 21.42% of SSEPE not being alive at 1 year mark. 5 years after admission 45.57% of SRDNSE had died compared to 34.52% of those with SRSEP. At 10 year this difference was maintained with death of 57% from SRDNSE versus 40.47 % from SRSEPE group.

6. In the SRDNSE group 22.8% of all deaths within 5 years were related to alcohol and drug-related complications. In the SRSEPE group 57% of all deaths at 5 years were related to seizure complications.

7. Incidence of recovery with no deficit was better in SRSEPE group 49% compared to 30% in SRDNSE group.

Refractory Status epilepticus in Neuro ITU 193 cases

Status epilepticus and seizures in the neuro-ICU are often the result of a primary disease of the brain. Patients who are admitted to the neuro-ICU suffer from a variety of traumatic and nontraumatic cerebral disorders that can predispose them to SE. These conditions, among others, include cerebral venous thrombosis, intracranial hemorrhage, large cerebral infarction or intracranial neoplasm, meningitis or encephalitis, post craniotomy, and traumatic brain injury.

1. In our study of neuro ITU cohort (193 cases) more patients in known prior epilepsy group had previous ITU stay (almost 40%) which in most cases was due to prior status epilepticus or other neurological Illness.

2. Even in neuro ITU cohort of 193 case, alcohol and drugs use in isolation or as an associated cause with another contributor stood out as more prevalent cause of SE with 23% of all cases.

3. On subgroup analysis, in neuro ITU group, CVD, ICH, SDH, SAH, HI, AVM caused De novo status epilepticus in 23% compared to 4% in known epilepsy group presenting with status epilepticus.

4. If we combine progressive epilepsy and issues with anti-epileptic medications as cause of status epilepticus in known epilepsy patients, it makes $1/4^{th}$ of total causes of SE in this group.

5. In neuro ITU cohort, at 1 year post SE, nearly quarter of patients in both groups died with slightly more incidence in mortality in RDNSE group. By the end of 5-year post SE nearly 40% of patients in DNSE had died compared to 33.8% in SEPE group.

6. It was interesting to note that CVD, ICH, HI was most common cause of mortality in N-RDNSE group 23.40%. In N-RSEPE group most common cause of mortality appears to be seizures and its complications (33%).

7. When we compared the refractory DNSE group from original cohort (419 patients) with neuro ITU subgroup of refractory DNSE group ((122 patients) the association of alcohol and drugs with mortality was less prominent in later group. In original cohort 35% of all death 4 years post RSE were related to substance abuse. In neuro ITU subgroup of RDNSE only 10.67% deaths were related to alcohol and drugs over this period of time.

Neuro ITU versus general ITU status epilepticus

1. Comparison was made between causes of SE in 440 cases from general ITU with 193 neuro ITU cases. Most common causes of general ITU SE in decreasing order were alcohol 54%, idiopathic 7%, metabolic 6%, sepsis 4.5% and no information 4.5%. Whereas in neuro ITU most common causes were alcohol 34%, brain bleeds/CVD 16%, CNS infection 9.3% and inflammation 7.7%.

2. Comparison was made between outcomes of general ITU with neuro ITU cases. It was clear that neuro ITU status epilepticus cases had more mortality than general ITU cases (17.6 % vs 8.6%). Similarly, recovery with neurological deficit was more in neuro ITU group 29.5% compared to 13.8% in general ITU group.

This study demonstrates that Status Epilepticus cases with De Novo status SE (without out prior history of epilepsy), tend to have greater morbidity and immediate and long-term mortality. This difference is maintained in subgroup analysis of neuro ITU cases and cases of supra refractory status epilepticus (staying in ITU more than 24 hours). Patient with prior epilepsy tend to have better morbidity and mortality outcomes both in short term and long-term. It is evident from this study that SE in the background of alcohol and drugs has poor prognosis, and these factors have major implication on both, morbidity, and mortality. Detailed analysis of each group is provided in later chapters. It was clear from this study that neuro ITU status epilepticus cases had more mortality and morbidity than general ITU case.

Discussion

There is extremely limited data available about refractory and supra refractory status epilepticus treatment, causes, morbidity and mortality. Therefore, study of this group of similarly and consistently severe seizures is important. Firstly, the separation of DNSE from SEPE is helpful in beginning to delineate prognosis, the need for further investigation, and the role of ineffective or absent AEDs in causation. The mortality rate of RSE and SRSE is high, and importantly it represents a call to action for the medical community. The study highlights addiction to alcohol and drugs as a prominent factor in causation of status epilepticus, especially in De Novo SE group. The greater admission mortality with DNSE, which persists in the years following discharge should confirm that SE with a background of addiction or abuse should not simply be considered as a ‘provoked seizure’ and treated with acute support

and encouragement to abstinence. Instead, it suggests that a presentation with DNSE is a sign of a system in peril. While public health measures are vital in reducing the disease burden of triggers such as alcohol and addiction, each episode should prompt a chain of multispecialty care in order to address this recurring and persisting public health disaster, which comprises of too many personal tragedies.

Bullet Points

This study looks at the causes, outcomes, and regional incidence of Refractory and supra refractory Status Epilepticus across 18 years in Glasgow.

-Mortality is increased in short term and the long-term in both De Novo Status Epilepticus and Status Epilepticus complicating Epilepsy but there is clear difference between the 2 groups. -- Patients with DNSE have higher risk of morbidity-, short- and long-term mortality and complications than compared to SEPE.

-There is no evidence that use of newer AEDs has reduced the incidence of Status Epilepticus complicating epilepsy.

-Addressing the mortality associated with SE requires a combination of public measures and a holistic approach to individual cases of status epileptics.

- Patient admitted to neuro ITU have more critical course if illness, most have refractory epilepsy and neurosurgical cause of SE. Hence, they have poor mortality and morbidity outcomes compared to general ITU group.

Chapter 2

Epilepsy and status epilepticus definitions, classification, epidemiology, and classification

Epidemiology, Incidence, and prevalence of epilepsy

Epilepsy is common neurological condition. There are estimated 70 million people with epilepsy in the world of whom 75% live in resource poor countries (1, 2). Incidence is number of newly diagnosed cases within a period of time. In UK annual Incidence rate is 46 per 100,000 compared to annual incidence rate of 100 per 100,000 in developing countries. 75 new cases are diagnosed each day in UK. Prevalence is proportion of a population with disorder at a given time. Overall prevalence of epilepsy is around 1 in 131 people. There are estimated 300,000 people with epilepsy in UK. While many people presenting with seizures do so with a prior history of events, between one-third and half present with a single unprovoked seizure (3). Not all people with a single seizure go on to develop epilepsy (Defined as at least two recurrent seizures 24 hours apart). This was demonstrated in the Rochester study which followed a population over a 50-year period. The incidence of a first unprovoked seizure was 61 per 100,000 compared to the incidence of epilepsy of 44 per 100,000 (4)**.** Two-thirds of people with active epilepsy have their epilepsy controlled satisfactorily with anti-epileptic drugs (AEDs). Other approaches may include surgery. In UK there is consensus regarding adults with single unprovoked seizure that we do not treat isolated unprovoked seizures but there is trend to treat after 2 or more seizures in 12 months. Epilepsy is more common in males than females. Incidence rates also vary considerably with age. Studies in industrialized world show a bimodal distribution. There is high incidence in first year of life and early childhood, with relative decrease in adolescence. Incidence is at lowest between age 20 –40 steadily increases after age 50. Evidence from community-based studies suggest that 70% people with epilepsy will achieve remission, usually in early course of disease and indeed longer the epilepsy remains active the poorer is prognosis (5). Interestingly 30% of those attending tertiary care referral centers with refractory epilepsy don't have epilepsy, most commonly these people have conditions like syncope and dissociative seizures (6)

Definition of Epilepsy

Seizures and epilepsy are not the same. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. Translation: a seizure is an event and epilepsy is the disease involving recurrent unprovoked seizures. The above definitions were created in a document generated by a task force of the International League against Epilepsy (ILAE) in 2005 (103). The definitions were conceptual, (theoretical) and not sufficiently detailed to indicate in individual cases whether a person did or did not have epilepsy. Therefore, the ILAE commissioned a second task force to develop a practical (operational) definition of epilepsy designed for use by doctors and patients. The results of several years of deliberations on this issue have now been published and adopted as a position of the ILAE (7). A commonly used definition of epilepsy heretofore has been two unprovoked seizures more than 24 hours apart. This definition has many positive features, but also a few limitations. This definition does not allow the possibility of "outgrowing" epilepsy. Inclusion of the word "provoked" seems to imply that people who have photosensitive seizures provoked by flashing lights or patterns do not have epilepsy; whereas most people think that they do. Some individuals who have had only one unprovoked seizure have other risk factors that make it highly likely that they will have another seizure. Many clinicians consider and treat such individuals as though they have epilepsy after one seizure. Finally, some people can have what is called an epilepsy syndrome and these individuals should meet the definition for having epilepsy even after just one seizure. You should not have an epilepsy syndrome but not epilepsy. The new definition of epilepsy addresses each of these points. ILAE definition of epilepsy 2014 (7)

A person is considered to have epilepsy if they meet any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome. Epilepsy is considered resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for

the last 10 years, with no seizure medicines for the last 5 years.

Unprovoked seizures separated in time

Seizures clustering within 24 hr confer approximately the same risk for later seizures as does single seizure. The ILAE Task Force retained the current thinking that unprovoked seizures clustering in a 24-hr period are considered to be single unprovoked seizure for purposes of predicting recurrence risk**.** This changing concept of epilepsy helps us to broaden our vision about diagnosis of epilepsy and identify those at high risk of recurrence (7).

Classification of seizures

In 2017, the ILAE released a new classification of seizure types, largely based upon the existing classification formulated in 1981. Primary differences include specific listing of certain new focal seizure types that may previously only have been in the generalized category, use of awareness as a surrogate for consciousness, emphasis on classifying focal seizures by the first clinical manifestation (except for altered awareness), a few new generalized seizure types, ability to classify some seizures when onset is unknown, and renaming of certain terms to improve clarity of meaning. The purpose of such a revision is to recognize that some seizure types can have either a focal or generalized onset, to allow
classification when the onset is unobserved, to include some missing seizure types, and to adopt more transparent names. Because current knowledge is insufficient to form a scientifically based classification, the 2017 Classification is operational (practical) and based
on the 1981 Classification, extended in 2010. Changes include the following:

(1) “Partial” becomes “focal”.
(2) Awareness is used as a classifier of focal seizures.
(3) The terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are eliminated
(4) New focal seizure types include automatisms, behavior arrest, hyperkinetic, autonomic, cognitive, and emotional.
(5) Atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset.
(6) Focal to bilateral tonic–clonic seizure replaces secondarily generalized seizure.

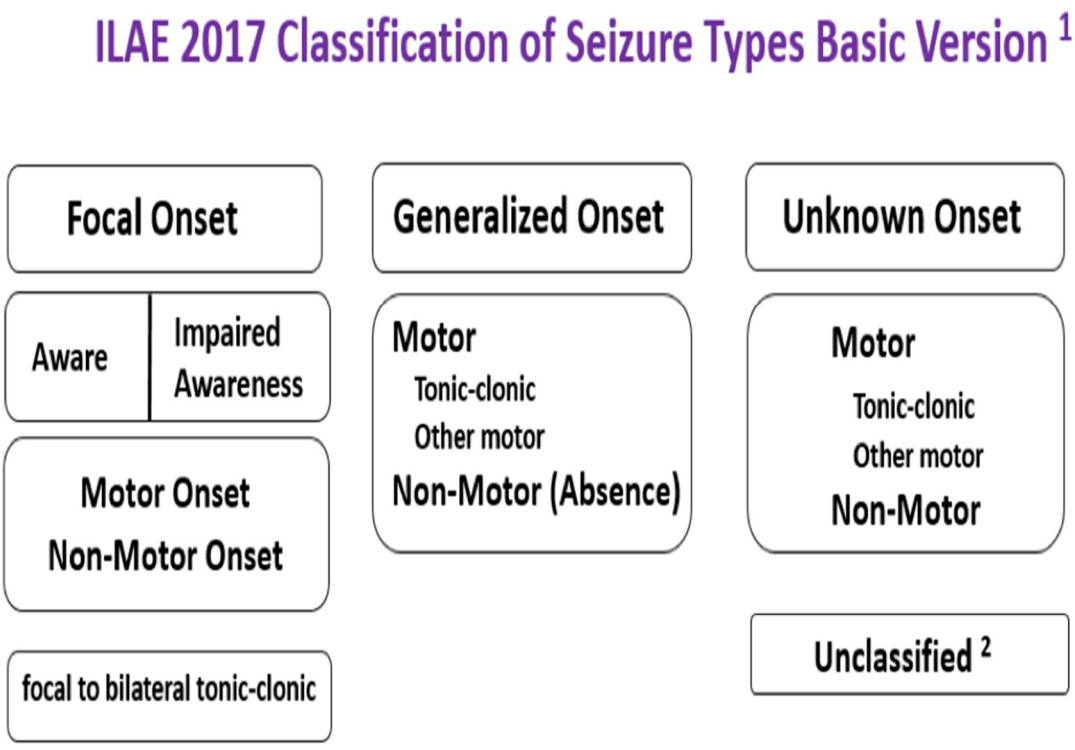

Figure 1.1 Classification of seizure ILAE 2017

Operational classification of seizure types. Fisher et al. Instruction manual for the ILAE 2017 (8)

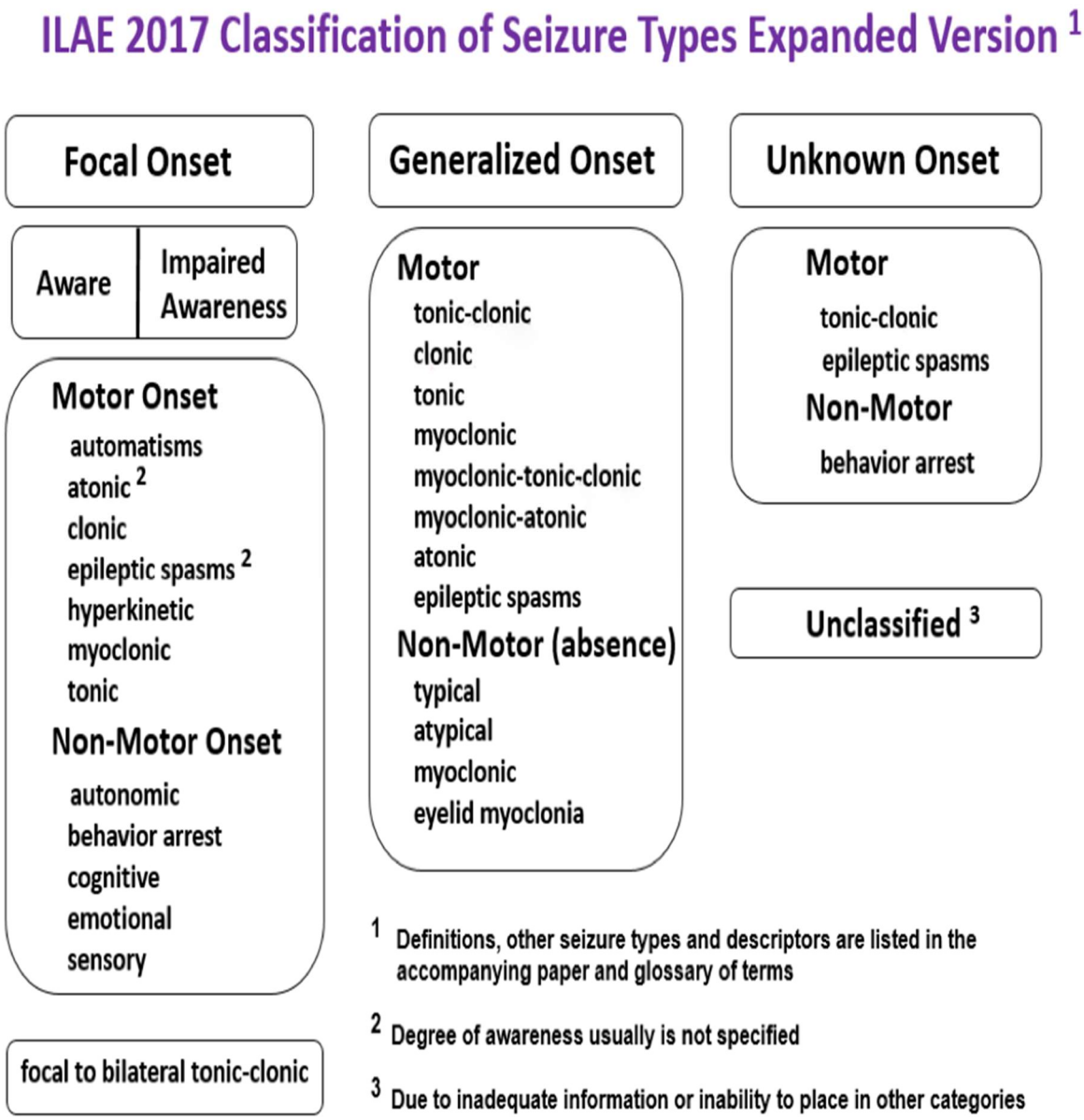

Figure 1.2 Operational classification of seizure types.
Fisher et al. Instruction manual for the ILAE 2017 (8)

Classification of Epilepsies

The new Classification of the Epilepsies is a multi-level classification, designed to cater for classifying epilepsy in different clinical environments. This is in acknowledgement of the wide variation in resources around the world meaning that different levels of classification will be possible depending on the resources available to the clinician making the diagnosis. Where possible, a diagnosis at all three levels should be sought as well as the aetiology of the individual's epilepsy. The ILAE presents a revised framework for the

Classification of the Epilepsies, designed to work with the classification of seizure types, Levels of diagnosis: seizure type, epilepsy, type (focal, generalized, combined generalized and focal, unknown) and epilepsy syndrome. An etiologic diagnosis should be considered from when the patient first presents, and at each step along the diagnostic pathway, a patient's epilepsy may be classified into more than one etiological category. The term "benign" is replaced by the terms self-limited and pharmaco responsive to be used where appropriate. The term "developmental and epileptic encephalopathy" can be applied in whole
or in part where appropriate. (9)

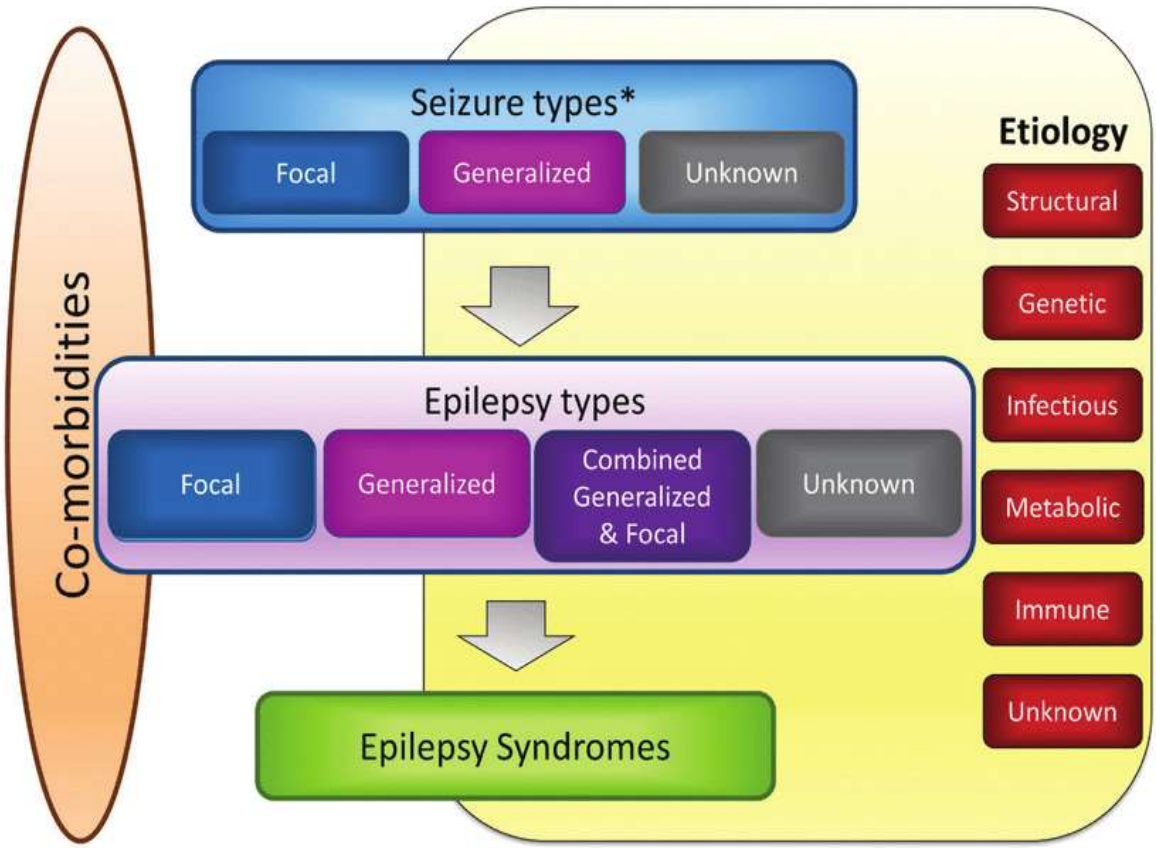

Figure 1.3 Framework of classification of the Epilepsies (9)
ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Scheffer IE et al.

Definition of status epilepticus 2015

Status epilepticus is 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, which 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. The case of convulsive (tonic–clonic) SE, both time points (t_1 at 5 min and t_2 at 30 min) are based on animal experiments and clinical research. (10)

New operational dimension of status epilepticus

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min	Unknown

Table 1.1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term.

Refractory SE (RSE)

Patients who do not respond to standard treatment regimens for status epilepticus are considered to be in RSE (11). For the purposes of guidelines, patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) are considered refractory.

Supra refractory SE

Introduced during the London-Innsbruck Colloquium on status epilepticus in 2011, the term "super-refractory status epilepticus" refers to SE of more than 24 h duration despite appropriately dosed treatment with anaesthetic agents (12).

History of status epilepticus

Even though status epilepticus has been recognized since antiquity, its existence was largely ignored until the mid-nineteenth century. Status epilepticus was for many years very much at the margins of epilepsy. In the early period of its modern history, it was considered rare but hazardous, a relatively minor footnote in a distant corner of the epilepsy panorama. Since the mid-1970s, though, it has assumed much greater importance. A condition that we would now term status epilepticus was recognized centuries ago, and described on a Babylonian cuneiform tablet dated 600–700 B.C (13).

If the possessing demon possesses him many times during the middle watch of the night, and at the time of his possession his hands and feet are cold, he is much darkened, keeps opening and shutting his mouth, is brown and yellow as to the eyes… It may go on for some time, but he will die.

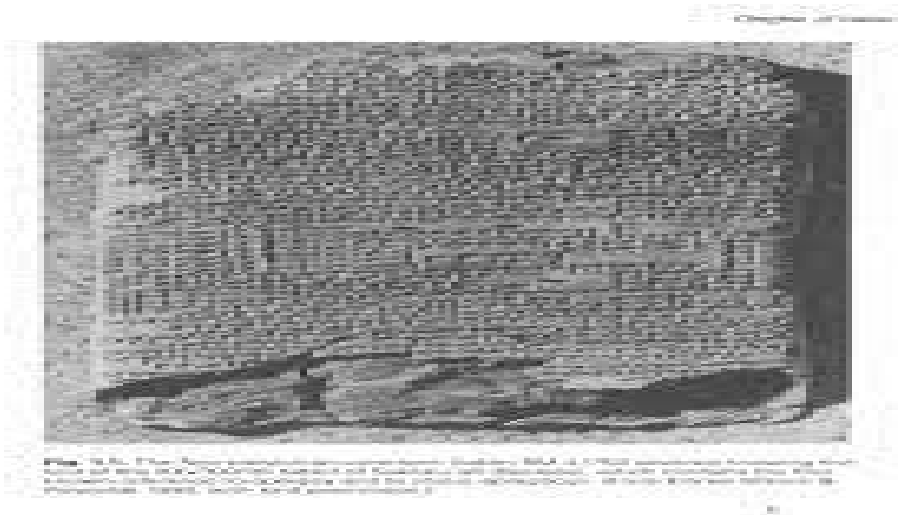

Figure 1.4 (XXV—XXVI th tablet (obverse) of the Sakikku cuneiform, 718/612 BC) (13)

However, the existence of prolonged seizures was largely ignored, or at least not written about, until the 19th century (14). It is traditionally claimed that the term état de mal was first used in the medical literature by Louis Calmeil in 1824 as part of his doctoral thesis for the University of Paris. Calmeil's writing was based on his experiences of epilepsy in the Parisian asylums of the Salpêtrière and Charenton. He pointed out that the expression (état de mal) was in common usage by the patients themselves at the Salpêtrière and furthermore recognized to have a severe and often fatal outcome. In his thesis, he distinguished between status epilepticus and a succession of fits by the fact that in status epilepticus the patient did not recover consciousness between fits. (15) Clark and Prout in 1903 divided epilepsy into idiopathic and symptomatic. They recognized that different forms of status occur, for instance petit mal (absence status), focal motor, and grand mal (tonic–clonic) status epilepticus, and that was the predominant form of fatal status epilepticus (16) Delasiauve, who was based at the Bicêtre, then described the symptoms, prognosis, and treatment of status epilepticus, emphasizing that the real danger of status epilepticus lay not in the intensity or the frequency of the fits but rather in the failure of the "embarrassed functions to recover their equilibrium" in between successive seizures. This was the period in which the clinical descriptions and definitions of status epilepticus were being formulated (17). The first appearance of the latinized English expression "Status Epilepticus" was in Bazire's translation of Trousseau's lectures in clinical medicine in 1868 (18).Today, status epilepticus occurs most commonly de novo, in patients without a history of epilepsy, as the result of acute brain injury but interestingly, such cases do not seem to feature at all in the writings on status epilepticus until the 1960s. A rare exception was the fatal case report published by Rake who remarks "Would not this be a case of death in the status epilepticus, which Bristowe mentions as a rare termination; and was it not strange that the patient had never before shown any symptoms of this disease? His father and several brothers and sisters had died in fits" (19). In 1909, the International League Against Epilepsy (ILAE) was formed in Budapest, and in the journal Epilepsia was launched. The introduction of phenobarbital in 1912 was of course a landmark in epilepsy therapeutics, and the drug was also soon recognized to be of great assistance in status, although not superseding bromides or other sedatives, which continued to be widely administered. phenytoin was introduced into clinical epilepsy practice in 1965, and this of course was to change epilepsy therapeutics totally. A report of the effectiveness of intravenous lignocaine as an anticonvulsant in three patients with status epilepticus (two focal, one generalized) was published in 1958. Of course, from the point of view of status epilepticus, the most important new discovery, and the one that ends this review

of the history of therapy was that of the benzodiazepines. Chlordiazepoxide (Librium) was the first to be licensed in 1960 and this was followed by diazepam (Valium) in 1963.

The International League Against Epilepsy (ILAE) defined status epilepticus more than 20 years ago, as a single epileptic seizure of >30 minutes duration or a series of epileptic seizures during which function is not regained between ictal events in a 30-minute period (20). Because of the clinical urgency in treating generalized convulsive status epilepticus. a 30-minute definition is neither practical nor appropriate in clinical practice. Once seizures have continued for more than a few minutes, treatment should begin. Considering the need for rapid evaluation and intervention in GCSE, ILAE has suggested new definition. This new definition has two aspects conceptual and mechanistic, and it focus on cause and duration of seizure. (10)

Incidence of Status Epilepticus

Most population-based studies have used a traditional 30-min duration of SE, and so the numbers given are the lowest estimates. Using the 5-min definition, determining the time from onset to starting emergency treatment, the incidence in clinical practice is much higher than in the epidemiologic studies. Incidence of status epilepticus is known to be 10-60 per 100,000 person per year. 13.3% have recurrent attacks. 58% patients have no previous epilepsy, which means De novo SE is not uncommon presentation (21,22). In 1996 DeLorenzo published a report (23) which presented a prospective, population-based study of status epilepticus (SE) in the city of Richmond, Virginia. The incidence of SE was 41 patients per year per 100,000 population. The frequency of total SE episodes was 50 per year per 100,000 population. Evaluation of the seizure types for adult and paediatric patients demonstrated that both partial and generalized SE occur with a high frequency in these populations. Same study demonstrated that SE has two peaks, one at early phase and second in late half of life, with reactively low incidence in middle age. Most SE patients had no history of epilepsy. These results indicate that SE is a common neurologic emergency. RSE incidence rates are mostly estimated, using data from retrospective studies. They are reported to be 31 % to 43 % of all patients with SE treated in intensive care units (24,25). It is assumed that RSE more commonly develops in patients with acute brain damage than in patients with pre-existing epilepsy (26,27). However, RSE may also occur in previously healthy adults as the first manifestation of epilepsy (‘de novo’ status epilepticus) (28).

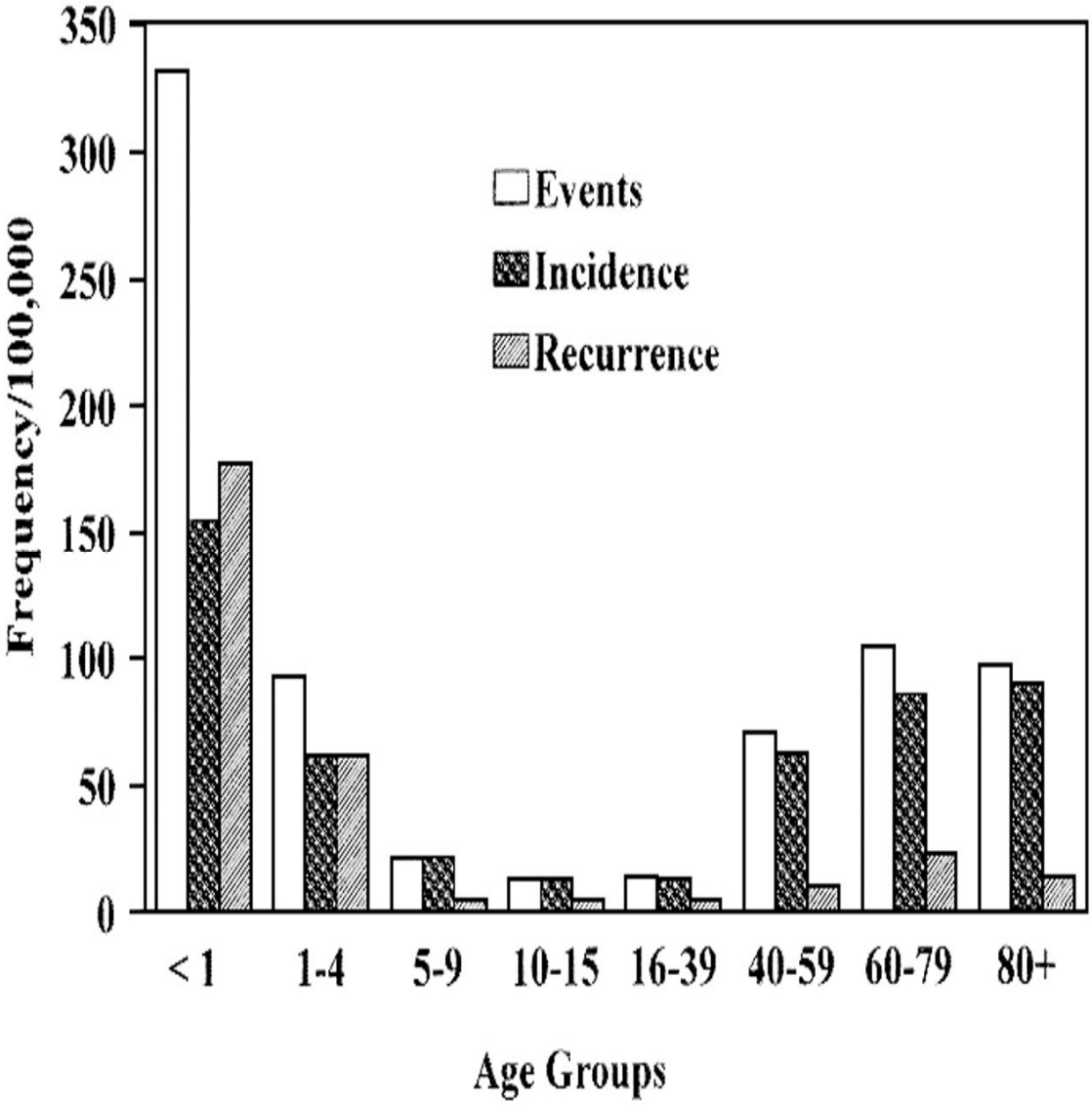

Figure 1.5. Incidence of SE DeLorenzo et al Neurology 1996. (23)
(Study demonstrated that SE has two peaks, one at early phase and second in late half of life, with reactively low incidence in middle age).

Classification of Status Epilepticus

For classification of SE ILAE has purposed the following four axes**:** (10)

1. Semiology
2. Etiology
3. EEG correlates
4. Age

Axis 1: Semiology

This axis refers to the clinical presentation of SE and is therefore the backbone of this classification. The two main taxonomic criteria are:

1. The presence or absence of prominent motor symptoms.

2. The degree (qualitative or quantitative) of impaired consciousness.

Status epilepticus presents in several forms:

1) Convulsive status epilepticus consisting of repeated generalized tonic– clonic (GTC) seizures with persistent postictal depression of neurologic function between seizures.

2) Nonconvulsive status epilepticus where seizures produce a continuous or fluctuating "Epileptic twilight" state.

3) Repeated focal seizures manifested as focal motor signs, focal sensory symptoms, or focal impairment of function (e.g., aphasia) not associated with altered awareness (Epilepsia partialis continua).

(A) With prominent motor symptoms
A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
A.1.a. Generalized convulsive
A.1.b. Focal onset evolving into bilateral convulsive SE
A.1.c. Unknown whether focal or generalized
A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
A.2.a. With coma
A.2.b. Without coma
A.3 Focal motor
A.3.a. Repeated focal motor seizures (Jacksonian)
A.3.b. Epilepsia partialis continua (EPC)
A.3.c. Adversive status
A.3.d. Oculoclonic status
A.3.e. Ictal paresis (i.e., focal inhibitory SE)
A.4 Tonic status
A.5 Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma

B.2.a. Generalized
• B.2.a.a Typical absence status
• B.2.a.b Atypical absence status
• B.2.a.c Myoclonic absence status
• B.2.b. Focal
• B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
• B.2.b.b Aphasic status
• B.2.b.c With impaired consciousness
• B.2.c Unknown whether focal or generalized
• B.2.c.a Autonomic SE

Table 1.2 SE classification based on semiology

2. Axis of aetiology

Instead of the terms idiopathic, symptomatic, and cryptogenic, the following three terms and their associated concepts are recommended:

1. **Genetic:** The concept of genetic epilepsy is that the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests (e.g., SCN1A and Dravet syndrome) or the evidence for a central role of a genetic component may come from appropriately designed family studies (10).
2. **"Structural/metabolic**": Conceptually, there is a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Structural lesions of course include acquired disorders such as stroke, trauma, and infection. They may also be of genetic origin (e.g., tuberous sclerosis, many malformations of cortical development); however, as we currently understand it, there is a separate disorder interposed between the genetic defect and the epilepsy (10).
3. **"Unknown cause":** Unknown is meant to be viewed neutrally and to designate that the nature of the underlying cause is as yet unknown; it may have a fundamental genetic

defect at its core or it may be the consequence of a separate as yet unrecognized disorder. Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks. Generalized seizures can be asymmetric. Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures (10).

• Aetiology of status epilepticus
• Known (i.e., symptomatic)
• Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
• Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
• Progressive (e.g., brain tumour, Lafora's disease and other PMEs, • dementias)
• SE in defined electro clinical syndromes
• Unknown (i.e., cryptogenic)

Table 1.3 SE classification based on etiology of status epilepticus

Axis 3: Electroencephalographic correlates of SE

None of the ictal EEG patterns of any type of SE is specific. Epileptiform discharges are regarded as the hallmark, but with increasing duration of SE, the EEG changes and rhythmic non epileptiform patterns may prevail. Similar EEG patterns, such as triphasic waves, can be recorded in various pathologic conditions, leading to substantial confusion in the literature. Currently there are no evidence-based EEG criteria for SE. Based on large descriptive series And consensus panels, (29-33) ILAE propose the following terminology to describe EEG patterns in SE:

1.Location*:* generalized (including bilateral synchronous patterns), lateralized, bilateral independent, multifocal.

2.Name of the pattern*:* Periodic discharges, rhythmic delta activity or spike-and-wave/sharp-and-wave plus subtypes.

3.Morphology*:* sharpness, number of phases (e.g., triphasic morphology), absolute and relative amplitude, polarity.

4.Time-related features: prevalence, frequency, duration, daily pattern duration and index, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or static).

5.Modulation*:* stimulus-induced vs. spontaneous.

6.Effect of intervention *(medication) on EEG.*

Axis 4: Age

1.Neonatal (0 to 30 days).

2.Infancy (1 month to 2 years).

3.Childhood (> 2 to 12 years).

4.Adolescence and adulthood (> 12 to 59 years).

5.Elderly (≥ 60 years).

1. These forms of SE may be encountered prevalently in some age groups, but not exclusively.
2. SE occurring in neonatal and infantile-onset epilepsy syndromes
3. Tonic status (e.g., in Ohtahara syndrome or West syndrome)
4. Myoclonic status in Dravet syndrome
5. Focal status
6. Febrile SE
7. SE occurring mainly in childhood and adolescence
8. Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)
9. NCSE in specific childhood epilepsy syndromes and etiologies (e.g., Ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, epilepsy with myoclonic-atonic seizures, other childhood myoclonic encephalopathies)
10. Tonic status in Lennox-Gastaut syndrome
11. Myoclonic status in progressive myoclonus epilepsies
12. Electrical status epilepticus in slow wave sleep (ESES)
13. Aphasic status in Landau-Kleffner syndrome
14. SE occurring mainly in adolescence and adulthood
15. Myoclonic status in juvenile myoclonic epilepsy
16. Absence status in juvenile absence epilepsy
17. Myoclonic status in Down syndrome
18. SE occurring mainly in the elderly
19. Myoclonic status in Alzheimer's disease
20. Nonconvulsive status epilepticus in Creutzfeldt-Jakob disease
21. De novo (or relapsing) absence status of later life

Table 1.4. SE in selected electroclinical syndromes according to age

Causes of status epilepticus

There are many recognised causes of status epilepticus (23,34, 35). For the developing world, infectious diseases seem to play an important role as an etiologic factor. Prospective study in Sao Paolo, Brazil (24), recollected data from 102 patients with SE admitted to a local hospital emergency department. Patients were subdivided into two groups: A, consisting of epileptic patients, and B, individuals with no previous history of epilepsy. In Group A, the main causes of SE were non-compliance with AEDs (31.8%) and undetermined aetiology (39%) ($p < 0.05$). In Group B, three aetiologies predominated: CNS infection (26.6%), stroke (24.4%) and metabolic disturbances (17.7%) ($p < 0.05$). More than 15% of patients with epilepsy have at least one episode of status epilepticus and low antiepileptic drug levels are a potentially modifiable risk factor. In adults with pre-existing epilepsy, the most common aetiologies are low antiepileptic drug (AED) levels (accounting for at least one fourth of SE, remote symptomatic aetiologies, and Stroke (23). This subgroup with epilepsy and low AED levels has a good prognosis, with a low mortality of 4.0–8.6% (21). Overall, acute symptomatic causes are the most common aetiology, accounting for 48–63% of all SE cases. Stroke is the leading cause among the acute symptomatic cases, accounting for 14–22% of SE in adults. In older adults, remote stroke is a major cause (35).

Common causes Status epilepticus

Acute processes
Metabolic disturbances: electrolyte abnormalities, hypoglycaemia, renal failure
Sepsis
Central nervous system infection: meningitis, encephalitis, abscess
Stroke: ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral sinus thrombosis
Head trauma with or without epidural or subdural hematoma
Drug issues
Drug toxicity
Withdrawal from opioid, benzodiazepine, barbiturate, or alcohol
Non-compliance with AEDs
Hypoxia, cardiac arrest
Hypertensive encephalopathy, posterior reversible encephalopathy syndrome
Autoimmune encephalitis (i.e., anti-NMDA receptor antibodies, anti-VGKC complex

antibodies), paraneoplastic syndromes

Chronic processes

Pre-existing epilepsy: breakthrough seizures or discontinuation of AEDs

Chronic ethanol abuse in setting of ethanol intoxication or withdrawal

CNS tumours

Remote CNS pathology (e.g., stroke, abscess, TBI, cortical dysplasia)

Special considerations in children

Acute symptomatic SE is more frequent in younger children with SE

Prolonged febrile seizures are the most frequent cause of SE in children

CNS infections, especially bacterial meningitis, inborn errors of metabolism, and ingestion are frequent causes of SE

VGKC voltage-gated potassium channel and NMDA N-methyl-D-aspartic acid; SE status epilepticus.

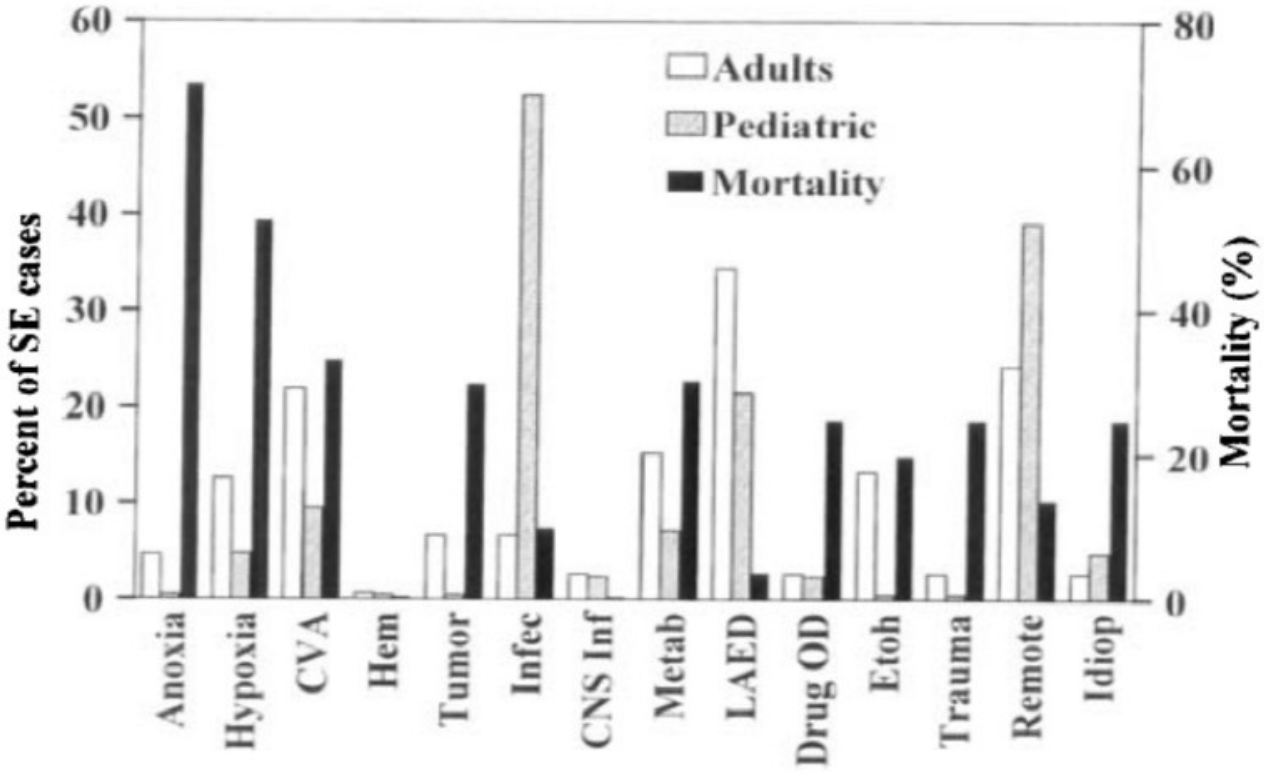

Figure 1.6 DeLorenzo et al 1996. Aetiologies of status epilepticus (SE) for adults and paediatric patients and mortality for adult etiologist. CVA, cerebrovascular accidents Taken from: DeLorenzo et al. 1996 (23). Hem, hemorrhage; Infec, systemic infections with fever; CNS Infec, infection of the central nervous system; Metab, metabolic; LAED, low antiepileptic drug levels; Drug OD, drug overdose; ETOH, alcohol-related; Idiop, idiopathic.

Treatment of Status Epilepticus

Benzodiazepines are widely recognised as an effective first-line therapy (36,37). No optimal second-line therapy has been agreed, but prospective open-label paediatric trials in the UK and Australasia found approximately equivalent response rates comparing phenytoin with levetiracetam (38,39). The success of second-line drugs is important because longer durations of status epilepticus itself leads to increasing likelihood of further seizure activity through positive feedback mechanisms. Failure to stop status epilepticus early is associated with irreversible neuronal injury and the complications caused by metabolic and respiratory derangements of status epilepticus (40,41).

Most seizures remit spontaneously without intervention. If spontaneous cessation does not occur, then management should be escalated. Emergency treatment should be sought or given once a seizure has persisted, or there are serial seizures, for five minutes or more. The treatment of SE, by convention, occurs in stages. Traditionally, these stages have been termed 1st, 2nd, 3rd, and 4th line, which do not reflect the emergent need for SE control. Therefore, different guidelines have revised the traditional SE treatment paradigm to Emergent initial therapy, urgent control therapy, and refractory therapy. SE patients refractory to initial therapy may be best treated in experienced, high volume centres. Definitive control of SE should be established within 60 min of onset. All patients presenting with SE will need emergent initial AED therapy (i.e., 1st line) and urgent control AED therapy (i.e., 2nd line) in addition to AED maintenance therapy, even if SE is immediately controlled. Refractory SE therapy (i.e., 3rd and 4th line) is reserved for those failing the first 2 AEDs administered. If SE is caused by a metabolic disorder (e.g., hypoglycaemia), the underlying metabolic disorder should be corrected, in which case maintenance therapy may or may not be necessary (34).

Different stages of status treatment

- **Stabilization phase** (0-5 minutes of seizure activity) includes standard initial first aid for seizures and initial assessments and monitoring.
- **Initial therapy phase** (5-20 minutes of seizure activity) when it is clear the seizure requires medical intervention, a benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given its demonstrated efficacy, safety, and tolerability.
- **Second therapy phase** (20-40 minutes of seizure activity) when response (or lack of response) to the initial therapy should be apparent. Reasonable options include

phenytoin, valproic acid and levetiracetam. There is no clear evidence that any one of these options is better than the others. Because of adverse events, IV phenobarbital is a reasonable second-therapy alternative if none of the three recommended therapies are available.

- **Third therapy phase** (40+minutes of seizure activity). There is no clear evidence to guide therapy in this phase. The guideline found strong evidence that initial second therapy is often less effective than initial therapy, and the third therapy is substantially less effective than initial therapy. Thus, if second therapy fails to stop the seizures, treatment considerations should include repeating second-line therapy or anaesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring), (34)

It is well established that early status is easy to treat. There seems to be less physiological compromise and minimal neuronal damage. In contrast to this late SE is difficult to treat and is associated with more neuronal damage and has more physiological compromise.

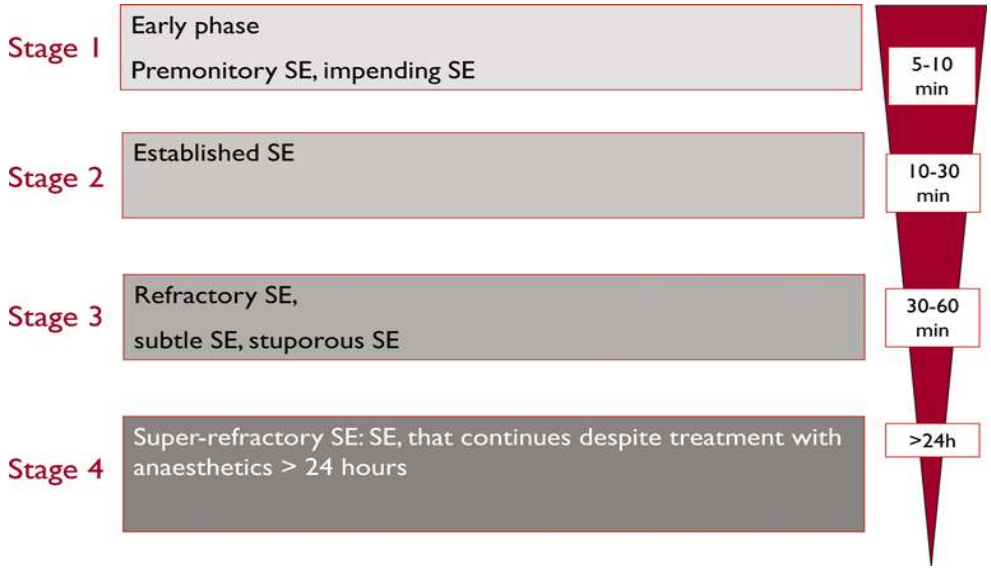

Figure 1.7. Stages of SE Trinka et al (2012)

The stages of treatment of status epilepticus. It is universal practice to stage therapy of status epilepticus. A typical protocol is summarized above. If Stage 1 therapy is ineffective after 30 min, Stage 2 therapy is initiated, and if this is ineffective within 2 h, Stage 3 therapy with general anaesthesia is instituted. Status epilepticus that has either not responded or has recurred 24 h after the initiation of anaesthetic therapy can be considered to have reached the stage of 'super-refractory status epilepticus'. IV = intravenous

Under dosing of benzodiazepines in SE

In clinical practice, treatment guidelines are not followed in a substantial proportion of patients. This underdosing correlates with lack of cessation of SE. A study published by Kellinghaus in 2019 demonstrated issue with under dosing very well and suggest that sufficiently dosed benzodiazepines should be used as a first treatment step. (43) In study median latency between SE onset and first treatment was 30 minutes in GCSE and 150 minutes in non-GCSE. The first intravenous compound was a benzodiazepine in 86% in GCSE and 73% in non-GCSE. Bolus doses of the first treatment step were lower than recommended by current guidelines in 76% of GCSE patients and 78% of non-GCSE patients. In 319 GCSE patients (70%), SE was ongoing 1 hour after initiating treatment and in 342 non-GCSE patients (58%). 12 hours after initiating treatment. Multivariate Cox regression demonstrated that use of benzodiazepines as first treatment step and a higher cumulative dose of anticonvulsants within the first period of treatment were associated with shorter time to cessation of SE for both groups.

Repeated benzodiazepine dosing

Walker in 1998 demonstrated in a study (44) that repeat dosing of DZP (benzodiazepine) Leads to substantial accumulation, and high, persistent serum and CSF concentrations, which may explain the toxic effects of repeat DZP dosing. In this study in a rat model was used that permits simultaneous serum and cerebrospinal fluid (CSF) sampling, they characterized the pharmacokinetics of DZP and its metabolite, desmethyldiazepam, in CSF and blood. DZP was administered by intraperitoneal injection as either a single dose (20 or 30 mg/kg) or repeat doses (10 or 20 mg/kg × 3, 1 h apart). After a single intraperitoneal dose, DZP was rapidly absorbed with a time to maximum concentration of 10 min. The serum concentrations then declined biexponentially. DZP rapidly entered the CSF; the CSF to serum ratio reached equilibrium within 10 min and was equivalent to the ratio of free to total serum concentration. Repeated DZP dosing resulted in a threefold decrease in volume of distribution and clearance ($p < 0.001$). This was reflected in the CSF concentration data; however, after the third dose, the ratio of CSF to serum concentration, also increased greatly, representing further persistence of DZP in the CSF compartment. This study concluded that repeat dosing of DZP leads to substantial accumulation, and high, persistent serum and CSF concentrations, which may explain the toxic effects of repeat DZP dosing. Repeat dosing of DZP using a tapering protocol, however, may increase the effectiveness of DZP in treating SE by preventing relapses without substantially increasing toxicity.

Early treatment is effective

Dreifuss (45) in his study showed that diazepam is superior to placebo in SE. In patients 125 study patients (64 assigned to diazepam and 61 to placebo) with a history of acute repetitive seizures, 91 (47 children and 44 adults) were treated for an exacerbation of seizures during the study period. Diazepam treatment was superior to placebo with regards to the outcome variables related to efficacy: reduced seizure frequency (P<0.001) and improved global assessment of treatment outcome by the care giver (frequency and severity of seizures and drug toxicity) (P<0.001). Post hoc analysis showed diazepam to be superior to placebo in reducing seizure frequency in both children (P<0.001) and adults (P=0.02), but only in children was it superior with regard to improvement in global outcome (P<0.001). The time to the first recurrence of seizures after initial treatment was longer for the patients receiving diazepam (P<0.001). Thirty-five patients reported at least one adverse effect of treatment. somnolence was the most frequent. Respiratory depression was not reported.

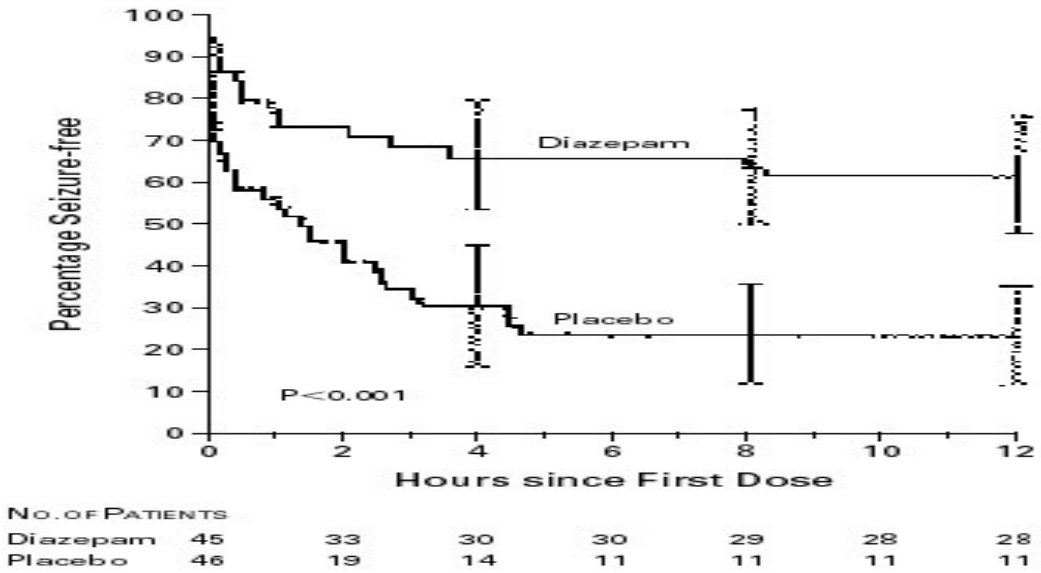

Figure 1.8. Kaplan–Meier Estimate of the Time to a First Recurrence of Seizures

Data from all patients were censored at 12 hours, the observation period for children. Only two patients, both in the placebo group, had their first seizure recurrence between 12 and 24 hours after the initial treatment. The vertical bars show 95 percent confidence intervals.

Midazolam vs Diazepam

There are studies which have shown superior effect of buccal midazolam compared to rectal diazepam. Published metanalysis (46) data support the efficacy and safety of non-intravenous routes of administration for midazolam, when compared to diazepam administered via any route in treating patients with status epilepticus, in the doses studied. Midazolam has

characteristics that may make it an optimal choice for the treatment of seizing patients. Midazolam has shorter elimination half-life and faster distribution time.

Study	Age years	N	Treatment	Effects
Scott et al. lancet 1999	5-19	18	Buccal MDZ Rectal DZP	75% 59%
McIntyre et al. Lancet 2005	0.5-15	177	Buccal MDZ Rectal DZP	56% 27%
Mpimbaza et al. Paediatrics 2008	0.25-12	330	Buccal MDZ Rectal DZP	70% 57%

Table 1.5. Studies comparing midazolam to diazepam

	Vol of distribution L/kg	Distribution t1/2 minutes	Elimination t1/2 hours
Diazepam	1-2	30	30
Lorazepam	2	180-600	15
Clonazepam	3	120-180	30
Midazolam	1-2	6	2-4

Table 1.6. Different forms of benzodiazepines and their pharmacokinetics

The 3 benzodiazepines most commonly used in the treatment of SE are diazepam, lorazepam, and midazolam. Each drug has slightly different properties and routes of administration.

Diazepam achieves higher brain concentrations with a rapid onset of action. It is, however, highly lipid soluble, leading to rapid redistribution and decreases in brain concentrations. Clinical effectiveness is only about 20 to 30 minutes. Relapse rate is high thus a second drug is required if diazepam is used as a first-line drug.

Lorazepam has a slightly longer onset of action; however, it is less lipid soluble than diazepam and has a duration of action greater than 12-15 hours.

Midazolam is water soluble, has rapid distribution half-life but does not stay in system longer as has elimination half-life of 2-4 hours.

Aggressive treatment of SE, is it working?

Study by Neligan and Walker 2016 (47) reviewed Epilepsy and SE mortality data from 2001 to 2013, in addition to annual age group populations for England and Wales, were obtained from the Office of National Statistics website. Age-adjusted mortality rates for epilepsy and SE with 95% confidence intervals (CIs) were calculated using the European Standard Population. Trends in mortality rates for both epilepsy and SE were investigated using the Spearman coefficient. The crude mean epilepsy mortality rate per 100,000 person-years between 2001 and 2013 was 1.87 (95% CI 1.83–1.91), with a corresponding SE mortality rate of 0.14 (95% CI 0.13–0.15). The mean age-adjusted epilepsy mortality rate per 100,000 person years was 3.24 (95% CI 3.12–3.35), with a corresponding SE mortality rate of 0.24 (95% CI 0.21–0.27). All epilepsy deaths significantly decreased from 2001 to 2013 (Spearman's ρ −0.733, p = 0.004); this decrease was predominantly due to a decrease in SE deaths (Spearman's ρ −0.917, p < 0.001). In summary, finding support the hypothesis that the policy of early and aggressive treatment of SE may be improving the prognosis of this condition in England and Wales.

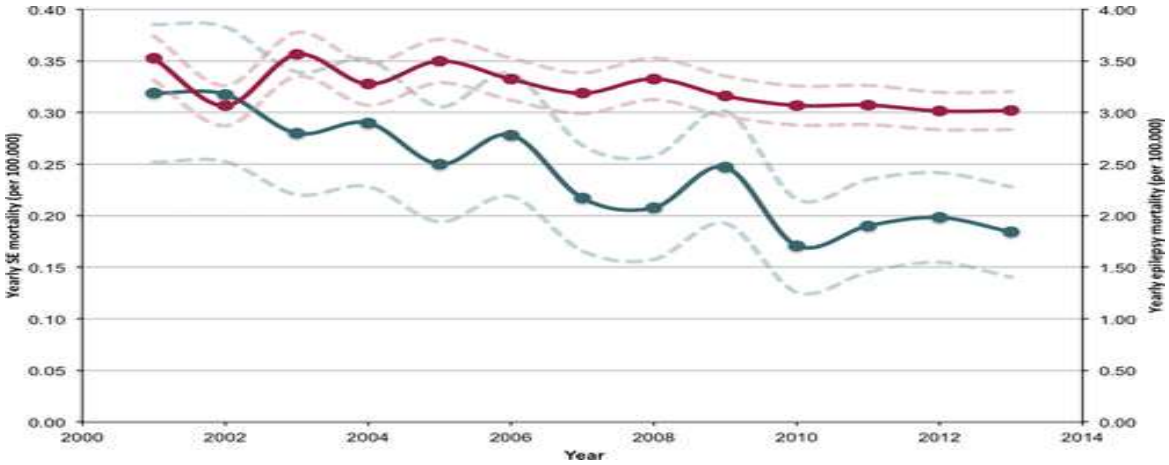

Figure 1.9. Trends in age-adjusted non-SE epilepsy (red) and SE (blue) mortality rates with 95% confidence intervals (dotted lines) in England and Wales 2001–2013. (64)

SE treatment and some important Randomised control trials leading to change in practice

Lorazepam is superior to Phenytoin (48)

Sreenath and colleagues compared lorazepam alone to combination of Diazepam and Phenytoin in paediatric SE cases. Lorazepam was found to be as efficacious and safe as diazepam–phenytoin combination. Study recommends use of lorazepam as a single drug to

replace the two-drug combination of diazepam–phenytoin combination to control the initial seizure in paediatric convulsive status epilepticus.

Efficacy of IM midazolam vs IV lorazepam (49)

Published in 2013 RAMPART (the Rapid Anticonvulsant Medication Prior to Arrival Trial) was a double-blind randomized clinical trial to determine if the efficacy of intramuscular (IM) midazolam is noninferior by a margin of 10% to that of intravenous (IV) lorazepam in patients treated by paramedics for status epilepticus (SE). In children and adults with >5 min of convulsions and who are still seizing at paramedic arrival, midazolam administered by IM autoinjector was noninferior to IV lorazepam on the primary efficacy outcome with comparable safety. Patients treated with IM midazolam were more likely to have stopped seizing at emergency department (ED) arrival, without emergency medical services (EMS) rescue therapy, and were less likely to require any hospitalization or admission to an intensive care unit.

Valproate vs Phenytoin

In 2006 Misra and colleagues (50) compared valproate and phenytoin use in SE. Sixty-eight patients with convulsive status epilepticus (SE) were randomly assigned to two groups to study the efficacy of sodium valproate (VPA) and phenytoin (PHT). Seizures were aborted in 66% in the VPA group and 42% in the PHT group. As a second choice in refractory patients, VPA was effective in 79% and PHT was effective in 25%. The side effects in the two groups did not differ. It was suggested that Sodium valproate may be preferred in convulsive SE because of its higher efficacy.

Phenytoin vs Valproate vs Levetiracetam

More recently, in the Established Status Epilepticus Treatment Trial (ESETT) researchers compared the efficacy and safety of levetiracetam, fosphenytoin, and valproate in established status epilepticus. In summary, in this large randomised controlled trial we showed that approximately half of patients with established status epilepticus respond to high doses of levetiracetam, fosphenytoin, or valproate. These results were consistent across the three age groups: children, adults, and older adults. The primary safety outcome did not differ by study drug or age group. Any of the three drugs can be considered as potential first-choice, second-line drugs for benzodiazepine-refractory status epilepticus. (51)

Lignocaine is better than placebo

In 1958 Taverner and colleagues (52) compared IV saline vs lignocaine for treatment of SE and were able to demonstrate that in blinded study that patients who received lignocaine instead of saline, better seizure control indicating that Lignocaine has some anti seizures properties.

Levetiracetam and phenytoin

Cons SEPT and EcLiPSE trials in children compared Levetiracetam to Phenytoin. Concept (53) found Levetiracetam is not superior to phenytoin for second-line management of paediatric convulsive status epilepticus. Clinical cessation of seizure activity 5 min after completion of infusion of study drug occurred in 68 (60%) patients in the phenytoin group and 60 (50%) patients in the levetiracetam group. In EcLiPSE trial (54) although levetiracetam was not significantly superior to phenytoin, the results, together with previously reported safety profiles and comparative ease of administration of levetiracetam, suggest it could be an appropriate alternative to phenytoin as the first-choice, second-line anticonvulsant in the treatment of paediatric convulsive status epilepticus.

Treatment of refractory status Epilepticus

Refractory status epilepticus (RSE) can be defined as status epilepticus that continues despite treatment with benzodiazepines and one antiepileptic drug. This occurs in 23%–43% of patients with SE; not surprisingly the only prospective study (55). RSE treatment is not at all evidence-based, despite it being recognized as an important entity in emergency and intensive care settings. Outcomes depend on age and aetiology. The occurrence of RSE has been mostly associated with acute, severe and potentially fatal underlying etiologist, such as encephalitis, massive stroke, or rapidly progressive primary brain tumours, and may be accompanied by severe impairment of consciousness. (55). There is universal agreement that general anaesthesia is required as the backbone of therapy for super-refractory status epilepticus, at least in the first weeks. However, there is no agreement about the optimal choice of anaesthetic. The conventional choice is between three anaesthetic drugs—thiopental (or pentobarbital, which is a main metabolite of thiopental), propofol and midazolam. Each has advantages and drawbacks and there are no controlled or randomized comparative data on which to base a choice (56).

Treatment	Dose recommended Adults	Main advantages	Main disadvantages
Thiopental/ pentobarbital	Bolus: 2–3 mg/kg Infusion: 3–5 mg/kg/h	Strong anti-epileptic action, potential neuroprotective action, reduces intracranial pressure, long experience of its use	Zero order pharmacokinetics, strong tendency to accumulate and thus prolonged recovery phase, acute tolerance, cardiorespiratory depression, hypotension, drug interactions, toxicity
Midazolam	Bolus: 0.2 mg/kg Infusion: 0.1–0.4 mg/kg/h	Strong anti-epileptic action, less tendency to accumulate than barbiturate or other benzodiazepine	Tendency for acute tolerance to develop resulting in breakthrough seizures, hypotension and cardiorespiratory depression, hepatic metabolism
Propofol	Bolus: 3–5 mg/kg Infusion: 5–10 mg/kg/h	Excellent pharmacokinetics, ease of use. responsive anaesthetic agent, pharmacology extensively studied	PRIS, pain at the injection side, involuntary movements, no intrinsic anti-epileptic action
Ketamine	Bolus: 0.5–4.5 mg/kg Infusion: up to 5 mg/kg/h	Lack of cardiorespiratory depression and drug-induced hypotension. *N*-methyl-d-aspartate blockade and therefore potential neuroprotective action	Potential for neurotoxicity, hypertension

Table 1.7 Anaesthetic therapies. Different anaesthetic agents recommended doses advantages and disadvantages. Shorvon et al Brain 2011 (78).

Super-refractory status epilepticus is a serious condition. Yet, despite the fact that it remains an important clinical problem in all neurology centres worldwide, for many therapies, and treatment approaches, there is a remarkable lack of published data concerning effectiveness, safety or outcome. Shovron published (57) an article in 2012, which focused on outcome assessment on the immediate control of seizures as the primary endpoint of each therapy. In a total of 596 cases, the long-term outcome could also be ascertained, divided into five broad categories, and the results are shown in table 7. Overall, 35% of the patients died. Long-term mortality is known to be related not so much to the treatment used as to the underlying aetiology (probably the main determinant) and also the duration of status epilepticus (table 8).

Outcome	***n* = 596**
Deaths	207 (35%)
Severe neurological deficit	79 (13%)
Mild neurological deficit	80 (13%)
Undefined neurological deficit	22 (4%)
Recovery to baseline	208 (35%)

Table 1.8-Overall outcome of anaesthetic therapy modified from Shorvon et al Brain 2012 (57)

Outcome	**Thiopental/pentobarbital (*n* = 192)**	**Midazolam (*n* = 585)**	**Propofol (*n* = 143)**
Control	64% (123/192)	78% (458/585)	68% (97/143)
No control ever achieved	5% (9/192)	16% (93/585)	11% (16/143)
Breakthrough seizures	0% (0/192)	3% (19/585)	1% (2/143)
Withdrawal seizures	9% (18/192)	<1% (2/585)	6% (8/143)
Therapy failure because of side-effects	3% (5/192)	<1% (1/585)	6% (8/143)
Death during therapy	19% (37/192)	2% (12/585)	8% (12/143)

Table 1.9 Long-term outcome SE. Adapted from Shorvon et al Brain 2012

In same study (57), the death rate was higher in patients who had been treated with thiopental/pentobarbital (46%) compared with propofol (36%), midazolam (34%).

The recommendations for the treatment of SRSE are primarily based on case reports: data from randomized trials are missing. If the underlying condition, such as autoimmune or infectious encephalitis or intoxication, can be identified, treating this condition has a strong anticonvulsant effect in patients with SRSE (58)

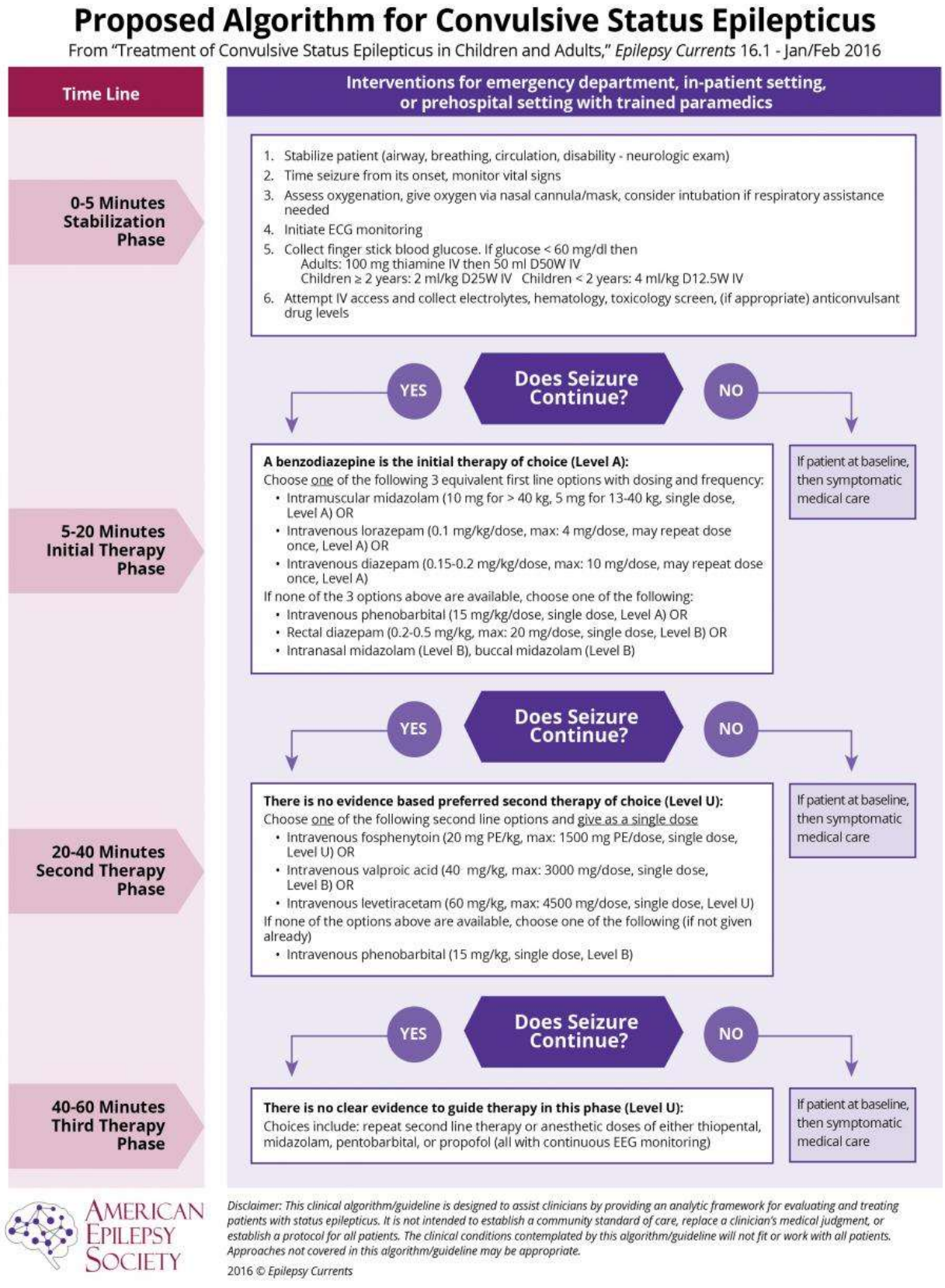

Figure 1.10 Treatment of SE AES guidelines 2016

Guidelines for the Evaluation and Management of Status Epilepticus Neurocrit Care (34)

SIGN guidelines for SE (59)

For sustained control in patients with established epilepsy give the usual AED treatment orally or by nasogastric tube (or IV if necessary for phenytoin, sodium valproate, phenobarbital, levetiracetam or Lacosamide. Within 30 minutes if seizures continue give sodium valproate 20–30 mg/kg IV 40 mg/min or phenytoin 18 mg/kg IV 50 mg/min with ECG monitoring. Rates of phenytoin infusion may need to be reduced if hypotension or arrhythmia occur in older people or where there is renal/hepatic impairment. If seizure continues then admit the patient to an ITU and administer general anaesthesia. Refer for specialist advice. Administer IV midazolam, propofol or thiopental sodium to treat adults with refractory convulsive status epilepticus.

Non-convulsive status (eg, absence status or continuous focal seizures with preservation of consciousness) may be difficult to diagnose. In non-comatose patients it may present as confusion, personality change or psychosis. Treatment should be considered as follows:
Maintenance or reinstatement of usual oral anti-epileptic therapy. Consider benzodiazepine Treatment (midazolam 10 mg buccally or intranasally, lorazepam 4 mg IV, or diazepam 10 mg IV). Use of IV benzodiazepines under electroencephalographic (EEG) control, particularly if the diagnosis is not established. Referral for specialist advice and/or EEG monitoring. Patients who do not respond to standard treatment regimens for status epilepticus are in refractory status epilepticus.

Maintenance AED medications

It is universally recommended that antiepileptic drug therapy should be used concurrently with anaesthesia in refractory and super-refractory status epilepticus. However, the published outcome of the use of antiepileptics in this situation is restricted. There is no published outcome analysis of any other antiepileptic in refractory or super-refractory status epilepticus, despite very widespread usage of a large range of drugs. Systematic data indicating which drugs or drug combinations should be preferentially used are not available. Suitable medications include anticonvulsants which can initially be administered intravenously or via nasogastric tube or percutaneous endoscopic gastrostomy, ensuring that therapeutic blood levels are rapidly attained. Levetiracetam, lacosamide, carbamazepine, perampanel, phenobarbital, phenytoin, topiramate, and valproate are widely used. However, only phenobarbital, phenytoin and valproate are approved for the treatment of SE, while the remaining anticonvulsants are not

explicitly approved for this indication. It is important to ensure adequate dosing and fast up titration. Combinations of more than 3 non-sedating anticonvulsants should be avoided. In case a drug shows no effect, it can usually be discontinued and replaced by another agent, even in the acute phase. In addition, continuous magnesium infusion can be attempted.

Other commonly used treatments in supra refractory status epilepticus

Magnesium: No good evidence. Magnesium sulphate infusion is another widely used therapy in super-refractory status epilepticus although again the published evidence base-related outcome is remarkably small.

Immunosuppression: Another treatment that is widely used in super-refractory status epilepticus is immunotherapy with steroids, intravenous immunoglobulins, and plasma exchange. Steroids have been used in the treatment of SE for several years. There are two reasons supporting the use of steroids to treat SRSE: First, autoimmune encephalitis is presumably the most common cause of SRSE, even if patients do not test positive for anti-bodies. Second, inflammatory processes such as the activation of pro-inflammatory cytokines, e. g. interleukin-1β and TNF-α, are likely to play an important role in epileptogenesis /ictogenesis; consequently, anti-inflammatory therapy may have a significant anti-seizure potential (80). Besides steroids, the administration of immunoglobulins and the use of plasmapheresis could be considered, although the currently available data are not sufficient to support a general recommendation in this respect (60)

Suggested diagnostic work-up for SE (34)

The steps included in the diagnostic work-up should be completed as soon as possible and occur simultaneously and in parallel with treatment. All patients:

1. Fingerstick glucose
2. Monitor vital signs.
3. Head computed tomography (CT) scan (appropriate for most cases)
4. Order laboratory test: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, AED levels.
5. Continuous electroencephalograph (EEG) monitoring

Consider based on clinical presentation

1. Brain magnetic resonance imaging (MRI)
2. Lumbar puncture (LP)
3. Comprehensive toxicology panel including toxins that frequently cause seizures (i.e., isoniazid, tricyclic antidepressants, theophylline, cocaine, sympathomimetics, alcohol, organophosphates, and cyclosporine).
4. Other laboratory tests: liver function tests, serial troponins, type and hold, coagulation studies, arterial blood gas, AED levels, toxicology screen (urine and blood), and inborn errors of metabolism.

Complications of SE

SE is a 3 staged condition.

1.Progressive systemic physiological stage.

2.Progressive neuronal damage.

3.Progressive difficulty in treating.

1. Physiological stages in a convulsion leads to increase in heart rate, blood pressure and Plasma glucose. There is increase in blood flow. This is a compensation stage, which is followed by decompensation stage, leading to arrythmia, hypotension, hypoxia, acidosis, loss of cerebral auto regulation. All these changes lead to late complications such as, rhabdomyolysis, liver and renal dysfunction, infection, disseminated intravascular coagulation and raised intra cranial pressure (103).

2.Progressive neurological damage is well described by many studies in past (61). In these studies we saw that prolonged electroencephalographic seizures were induced by the intravenous injection of bicuculline (0.5 to 1.4 mg/kg) in adolescent *Papio papio*, while they were paralyzed and artificially ventilated on air or oxygen. Physiological monitoring revealed an initial increase in cerebral blood flow. Arterial oxygen tension remained steady or decreased slightly. Rectal temperature rose, but did not exceed 40.0 C. After perfusion-fixation of the brain, light microscopy revealed neurons with ischemic cell change in seven animals who had had seizures lasting three hours 25 minutes to seven hours 30 minutes. These changes predominated in the neocortex (small pyramidal neurons), thalamus (anterior, dorsomedial, and ventral nuclei), and hippocampus (Sommer sector and endfolium). Comparison with previous studies in nonparalyzed baboons indicates that paralysis provides partial protection against

neuronal damage in the neocortex and hippocampus. Cerebellar damage (related to hyperpyrexia and arterial hypotension) is almost totally prevented by paralysis (62).

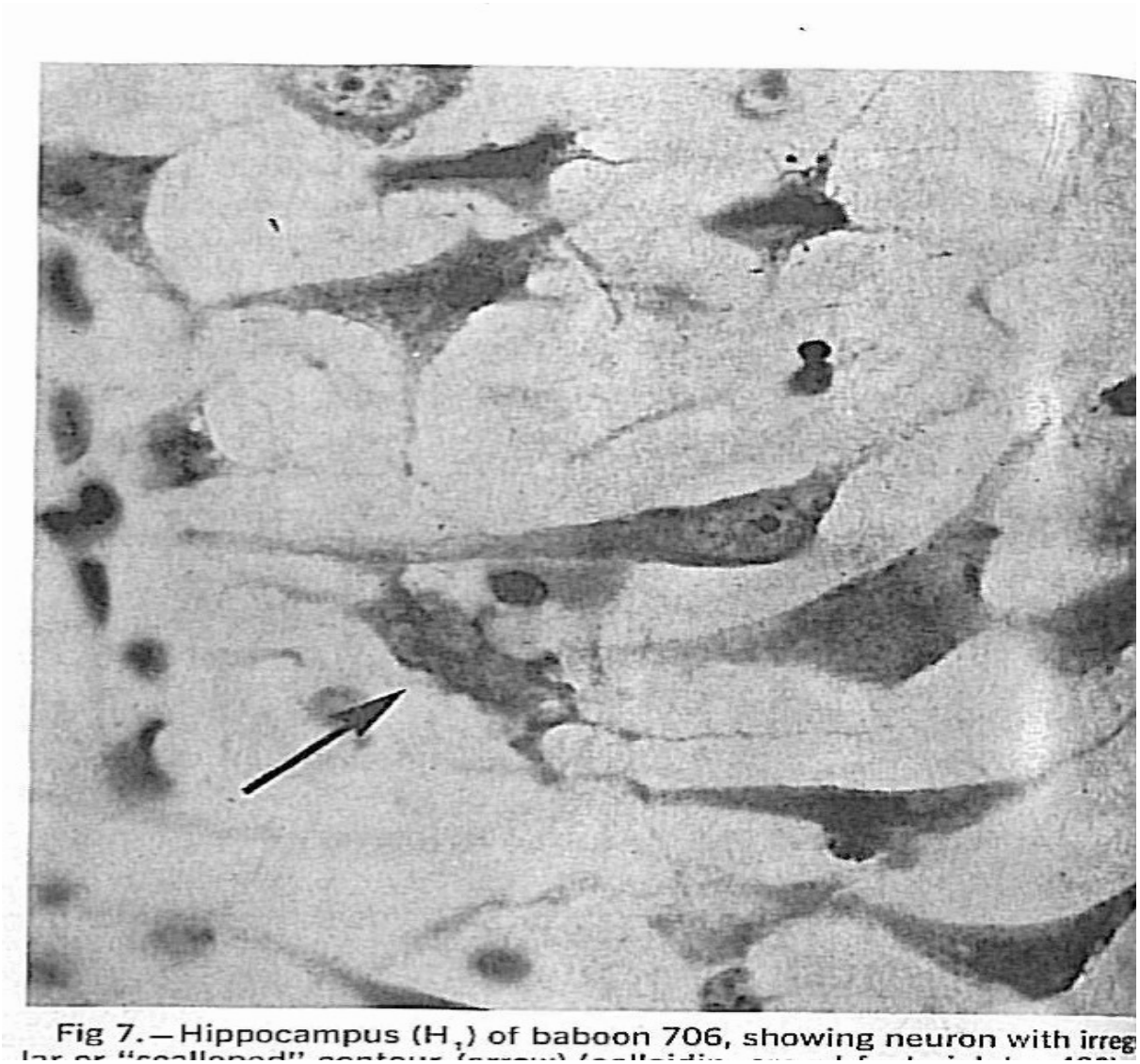

Figure 1.11, Hippocampus ischemic and structural neurological damage in SE shown in experimental study by Meldrum 1973 (61)

Hippocampus H, of baboon 706, showing neuron with ii lar or "scalloped" contour arrow celloidin, cresyl fast violet, x4801

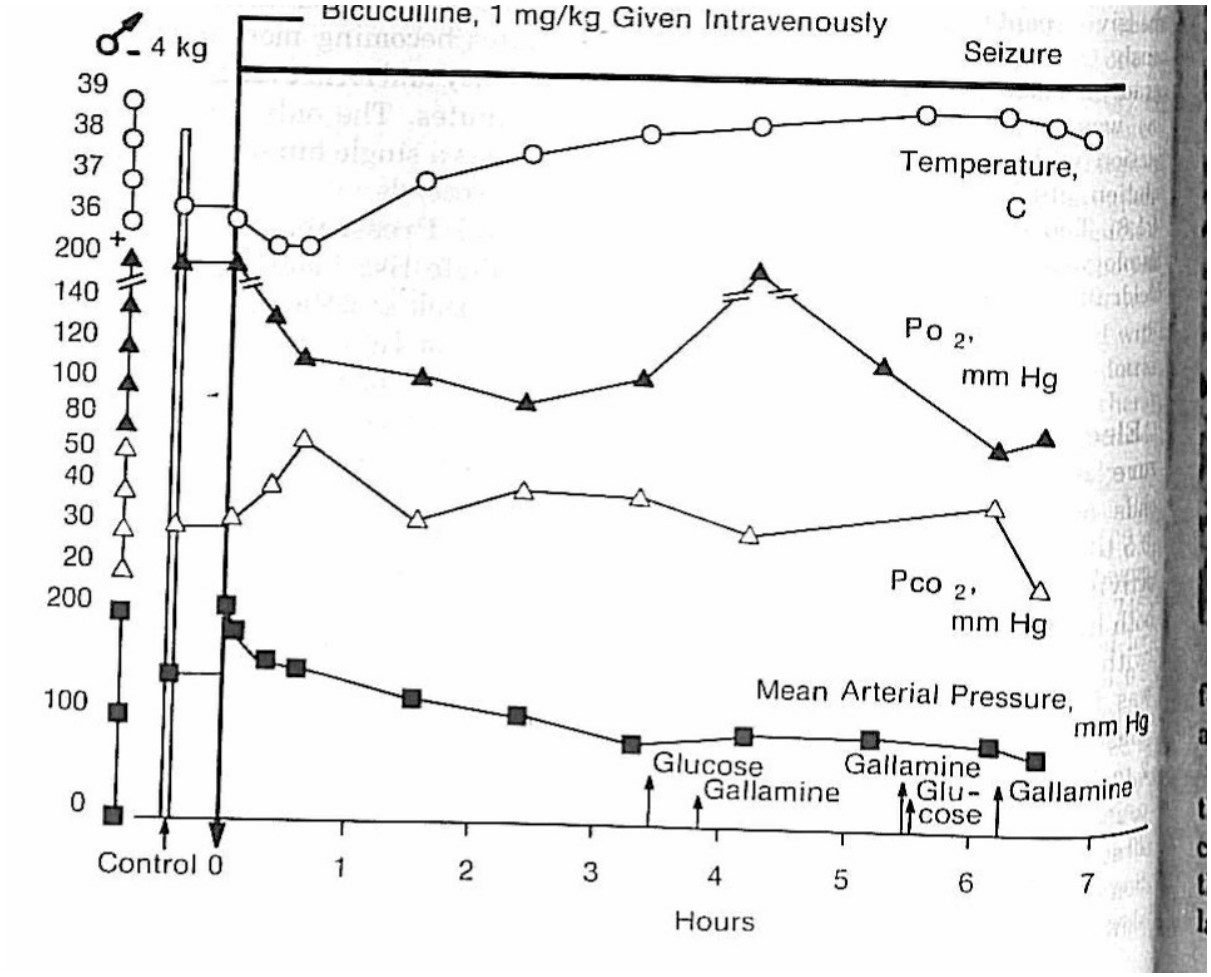

Figure 1.12. Physiological changes in SE shown in experimental study by Meldrum 1973 (61) Graph of physiological changes in baboon 670 male, weight 4 kg. Bicuculline, 1mg provoked EEG seizure activity lasting seven hours 5 minutes. Gallamine was given initially one hour before bicuculline, and the animal was subsequently ventilated on oxygen. Small doses of gallamine were repeated arrows. Atropine, 0.25 mg/kg, was given intravenously 45 minutes after bicuculine. Glucose 10 ml of 10% solution was given intravenously arrows. Baboon 670

More recently there have been studies which have shown that prolonged and repeated seizures can lead to structural brain damage. Vespa and colleague published a study in 2010 showing that posttraumatic nonconvulsive seizures occur frequently after TBI and, in a selected subgroups appear to be associated with disproportionate long-term hippocampal atrophy. These data suggest anatomic damage is potentially elicited by nonconvulsive seizures in the acute postinjury setting. (63)

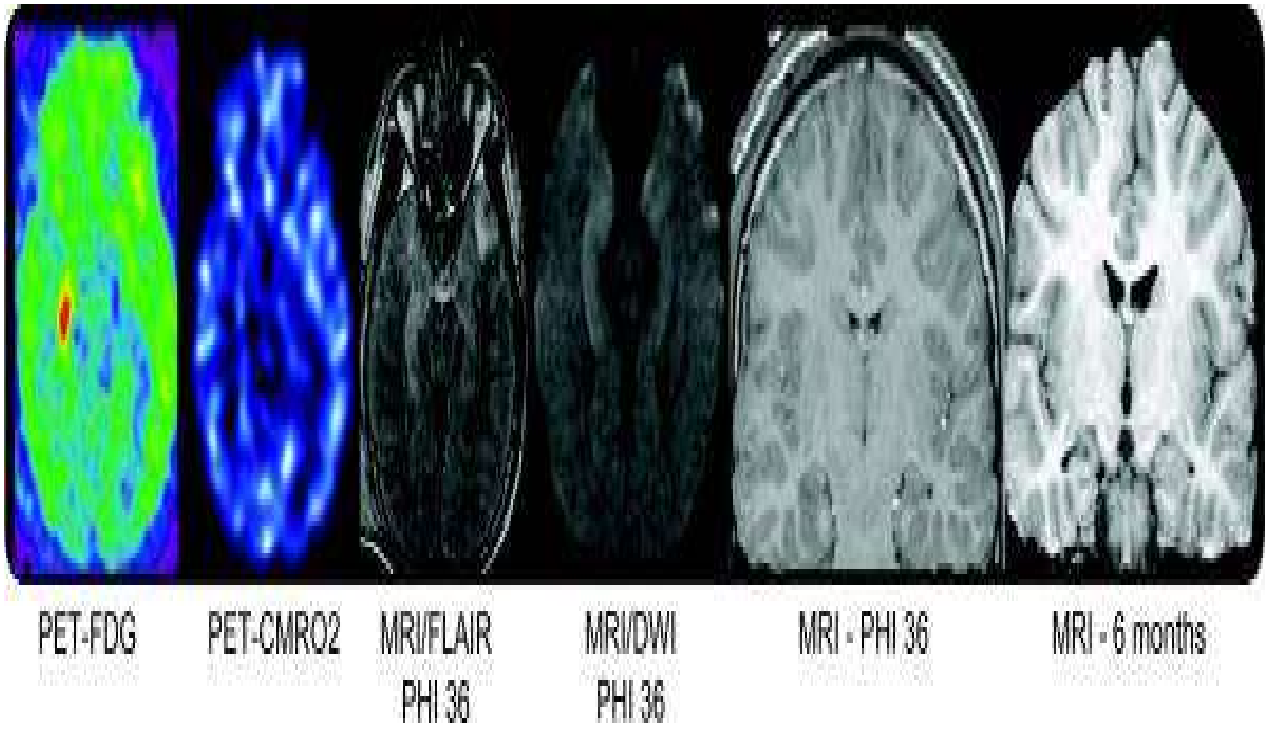

Figure 1.13, Vespa et al Neurology 2010 (63)

Hippocampal atrophy ipsilateral to the seizure focus.

Composite of acute PET scan and acute and chronic MRI volumetric scans on seizure subject 4. The patient has increased glucose metabolism in the right hippocampus without a similar increase in CMRO2. The hyperintensity on the fluid-attenuated inversion recovery (FLAIR) sequence was due to acute seizure activity and not traumatic hemorrhage. MRI at 6 months shows right hippocampal atrophy and also right temporal lobe atrophy. CMRO2 = oxidative metabolism PET; FDG = fluorodeoxyglucose PET; PIH = postinjury hour.

Progressive difficulty in treating Kapur in 1997 very effectively demonstrated the development of rapid functional plasticity of GABARs occurring over 45 min of continuous seizures (status epilepticus) in rats. Seizures induced in rats by administration of lithium followed by pilocarpine were readily terminated by the benzodiazepine diazepam when administered early during the seizures (after 10 min of seizures). However, during status epilepticus, there was a substantial reduction of diazepam potency for termination of the seizures (64)

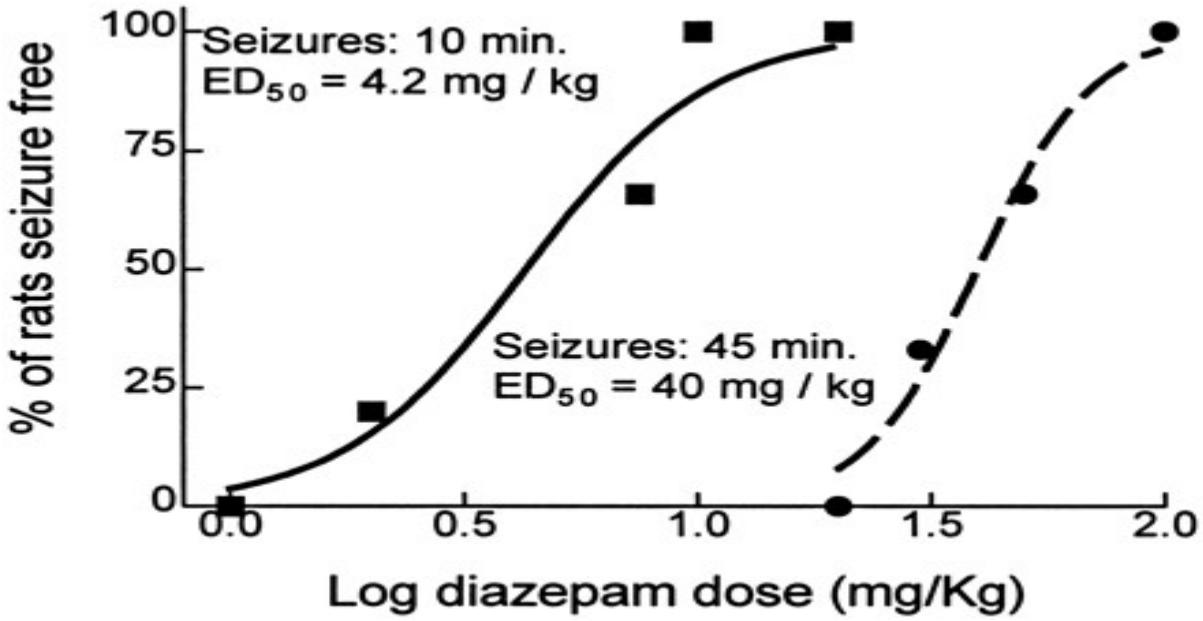

Figure 1.14 Effect of diazepam on brief seizure control

Kapur et al 1997. Diazepam was effective in controlling brief (10 min) seizures but lost efficacy after prolonged (45 min) seizures. Seizures were induced in 70–150 gm rats by intraperitoneal injection of LiCl at 3 mEq/kg followed 16–24 hr later by intraperitoneal injection of pilocarpine at 50 mg/kg. Behavioural seizures started within 1–5 min in all rats. Diazepam was administered 10 min (filled boxes, solid line; n = 14) or 45 min (filled circles, dashed line; n = 12) after pilocarpine injection. The percent of rats that stopped having seizures within 5 min of diazepam injection was plotted against the log of the diazepam dose.

Autoimmune status epilepticus (ASE)

A rare form of the disorder encountered in the intensive care unit. ASE can be refractory to anticonvulsant therapy and the symptoms include subacute onset of short-term memory loss with rapidly progressive encephalopathy, psychiatric symptoms with unexplained new-onset seizures, imaging findings, CSF pleocytosis, and availability of antibody testing makes an earlier diagnosis of ASE possible. In these patients, autoantibodies against cell surface or synaptic proteins disrupt receptors or voltage-gated ion channels, resulting in rapidly progressive encephalopathy, abnormal movements, psychiatric symptoms, and often recurrent seizures. Some of these patients with autoantibodies and new-onset seizures *autoimmune epilepsies* will develop convulsive or non-convulsive ASE (65). There is a broad range of auto antigens in autoimmune encephalopathies with seizures both among those with intracellular antigens (GAD, Hu, DNER, Sox1 Ampiphysin, Ma, and CV2) and surface antigens (LG1,

CASPR2, NMDAR, GlyR, AMPAR, $GABA_BR$, mGluR5, DPPX, $GABA_AR$, and Neurexin-3a). These patients can present with antiepileptic drug resistant epilepsy; however, potential for reversal with immunotherapy and early treatment has shown improved survival and cognition (66). NMDA encephalitis needs special metion under heading of auto immune encephalitis**.** The condition was first identified in 2007 (67) who described 100 cases. In 2010 Irani and colleagues published case series of 44 patients and further characterized NMDA encephalitis (68). Most common presenting features included seizures, confusion, amnesia, behavioural changes, and psychosis. Rarer presenting features included hyperacusis, deafness, ataxia and dystonia. The most distinctive clinical features occurred later and included involuntary choreoathetoid orofacial movements, tachy- or bradycardia and a spontaneous fall in conscious level; central hypoventilation occurred in only seven patients. Most patients progressed to a severe clinical syndrome and required admission to intensive Care. Irani described pathogenic potential of the antibodies and show that serial NR1-antibody levels (subunit of NMDA) correlate with clinical severity over time within individuals and across the cohort. Moreover, early immunotherapy appeared to be important in improving outcomes, reducing NMDAR-antibody levels, and protecting against relapses, which occurred in 23%.

Prognosis of Status Epilepticus

Overall mortality

It has been suggested that RSE has a higher short-term and long-term mortality than SE, although this is not invariably replicated. The mortality rates of RSE and SRSE range from 15% to 54% and thus exceed the mortality of non-refractory SE (11–37%) by far. Mortality in some studies, is reported up to 20-50 % in ICU setting (21,22). Febrile SE is important aetiology of SE in children, but it was noted to have a low mortality (1.6%) (69, 70), and most deaths during hospitalization occur in children with acute or remote symptomatic causes.

Acute complication

Acute complications in SE result from hyperthermia, pulmonary oedema, cardiac arrhythmias, and cardiovascular collapse. Long-term complications include epilepsy (20% to 40%), encephalopathy (6% to 15%), and focal neurologic deficits (9% to 11%). The aetiology is the major determinant of mortality.

Aetiology of SE and it's relation with mortality

Mortality of RSE and SRSE is largely influenced by the etiologic and is markedly higher as compared to non-refractory status epilepticus. In the adult population, SE was associated with a mortality of 26% that could rise to 50% in those aged >80 years. CVA plays a major role in mortality, contributing to a mortality rate of approximately 40% (88), while cardiovascular, CNS infections, TBI, systemic metabolic derangements and progressive symptomatic aetiologies have at least a 30% mortality rate (71,88). In another study the mortality rate for the population was 22%, 3% for children and 26% for adults. This indicates that for some reason children's brain in more resilient to SE related insults or may be adults due to other co morbidities acquire more mortality and morbidity or may be this difference is due to difference in aetiologies in adults versus children (23). The work done by Meldrum suggests that 82 min or more of ongoing seizure activity in baboons can cause irreversible neuronal injury (61). Mortality of RSE and SRSE is largely influenced by the etiologic and is markedly higher as compared to non-refractory status epilepticus. The increased 1-year mortality in RSE has been associated with older age, or poorer neurological status on discharge from hospital (82). It is shown in studies that there is progressive neuronal damage as time passes and SE becomes more drug resistant (83, 84, 85, 86).

Prognostic factors

Length of stay in ITU and length of time spent in clinical state of SE are also prognostic factors. In the most recent study, 24.5% of patients with RSE, 37.9% of patients with SRSE, but only 9.8% of patients with non-refractory SE died (87). The high variability of the reported mortality rates is explained by the significant heterogeneity of the patient populations studied. A study published in 2017 looked at long term outcomes of RSE. During 1-year follow-up, nearly 50% of the ICU-treated RSE patients recovered to baseline function, whereas 30% showed new functional defects and 20% died. SRSE does not have a necessarily poorer outcome. The outcome was worse in older patients and in patients with progressive or fatal aetiologies (88). Previous studies showed that older age and acute symptomatic aetiology are related to poor outcome (72) Results are less consistent for other variables: time to treatment or to seizure Control, (73, 74, 75) gender, (73,74) and ethnicity (74, 76). There are studies which have shown that older age and marked impairment of consciousness are predictive of death (77). The risk factors for morbidity and mortality related to SE have not previously been well-defined,

although small cohort studies (78, 79, 80, 81) have suggested that older age at onset, generalised seizure at onset, treatment delay, impaired consciousness at presentation, or lack of EEG monitoring may all impair prognosis.).

Continuous EEG Monitoring

EEG monitoring has a role in ITU management of clinical and sub clinical seizures. The appropriate titration of anaesthetic agents during status epilepticus may be based on the appearance of burst suppression on the EEG. Furthermore, continuous recording will give an indication of worsening of generalised convulsive status epilepticus regardless of the presence or absence of sedating drugs or paralysing agents. It is striking that in a relatively recent survey less than a third of units monitored status by continuous EEG or cerebral function monitor, and almost a half used clinical monitoring only (90).

The treatment of SE in the ITU usually requires EEG monitoring to direct treatment. Continuous EEG may be part of multimodal ICU monitoring, e.g, to monitor sedation depth and pharmacological burst-suppression, to detect secondary ischaemia, or for coma prognostication (91,92). EEG monitoring is becoming an important technique for assessing neurologic status in the critically ill. Many of these patients, including those with known brain injury such as TBI, stroke, or SAH, as well as patients without structural brain injury, are at high risk for NCSE, which can only be detected by EEG. Therefore, EEG should be considered not only in those with acute brain injury and impaired mental status but also in all ICU patients with unexplained alteration in consciousness, even if they do not have a history of seizures or brain injury (93).

1. Detection of nonconvulsive seizures and characterization of spells in patients with altered mental status with:
   - A history of epilepsy
   - Fluctuating level of consciousness
   - Acute brain injury
   - Recent convulsive status epilepticus
   - Stereotyped activity such as paroxysmal movements, nystagmus, twitching, jerking, hippus, autonomic variability
2. Monitoring of ongoing therapy
   - Induced coma for elevated intracranial pressure or refractory status epilepticus
   - Assessing level of sedation
3. Ischemia detection
   - Vasospasm in subarachnoid hemorrhage
   - Cerebral ischemia in other patients at high risk for stroke
4. Prognosis
   - Following cardiac arrest
   - Following acute brain injury

Table 1.10. Indication for continuous EEG monitoring Friedman et al 2009 (93)

Study published by Hill in 2019 indicated that there was a >10-fold increase in EEG use from 2004 to 2013 for in patient care. However, this procedure may still be under used; continuous EEG was associated with lower in-hospital mortality but used for only 0.3% of the critically ill population (94). Same study showed that the patient requiring continuous EEG appeared more ill, but use of continuous EEG use was associated with reduced in-hospital mortality after adjustment for patient and hospital characteristics. This finding held for the diagnoses of subarachnoid or intracerebral hemorrhage and for altered consciousness but not for the seizure/status epilepticus subgroup. Cost and length of hospitalization were increased for the cEEG cohort.

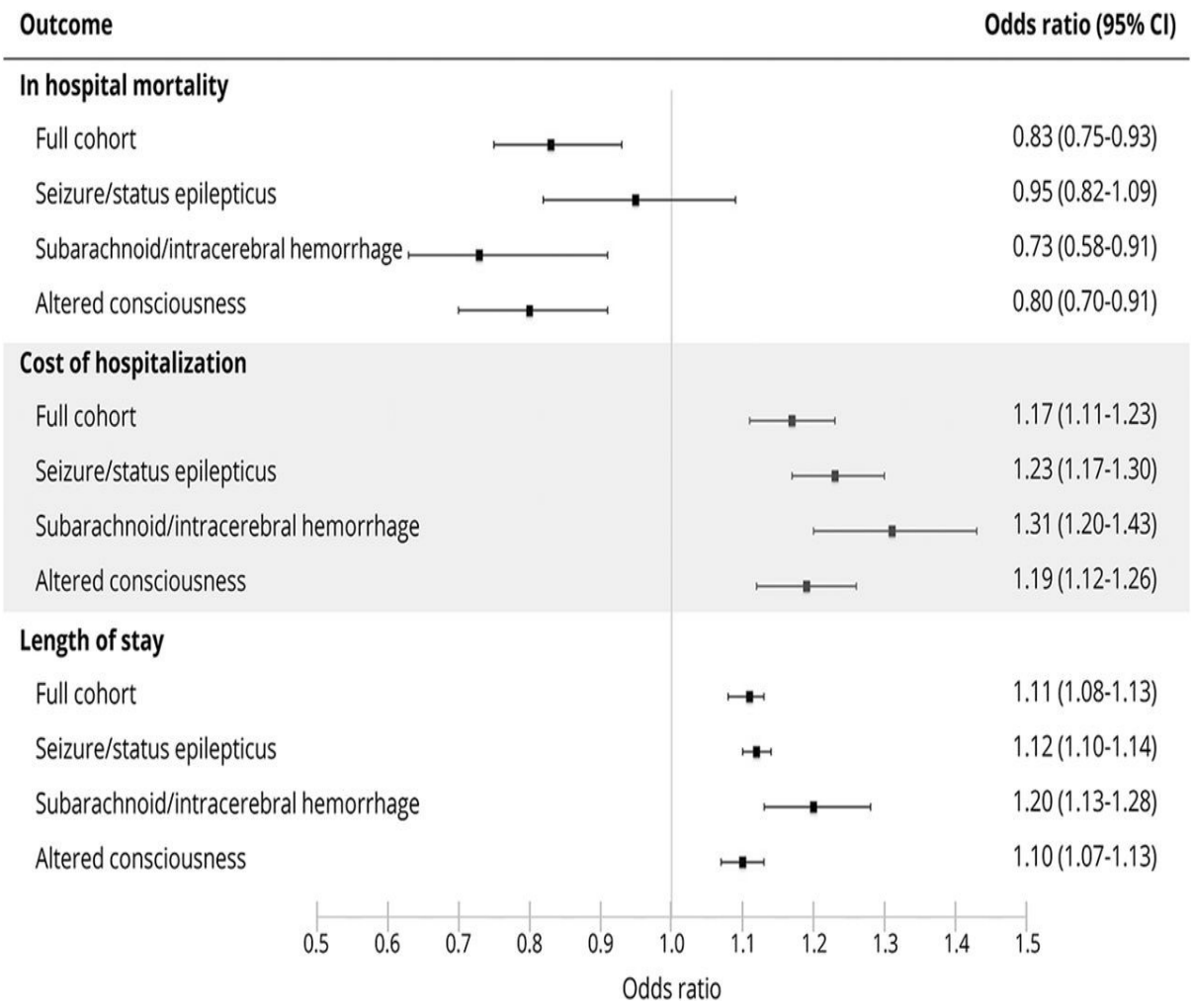

Table 1.11. Outcomes of continues EEG monitoring, Hill et all 2019 (94)

Drugs and alcohol and status epilepticus

Alcohol and drugs are major health issue in many parts of world. Scottish government reported Drug-related deaths in Scotland increased by 6% last year this is according to official statistics Published on 15 Dec 2020 (95). National Records of Scotland figures show there were 1,264 deaths, the highest figure on record. Males accounted for 69% of the drug-related deaths in 2019, a similar proportion to recent years. The median age of drug-related deaths has increased from 28 to 42 over the last 20 years. Three-quarters of all drug-related deaths were in the following five Health Board areas: Greater Glasgow & Clyde (404), Lanarkshire (163), Lothian (155), Tayside (118) and Ayrshire & Arran (108). Together, they accounted for a slightly higher proportion of the total than in most of the previous ten years.

Alcohol and drugs are common trigger for seizures, especially in the hangover period when your brain is dehydrated. It also disrupts sleep patterns which can be a common trigger for seizures. Alcohol and drugs can make epilepsy medication less effective or make the side

effects of medication worse. The potentially serious outcomes from ingestion of and dependence on toxins make this an important topic for epileptologist. Liver enzyme induction occurs rapidly with alcohol, reducing the serum level of some AEDs. Although data are more extensive on the older drugs, there is a clear risk of such effects on some of the newer drugs undergoing hepatic metabolism. In addition, alcohol may increase the side effects usually attributed to AEDs. It is also likely that patients with drugs or alcohol addiction have poor adherence for AEDs.

Seizures associated with illicit drug use are variably recognized in emergency departments (96), but it is important that their role is quickly identified to avoid excessive antiepileptic drug (AED) use and investigation. Seizures occur in one third of patients withdrawing from alcohol and may even develop into status epilepticus (97). A 249 adult patient study published in 1993 showed that in 10.8% patients had alcohol abuse as the only identifiable precipitating cause of SE. In 44% of the study group, SE was the first presentation of alcohol-related seizures. Seizures with focal features were observed in patients 40.1% (98). In 2012 Dr Leach and colleague wrote an extensive paper on pathophysiology and presentation of alcohol and drugs in epilepsy (99). Alcohol has significant metabolic effects as described below.

Acute effects of alcohol. Acute alcohol ingestion quickly increases glutamate binding to *N*-methyl-D-aspartate (NMDA) receptors, and potentiates the γ-aminobutyric acid (GABA) effects, particularly in receptors with delta-subunits. The regional distribution of these subunits explains why the cerebellum, cortical areas, thalamic relay circuitry, and brainstem are the main centres that mediate the intoxicating effects of alcohol. Contrary to popular myth, high blood alcohol levels alone are probably not responsible for seizures. In fact, GABAergic effects may raise the seizure threshold with alcohol levels. Effects on kainate receptors, serotonin, and glycine receptors are accompanied by changes in G-protein coupling, modifying the function of both potassium and calcium channels (99, 104).

Chronic effects. Chronic alcohol ingestion induces tolerance and physical dependence. Long-term use increases NMDA subunit proteins with tonic inhibition of these receptors, predisposing to rebound activation on alcohol withdrawal. Active alcohol ingestion increases blood levels of excitotoxic compounds such as glutamate, aspartate, and homocysteine; alcohol withdrawal further increases homocysteine, increasing the seizure risk. Serum homocysteine levels may be a marker of the risk of alcohol withdrawal seizures. The other effects of long-term alcohol abuse, such as hypokalaemia, complications of head injury, and clotting problems

with cerebrovascular hemorrhage, lower seizure threshold and increase the chances of prolonged or sustained seizure activity (99, 105).

Withdrawal effects. During acute withdrawal, particularly with disturbed sleep, the proconvulsant effect may be sufficient to induce seizures in susceptible patients. Such seizures occur 6–48 h after cessation of drinking, sometimes with status epilepticus. All age groups are at risk, including the elderly. Chronic GABA potentiation may change subunit expression, allowing additional hyperexcitation on alcohol withdrawal and increasing the seizure risk. Furthermore, alcohol withdrawal increases the QT interval, maximal at 6–48 hr after stopping, and thereby increases the risk of sudden unexpected death in epilepsy (SUDEP). In addition, the theoretical risk of kindling may induce seizure activity by withdrawal via neurologic changes that predispose to seizure induction by future diminishing stimuli (99, 106).

Clinical effects of alcohol toxicity. Acute alcohol intoxication depresses the central nervous system, with euphoria and disinhibition in the earliest stages, and then leading to drowsiness, ataxia, vertigo, and finally somnolence and coma with increasing blood levels. There is a characteristic fetor. Cerebellar signs appear with increasing blood levels. Localizing neurologic signs suggest the need to a search for signs of trauma. If there is doubt, then proceed to neurologic imaging. Alcohol withdrawal leads to a well-recognized syndrome in susceptible individuals, comprising blackouts (periods of memory loss), tremors, muscle rigidity, delirium (so-called “delirium tremens”), and seizures (99).

Alcohol withdrawal seizures

Seizures may occur shortly after chronic ethanol intake is suddenly discontinued. Alcohol withdrawal seizures are usually associated with a history of daily alcohol consumption, but briefer drinking sprees may also culminate in seizures. Generalized tonic-clonic seizures are most common; focal seizures occur in 5 to 24 percent of cases and suggest an aetiology other than alcohol withdrawal. More than 90 percent of seizures occur within 7 to 48 hours after cessation of drinking. Approximately 60 percent of patients have more than one seizure, but fewer than 15 percent have more than four. Status epilepticus is unusual and occurs in only 3 percent of cases, but alcohol withdrawal is shown to be responsible for approximately 10-15 percent of all cases of status epilepticus in literature (100).

Alcohol and seizures relation to deaths

There have been some forensic studies about alcohol and seizures relation to deaths. Clark reviewed the cause of sudden death in 500 chronic alcoholics. He reported a group of "obscure deaths", i.e., deaths where necropsy revealed no distinct cause of death, *a certain number* (number of cases not stated) of these died "apparently of inhalation of vomit", and *a few* (number not stated) of these deaths were witnessed and epileptic-type seizures described. He concluded that it is possible that most or all of these deaths result from alcohol withdrawal seizures. Some of these cases might be alcohol-related seizures, but we lack information of possible known epilepsy and epilepsy type (101).

There is currently little knowledge on the alcohol-drinking behaviour of epilepsy patients. In the 1940s, William G. Lennox comprehensively analysed alcohol consumption and the occurrence of alcohol-related seizures in 1,254 subjects with epilepsy (102). However, only about 30% of patients used alcohol, thus excluding 70% from any analysis of potential alcohol-related effects on the disease. The occurrence of alcohol-related seizures was reported by 21.1% of subjects who had used alcohol and was more often stated by patients with symptomatic than with idiopathic or cryptogenic epilepsy (as classified at that time). Apart from this, there is little research on the occurrence of alcohol-related seizures in patients with epilepsy.

Chapter 3

Refractory Status Epilepticus in Adults Admitted to ITU in Glasgow 1995-2013. A longitudinal Audit

Analysis of 633 refractory cases of provoked and unprovoked Status Epilepticus and comparison between status Epilepticus with Previous Epilepsy (SEPE) and De Novo Status Epilepticus (DNSE)

Introduction

Status epilepticus (SE) is defined as continuation of seizures for more than 5 min [10] and is a medical emergency that requires immediate assessment and treatment [59]. Subdivision of stages of SE have been defined depending on the degree of response to treatment and duration of treatment needed. The ILAE's classification [10] defines two 'operational dimensions', being the initial seizure duration requiring treatment (T1) of five minutes, and the seizure duration associated with neurological sequelae (T2) of 30 minutes. Refractory status epilepticus (RSE) is defined as SE that continues despite treatment with benzodiazepines and at least one antiepileptic drug, while Super Refractory Status Epilepticus (SRSE) consists of continuous or recurrent seizures lasting for 24 h or more despite administration of an intravenous (IV) anaesthetic, or recurrence of SE on weaning from anaesthesia [41].

Results

We identified a total of 800 admissions to ITU with relevant diagnostic codes. We excluded 167 cases with insufficient information available, or with no supportable diagnosis of RSE, leaving 633 admissions to ITU with RSE with supporting information. Two hundred and fourteen (34%) patients had experienced prior seizures or a diagnosis of epilepsy (Status Epilepticus with Previous Epilepsy – SEPE), while 419 (66%) patients were admitted to an ITU for an index seizure (De Novo Status Epilepticus - DNSE). The nature of the SE was assessed (Supporting Table 2.1b) 590 (93.20%) being generalized tonic colonic SE, and 24 (3.79%) were focal SE. Thirteen cases (2.1%) were eventually thought to be non-convulsive SE. In 6 cases (0.9%) no information on type of SE was available.

Demographic Information

The demographic details of the whole cohort and subgroups are shown in Table 2.1a, 2.1b. Age and gender distributions were similar in both DNSE and SEPE groups. There was a male preponderance in both groups, which may reflect the incidence of causative factors seen in subsequent tables. The incidence of alcohol-related problems was slightly higher in DNSE than among SEPE patients. Analysis of addiction issues and other risk factors (Table 2.3) show increased rates related solely to addiction and abuse in the group with DNSE compared to SEPE (41% versus 18%). GTCS was most common type of status leading to ITU admission (93%).

	Total n=633 (100%)	DNSE n=419 (66%)	SEPE n=214(34%)
Age (years) Mean, Range	48 15-91	50 15-91	44 15-90
Female: Male	249:384 1.0:1.54	162:257 1.0:1.58	87:127 1.0:1.46
Documented Drug abuse	103 (16%)	71 (17%)	32 (15%)
Documented Alcohol abuse	312 (49%)	227 (54%)	85 (40%)
Previous ITU with neurological condition	108 (17%)	27 (6.40%)	81 (38%)
Days in hospital Mean, Median (Range)	21.4, 8 (0.5 – 1497)	28, 10 (0.5 – 1497)	8.7, 6 (0.5- 30)
Days in ITU Mean, (Range)	3.6 (0.5 -165)	3.65 (0.5-165)	3.7 (0.5-26)
Number of Deaths over 10 years following admission	303 (47.86%)	220 (52.50%)	83(38.7%)
Deaths during index admission	74 (11.69%)	58 (13.80%)	16(7.47%)
Deaths within 1-year following date of Admission	141 (22.0%)	106(25.0%)	35(16.0%)

Table 2.1a Demographic Data, nature of Status Epilepticus and identified Causes

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Type of status:	Total n=633 (100%)	De Novo SE n=419 (66%)	SEPE n=214(34%)
Focal seizure	24 (3.80%)	10 (2.0%)	14 (6.0%)
GTCS	590 (93.0%)	395 (94.0%)	195 (91.0%)
Not Known	6 (0.9%)	6 (1.50%)	0
NCSE	13 (2.0%)	8 (2.0%)	5 (2.3%)
Long Term AED Treatment among survivors on discharge (N on AED / N of survivors)	310/559 (55.45%)	134/361 (37.0%)	176/198 (89.0%)

Table 2.1b – Status Classification and Use of AED

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Focal and GTCS (generalised tonic clonic seizure) are named as per ILAE seizure classification 2006.

Annual Incidence

The annual number of cases of RSE (both SEPE and DNSE) in Glasgow showed wide variation, and we have for clarity formed 3-year cohorts. Both DNSE and SEPE show a parallel pattern of a steady rising incidence up to the 2007-09 epoch, peaking at just under 20/100,000 per year followed y a slight drop (figure 2.1).

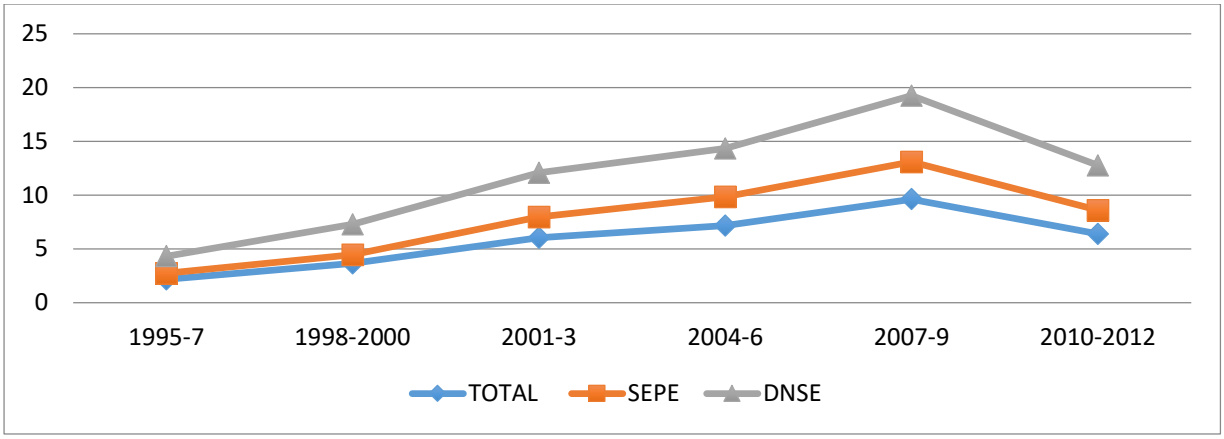

Figure 2.1 Average incidence of Status epilepticus by cause /100,000/year. Y axis is for number of cases of Status epilepticus, X axis is for time epochs at 3 yearly intervals. It can be seen that there has been steady increase in incidence of both types of status epilepticus over time till 2009. DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Baseline AED Treatment

Among 214 cases with SEPE, 170 (89%) were being prescribed AEDs at the time of admission, but the exact nature of this treatment was only known in 163 patients because of missing data. Of these, 93 (57%) were receiving only established AEDs, with 24 (15%) solely on new AEDs and 46 (28%) on a mixture of established and new AEDs. Table 2.2a shows baseline AED use in patients with SEPE before and after 2003. In later years the use of newer AEDs increases markedly. AED use was also grouped by effect on hepatic enzymes (Table 2.2b). Enzyme inducing AEDs (EIAEDs - Carbamazepine, phenytoin, phenobarbitone and primidone) were being prescribed in 104 (63.8%) at the time of admission. Valproate (figure 2.2) was the single most prescribed AED, used in 68 patients (41.7%). Phenytoin was the second most prescribed (n = 53, 32.5%) and levetiracetam the 3rd most common AED 31 (19.0%). We choose 1995-2002 and 2003-2013 epochs for comparison as most new anti-epileptic came after 2002. It's interesting to note that very small number of patients were found to be on polypharmacy, we think part of this may be due to lack of full information about AEDs in notes. Some of these patients had no paper notes especially if more than 10 years passed since death, usually paper notes are not kept after this duration. In this case only source of information was electronic notes which came into practical use after 2009.

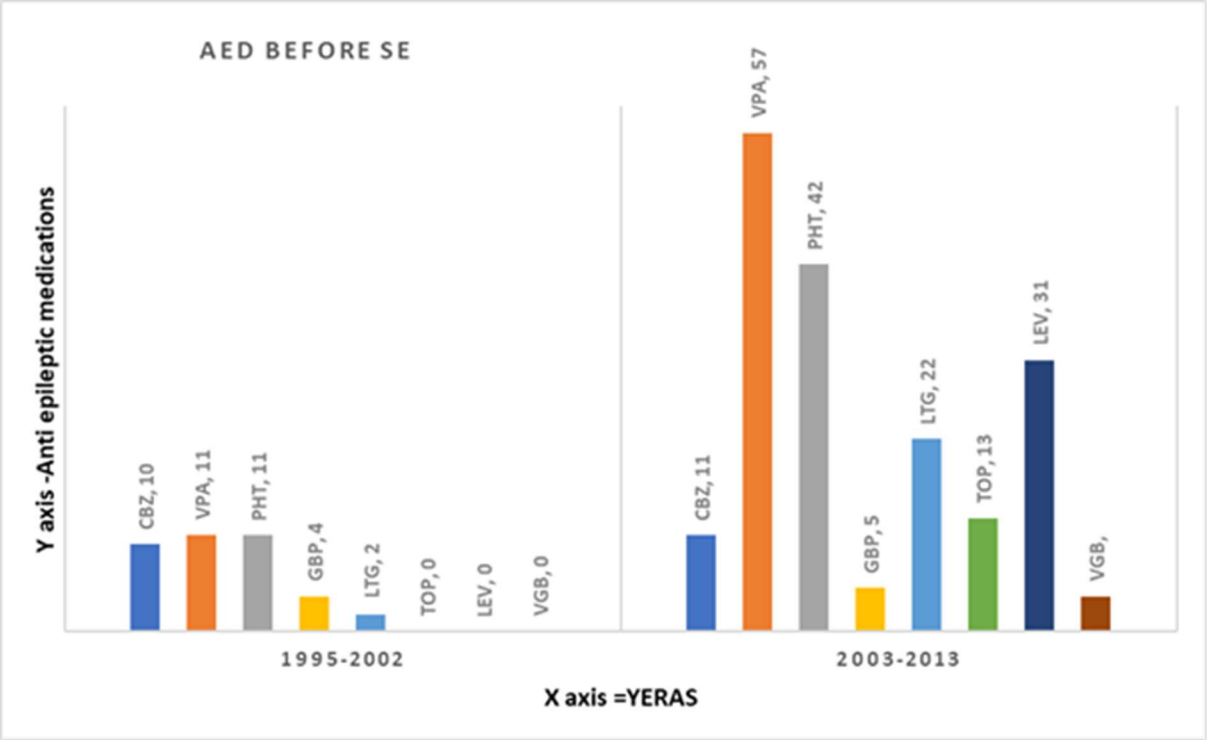

Figure 2.2 Prior to SE, base line AED's 1995-2002 n= 51 vs base line AED's 2003-2013 in Known epilepsy patients n=163.

	Polypharmacy	CBZ	VPA	PHT	GBP	LTG	TPM	LEV	VGB	Unknown
1995-2002 n=51	16	10	11	11	4	2	0	0	0	29
2003-2013 n=163	45	11	57	42	5	22	13	31	4	23

Table 2.2a– Number of patients on Individual Baseline AEDs in SEPE Group by Year of Admission CBZ=Carbamazepine, VPA=Valproate, PHT=Phenytoin, GBP=Gabapentin, LTG=Lamotrigine, TPM=Topiramate, LEV=Levetiracetam, VGB=Vigabatrin,

	1995-2002	**2003-2013**
Enzyme inducer monotherapy	12	26
Non-Enzyme Inducer monotherapy	2	30
Polytherapy including Enzyme inducing AED	8	53
Polytherapy – no Enzyme Inducing AED	0	32

Table 2.2b – AED use grouped by hepatic Enzyme Activity

Identified Causes of SE

In 600 cases out of 633 specific causes were identified, these are listed in Table 2.3a, 2.3b. As expected, SEPE and DNSE have a different spread of contributory and causative factors due to underlying difference in pathophysiology. Provocation by alcohol +/or drug misuse is significant in 54.9% of those with DNSE and 33.7% of those with SEPE. In the SEPE group a wide range of causes was found. In those with a prior diagnosis of epilepsy, the progressive nature of the epilepsy syndrome and incomplete adherence or loss of effect of AED made up the majority of the SEPE. No cause was identified in 14%. Only 6 patients with hypoxic brain injury and associated status were identified, 4 of whom had no history of prior seizures.

	DNSE (N=419) n, (%)	SEPE (N=214) n, (%)
Sole Contributor being Alcohol +/or drugs	171 (40.80%)	39 (18.22%)
Cerebrovascular	55 (13.1%)	2 (0.93%)
Alcohol +/or drugs + Other contributors	48 (11.5%)	34 (15.88%)
Metabolic (e.g renal / hepatic failure)	27 (6.5%)	3 (1.4%)
CNS Lesion	17(4.1%)	14 (6.5%)
CNS infection	17 (4.1%)	3 (1.4%)
Idiopathic	16 (3.8%)	30 (14%)
CNS inflammation	11 (2.6%)	3 (1.4%)
Post Op	10 (2.40%)	6 (2.8%)
Systemic Sepsis	9 (2.10%)	17 (7.9%)
Medication	6 1.40%)	3 (1.4%)
Cardiovascular	4 (1.0%)	2 (0.93%)
Pregnancy	3 (0.70%)	0
Electroconvulsive Therapy	2 (0.50%)	0
Neurodegenerative	2 (0.5%)	0
Progressive epilepsy syndrome	n/a	24 (11.21%)
Poor adherence or loss of drug levels	n/a	22 (10.28%)
No Information Available	21 (5.0%)	12 (5.6%)
	419	214

Table 2.3a - Causes of Status Epilepticus 633 cases

DNSE = De Novo Status Epilepticus, SEPE = Status Epilepticus with Previous Epilepsy

Cause of DNSE	**Cause of SEPE**
Alcohol/ drugs (54.9%)	Alcohol /drugs (33.7%)
ICH, SDH, HI (13.1%)	Poor adherence AEDs (11.5%)
Metabolic (6.5%)	Progressive epilepsy syndrome (11.1%)
No Information Available (5.0%)	Idiopathic (14%)

Table 2.3b Top 4 causes Cause of SE in DNSE and SEPE

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Outcomes of RSE – Admission to ITU and Total Hospital Stay

The median duration of stay in ITU (i.e., time to discharge or death) was similar in both groups, with more than half staying in for 2 days or less (Table 2.4). While the median stay is similar across SEPE and DNSE groups, 10.5% and 13.8% of those with DNSE and SEPE respectively had an ITU admission lasting longer than 7 days or more. The longest-term stays arose only among those with DNSE, with 0.5% requiring ITU admission for longer than 6 weeks. Median duration of total in-patient hospital stay was slightly longer in DNSE (10 versus 6 days), which was also associated with the longest stays.

ITU Stay (days)	**Total n=633**	**DNSE n= 419**	**SEPE n=214**
Median **(days)**	1.0	1.0	2.0
Mean **(days)**	3.6	3.7	3.7
Range **(days)**	0.5-165	0.5-165	0.5-26
1-7 days n (%)	556 (87.8%)	370 (88.3%)	186 (86,2%)
>7 days n (%)	72 (11.4%)	44 (10.5%)	28 (13.8%)
>28 days n (%)	3 (0.5%)	3 (0.7%)	0
>42 days n (%)	2 (0.3%)	2 (0.5%)	0
Hospital Stay (days)			
Median **(days)**	8.0	10.0	6.0

Mean **(days)**	21.4	28.0	8.7
Range **(days)**	0.5-1497	0.5-1497	0.5-30
1-7 days n (%)	146 (23.1%)	23 (5.5%)	123 (57.5%)
>7 days n (%)	330 (52%)	240 (57.3%)	90 (42%)
>28 days n (%)	92 (14.5%)	91 (21.7%)	1 (0.5%)
>42 days n (%)	65 (10.3%)	65 (15.5%)	0

Table 2.4 – Duration of Hospital and ITU Admission for SE

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Outcomes of RSE – Death, Residual Neurological Deficit, or Full Recovery

As can be seen in Table 2.5a and 2.5b, the admission mortality rate was higher in DNSE than SEPE (13.8% versus 7.5%) (p = 0.0195, 95% CI 1%–11.59%). At 1 year, 5 years and 10 years post admission, this significant difference in mortality had persisted, (Figure 2.3). Where information was available (Table 2.6), we looked at the discharge status, showing incidence of full recovery in those with DNSE (19.98%) and SEPE (50%). Among those surviving the admission, the percentages with and without neurological deficit were significantly different in DNSE and SEPE. Half of SEPE group recovered without deficit whereas less then quarter of DNSE group recovered without deficit. Recovery with deficit was more marked in DNSE group with almost 30% patient compared to 19 % in SEPE group.

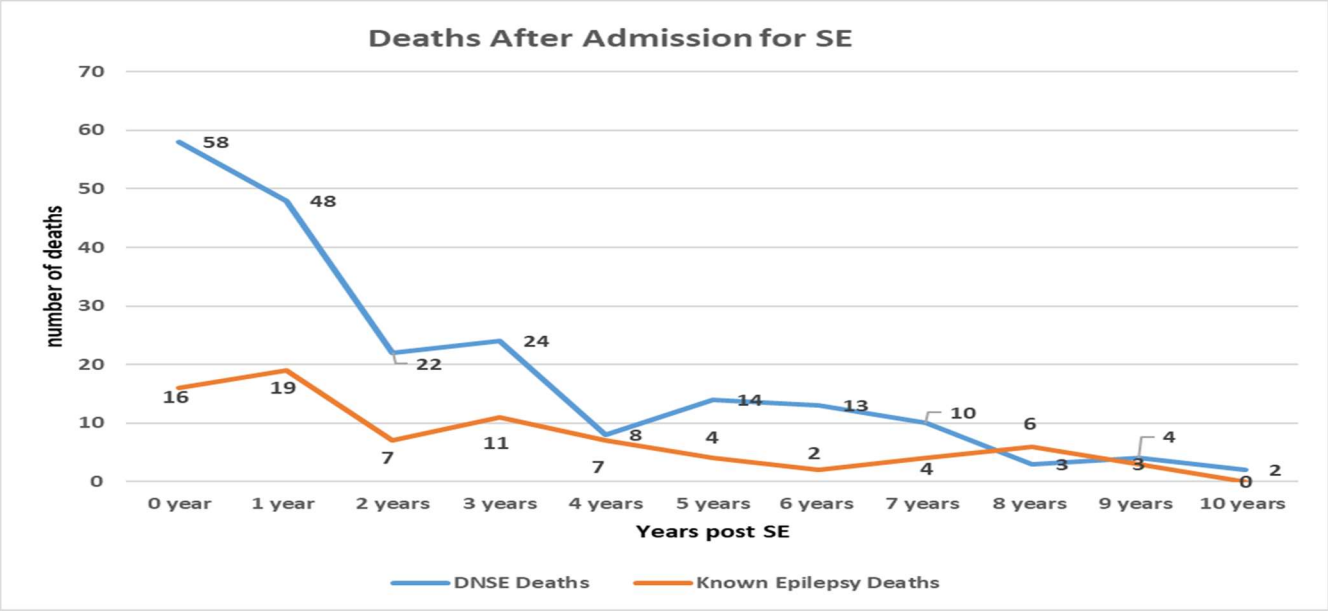

Figure 2.3 Time of Death after Admission for SE

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

	Total Cohort N= 633	**DNSE N= 419**	**SEPE N=214**	**95% CI for Difference between DNSE and SEPE**
Total Number of Deaths	303 (47.8%)	220 (52.5%)	83(38.7%)	
Deaths During Index admission	74 (11.69%)	58 (13.8%)	16(7.47%)	1%-11.6%
Deaths within 1 year of admission for SE	141 (22.0%)	106(25%)	35 (16.0%)	2.1%-15.8%
Deaths within 5 years of admission for SE	236 (37.3%)	174 (41.5%)	62 (27.60%)	5%-21%
Deaths within 10 years of admission for SE	285 (45.0%)	206 (49.0%)	79 (37.0%)	4.1%-20.5%

Table 2.5a - Cumulative Mortality Over 10 years

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Years	**DNSE Deaths**	**SEPE Deaths**
0 year	58	16
1 years	48	19
2 years	22	7
3 years	24	11
4 years	8	7
5 years	14	4
6 years	13	2
7 years	10	4
8 years	3	6
9 years	4	3
10 years	2	0

Table 2.5b - Year of Death after SE Admission

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

	Total Group (n=633)	DNSE (n=419)	SEPE (n=214)
Death during admission	74(11.69%)	58 (13.84%)	16 (7.47%)
Recovery with Neurological Deficit	232 (36.65%)	124 (29.59%)	41 (19%)
Full recovery no neurological deficit	124 (19.58%)	83 (19.98%)	107(50%)
No information	204 (32.22%)	154 (36.75%)	50 (23.36%)

Table 2.6 - Outcome after SE in DNSE and SEPE

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Outcomes of RSE - risk of subsequent epilepsy

One hundred and thirty-four patients with DNSE (37%) were started on long term AEDs and could be inferred as having developed epilepsy. Where alcohol and/or drug misuse was a sole single cause of SE, 48/ 171 (28%) of patients ended up being on long term AED. Eight of 16 patients with idiopathic DNSE remained on long-term AED treatment (Table 2.1b).

Causes of mortality Refractory status epilepticus

Total deaths number was 206 over 4 years in DNSE group. Alcohol and death related causes made 34.46% (n=71) of total deaths over 4 years in this group. 2nd most common cause was malignancy 12% (n=25) and 10.67% (n=22) patients had death due to CVD coming up as 3rd most common cause. In SEPE group total death count over 4 year was 78. Most common cause of death in this group was seizure related complication 73% (n=29), 2nd most common cause was alcohol and drug related complication 12.8% (n=10) and 3rd most common cause of mortality was sepsis 10.25% (n=8), (Table 2.8). Tables 2.7a, 2.7b and 2.8 show the contribution of addiction and abuse to deaths in both groups. At each time point, alcohol and drugs comprise the largest contributor to mortality. In those with SEPE (Table 2.7b) alcohol and drug use comprise a less striking contributor to mortality. The causes of the two groups of RSE are predictably different: in SEPE, the better outcome may signal the presence of a reversible cause of epilepsy exacerbation. In DNSE, our data suggests that underlying addiction or abuse issues are not a simple reversible cause or exacerbation but are in fact a negative prognostic marker for long term mortality. In the DNSE group 28% of all deaths within 1 year were related to alcohol and drug-related complications, increasing to 34.4% of all deaths over 10 years. In the SEPE group, 1-year mortality was 20.2%, with 31.6% dying because of seizures over 10 years. The rate of full neurological recovery was more in SEPE group compared to DNSE group.

Cause of death same admission (n=58)		**Cause of death 1-year post SE (n=48)**		**Cause of death 2-3-year post SE (n=46)**		**Cause of death 4-5-year post SE (n=22)**		**Cause of death 5-10-year post SE (n=32)**	
Alcohol & drugs	16	Alcohol & drugs	14	Alcohol & drugs	17	Alcohol & drugs	10	Alcohol & drugs	14
CVD, ICH	9	Malignancy	8	Sepsis	8	Sepsis	4	Malignancy	5
Encephalitis	7	Sepsis	6	Malignancy	8	Malignancy	4	CVS	3
Seizure	7	CVD	6	Seizure	4	PVD	1	CVD	3
CVS	7	Seizure	4	CVD, ICH	4	CVS	1	Metabolic	2

Table 2.7a - Main Causes of death in each epoch post admission in DNSE number of deaths=206

DNSE = De Novo Status

Cause of death same admission (n=16)		**Cause of death 1-year post SE (n=18)**		**Cause of death 2-3-year post SE (n=18)**		**Cause of death 4-5-year post SE (n=9)**		**Cause of death 5-10-year post SE (n=17)**	
Seizures	7	Seizures	9	Seizures	9	Alcohol and drugs	3	CVS	4
Alcohol and drugs	3	Sepsis	3	CVD	4	Progressive degenerative disease	2	Seizures	4
Sepsis	2	CVD	2	Malignancy	2	Seizures	2	Sepsis	3
CNS structural problem	1	Alcohol and drugs	2	Alcohol and drugs	2	CVD, ICH	1	Malignancy	3
Anoxic brain injury	1	Progressive neurological problem	1	Suicide	1	Metabolic	1	Unexplained	1

Table 2.7b - SEPE Group - Main Causes of death in each epoch post-admission number od deaths=78

SEPE = Status Epilepticus with Previous Epilepsy

Cause of death	DNSE 206 deaths in 4 years	SEPE 78 deaths in 4 years
1	Alcohol and death related 34.46%	seizure related complication 40%
2	Malignancy 12%	alcohol and drug related complication 12.8%
3	Cerebrovascular disease 10.67%	sepsis 10.25%

Table 2.8 Top 3 Causes of mortality over 4 years in main cohort

DNSE = De Novo Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy

Discussion

This is believed to be one of the largest studies of incidence and outcome in refractory SE [82,107, 108]. The longitudinal incidence of RSE in a single region spanning 6 hospitals over a period of almost two decades has been analysed. The criteria for recruitment ensures that these cases are at least refractory SE with 303 patients (48%) fulfilling the criteria for Super Refractory SE. The morphology of SE is similar that seen in other studies, but the focus on ITU treatment ensures that there is a preponderance of convulsive SE. Unlike other series, we did not exclude patients with primary hypoxic brain injury. The small numbers (n = 6) suggest that other cases may have been coded differently for general ITU admission, and that this means the recruitment is comparable to other series of SE.

Other series [109,110] have found a greater proportion of cases with NCSE. Reviews [109,110] acknowledge the difficulty in diagnosis NCSE where, as in the date and setting of this series, prolonged EEG monitoring is less available. The limitations of the study lie in examining patient records. Reliable coding is difficult to guarantee, however this limitation may lead to reduced sensitivity rather than a reduction in specificity. Such a limitation may explain some of the variability in the incidence across the epochs. Such data collection is time consuming and relies on accurate coding and case notification by local registers in each unit. At least some of the limitations of this method of data collection were ameliorated by the later adoption of a regional electronic system holding medical records across all hospitals in the region. Longitudinal incidence of SE across the region has shown a general increase in keeping with the increased prominence and reliance on the SIGN guidance in the late 20th Century and early

21st Century which meant early recognition and right coding of cases, according to definition of SE. This possibly brought consistency in identifying and treating cases. The later dip in incidence from 2010 remains difficult to explain. Groups have been delineated based on a prior history of seizures and think that the approach has been validated by demonstration of the differences between the groups in causation and outcome. The male preponderance is common to both diagnostic groups which appears unusual in studies of SE [108,112]. The study by Strzelczyk et al 2017 [108] made no mention of the incidence of addiction or substance abuse in its cohort. In Glasgow over the period 1995–2013 there was an increasing incidence of RSE, involving both DNSE and SEPE. The fact that DNSE also increases avoids any suggestion that the increase in SEPE is caused by a decreased effectiveness of newer AEDs. An increasing incidence has also been shown in studies of SE in other populations [47,113,114] and it has been postulated that promulgation of guidelines and protocols have led an increasing identification and treatment that also the decreasing mortality from SE in England and Wales [110].

While such increasing recognition of the need for emergency treatment of SE may be widespread, it may be especially focussed in Scotland with the adoption of national guidelines – the first SIGN guidance in 1997, with updates coming in 2003 and 2015 (SIGN 1997, SIGN 2003, SIGN 2015) emphasising the need for emergency care. Studies of SE [112,115–70] have suggested an annual incidence of 17–20/ 100,000 which is similar to the peaking incidence of RSE of all causes in our population. In our study the incidence of RSE is in keeping with other geographical studies of RSE [82,118]. Our data would suggest a similar incidence of SRSE, at 2.7/100,000, to that described by Kantanen (2017) [82]. The pattern of SE noted in our population was similar to other studies of adults [112] with the majority of cases comprising convulsive SE. In those with SEPE, there was no emergent pattern of AED use when looking at individual AEDs or when grouping by effect on hepatic enzymes. The increasing prior use of newer AEDs throughout the series dates was unsurprising and is in keeping with the contemporaneous change in prescribing pattern across the country. We acknowledge that other countries may have seen a more rapid uptake of the newer drugs, but the prescribing of AEDs in the UK is heavily influenced by the national guidelines produced via SIGN and NICE. We acknowledge that there are emergent data on newer drugs such as levetiracetam, topiramate, and lacosamide in treating SE. In our series ITU treatment of SE utilised the older AEDs more than other series which reflects the period under study and the reliance on national guidelines to dictate treatment plans.

Mortality of refractory status epilepticus

As can be seen in Table 2.5a, 2.5b and Table 2.6, the admission mortality rate was higher in DNSE than SEPE (13.8% versus 7.5%). The other large study of RSE suggested an admission mortality of around 15% across all cases of RSE [108]. One-year post admission, this difference in mortality rates in DNSE and SEPE was maintained, but expanded in subsequent years, such that 5 years after admission 41.5% of DNSE had died compared to 27.6% of those with SEPE. It may have been anticipated that refractory SEPE would respond better than those with DNSE, since many of these would be related to reversible causes. By one-year post-admission, mortality rates in our cohort are considerable, exceeding the 25% shown by Kantanen et al 2017 [82] Most of the RSE-associated mortality arises in the first few years. Mortality from SEPE and DNSE was significant during admission, being twice as common in the former group. The difference in mortality expanded over the next 5 years, such that 5 years after admission 41.5% of DNSE had died compared to 27.6% of those with SEPE.

Causes of RSE-Associated mortality

The prognosis of RSE is thought to depend on duration of seizures and the underlying pathology [70]. In our study, addiction and substance abuse issues are associated with an increased admission and subsequent mortality in both DNSE and SEPE. It may have been presumed that simple avoidance of any risk factor for directly provoked seizures (i.e., alcohol and / or drugs) would reduce mortality, but our data does not reflect this.

In this study was saw that alcohol and death related causes made 34.46% of total deaths over 4 years in DNSE group. In SEPE group most common cause of death was seizure related complications 73% but even in this group 2nd most common cause was alcohol and drug related complication 12.8%. Tables 2.7a, 2.7b and 2.8 show the contribution of addiction and abuse to deaths in the group with DNSE and SEPE. This data suggests that underlying addiction or abuse issues are not a simple reversible cause or exacerbation but are in fact a negative prognostic marker for long term mortality. In the DNSE group 28% of all deaths within 1 year were related to alcohol and drug-related complications, increasing to 34.4% of all deaths over 10 years. In the SEPE group, 1-year mortality was 20.2%, with 31.6% dying because of seizures over 10 years. This data shows significance relation between cause of SE and short plus long-term mortality.

Subsequent seizures

In patients with DNSE, this index seizure was followed by a need for AEDs in 37%, a level of recurrence which would confirm that an index episode of SE or RSE is no more liable to lead to a recurrence and need for AEDs than a single shorter seizure [116].

Neurological disability

Previous studies of SE among adults [117] have suggested neurological deterioration in only 3.3% among those surviving at least 30 days. Neurological deterioration in children with SE appears to be higher [70]. While the rates of neurological deficit are raised in both DNSE and SEPE but rate of recovery was much higher in SEPE group compared to DNSE which probably indicates poor outcomes for symptomatic DNSE and outcomes most likely reflects prognosis from underlying provocation causes ie drugs /alcohol complications, malignancy and strokes etc.

Conclusion

The separation of DNSE from SEPE is helpful in beginning to delineate prognosis, the need for further investigation, and the role of ineffective or absent AEDs in causation. The mortality rate of RSE is high, and importantly it represents a call to action for the medical community. The greater admission mortality with DNSE, which persists in the years following discharge should confirm that SE with a background of addiction or abuse should not simply be considered as a ‘provoked seizure’ and treated with acute support and encouragement to abstinence. Instead, it suggests that a presentation with DNSE is a sign of a system in peril. While public health measures are vital in reducing the disease burden of triggers such as alcohol and addiction, each episode should prompt a chain of multispecialty care in order to address this recurring and persisting public health disaster, which comprises of too many personal tragedies. It was noted in our study that relatively small number of patients were on polytherapy at the time they developed SE. One possible explanation for this can be relatively stable epilepsy in past with break through seizure leading to ICU admission for these patients, it is known that 25% of SE occur in people who have epilepsy and at some point in lives, 15% of people with epilepsy will experience an episode of SE in lifetime. It is not true that SE happens only to multidrug resistant epilepsy patients although they are more likely to have it.

Summary of findings

This study looks at the causes, outcomes, and regional incidence of adults with Refractory Status Epilepticus admitted to ITU over 18 years in Glasgow

RSE total cohort of 633 patients.

1.Provocation by alcohol +/or drug misuse was significant in 54.9% of those with DNSE and33.7% of those with SEPE.

2.The admission mortality rate was higher in DNSE than SEPE (13.8% versus 7.5%).

3.One-year post admission, this difference in mortality rates in DNSE and SEPE was maintained, but expanded in subsequent years, such that 5 years after admission 41.5% of DNSE had died compared to 27.6% of those with SEPE.

4.On subgroup analysis, total death number was 206 over 4 years in DNSE group. Alcohol and drug related causes made 34.46% (n=71) of total deaths over 4 years in this group. 2nd most common cause was malignancy 12% (n=25), 10.67% (n=22) patients had death due to CVD coming up as 3rd most common cause.

5. In SEPE group total death count over 4 year was 78. Most common cause of death in this group was seizure related complication 73% (n=29), 2nd most common cause was alcohol and drug related complication 12.8% (n=10) and 3rd most common cause of mortality was sepsis 10.25% (n=8).

6. At each time point, alcohol and drugs comprise the largest contributor to mortality in both groups but in those with SEPE alcohol and drug use comprise a less striking contributor to mortality.

7. In the DNSE group 28% of all deaths within 1 year were related to alcohol and drug-related complications, increasing to 34.4% of all deaths over 10 years. In the SEPE group, 1-year mortality was 20.2%, with 31.6% dying because of seizures over 10 years.

8. Where information was available, we looked at the discharge status, showing incidence of full recovery in those with DNSE (19.98%) and SEPE (50%).

9. The rate of full neurological recovery was more in SEPE group compared to DNSE group.

10. Yearly death incidence in both groups clearly showing more deaths in RDNSE group and most death within 1-3 years after SE.

Chapter 4

Subgroup analysis for Supra Refractory Status Epilepticus (ITU stay 2-7 days).

Introduction

Patients who do not respond to standard treatment regimens for status epilepticus are considered to be in RSE (119). For the purposes of these guidelines, patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) will be considered refractory. Introduced during the London-Innsbruck Colloquium on status epilepticus in 2011, the term "super-refractory status epilepticus" refers to SE of more than 24 h duration despite appropriately dosed treatment with anaesthetic agents (78). In our study on review of clinical notes we identified a total of 231 admissions to ITU with supra refractory status epilepticus (ITU stay 2-7 days). Super-refractory status epilepticus is not uncommonly encountered in neurointensive care, but its exact frequency is not known. The retrospective studies have shown that 12–43% of the cases with status epilepticus become refractory (24,25,27,120). In the series of 35 patients (121), seven (20%) recurred within 5 days of tapering the anaesthetic drug and in all other studies at least 50% of those requiring anaesthesia will become super-refractory. From these published findings, it can be estimated that ∼15% of all the cases with status epilepticus admitted to hospital will become super-refractory (78). It has been suggested that RSE has a higher short-term and long-term mortality than SE, although this is not invariably replicated. The mortality rates of RSE and SRSE range from 15% to 54% and thus exceed the mortality of non-refractory SE (11–37%) by far. The increased 1-year mortality in RSE has been associated with older age, or poorer neurological status on discharge from hospital (82). It is shown in studies that there is progressive neuronal damage as time passes and SE becomes more drug resistant (83,84,85,86). The work done by Meldrum suggests that 82 min or more of ongoing seizure activity in baboons can cause irreversible neuronal injury (61). In the most recent study, 24.5% of patients with RSE, 37.9% of patients with SRSE, but only 9.8% of patients with non-refractory SE died (87). The high variability of the reported mortality rates is explained by the significant heterogeneity of the patient populations studied. A study published in 2017 looked at long term outcomes of RSE. During 1-year follow-up, nearly 50% of the ICU-treated RSE patients recovered to baseline function, whereas 30% showed new

functional defects and 20% died. SRSE does not have a necessarily poorer outcome. The outcome was worse in older patients and in patients with progressive or fatal aetiologies (88). Super-refractory status epilepticus is usually due to a severe brain insult (e.g., trauma, infection and stroke), and the cause is readily apparent from the history and neuroimaging. However, there are also a range of less common causes and a literature review of these identified 188 causes, which in the great majority of cases could be assigned to one of five categories: immunological disorders; mitochondrial disorders; uncommon infectious diseases; drugs or toxins; and uncommon genetic diseases (112). The mortality rate of status epilepticus increases the longer the episode continues (70), with death being due to a range of complications both status epilepticus and its treatment. These complications include hypotension, cardiorespiratory collapse and failure, hepatic failure, renal failure, acute hypersensitivity, and allergic reactions, disseminated intravascular coagulation and disorders of bleeding, infection, rhabdomyolysis, ileus and gastrointestinal disturbance and intensive treatment unit neuropathy.

Results

A total of 231 admissions to ITU with supra refractory status epilepticus (ITU stay 2-7 days) using relevant diagnostic codes was identified. Eighty-four (36.36%) patients with supra refractory SE had experienced prior seizures or a diagnosis of epilepsy, these were labelled Supra refractory status Epilepticus with Previous Epilepsy (SRSEPE), while 147 (63.63%) patients were admitted to an ITU for an index seizure leading to supra refractory status, we named them Supra refractory De Novo Status Epilepticus (SRDNSE). The nature of the SE was assessed (Table 3.1, 3.2) 231 (92%) being generalized tonic colonic SE, and 10 (0.4%) were focal SE. 7 cases (3%) were eventually thought to be non-convulsive SE. In 1 case (0.4%) no information on type of SE was available.

Demographic Information

The demographic details of the whole cohort and subgroups are shown in Table 3.1 and 3.2. Gender distributions were similar in both SRDNSE and SRSEPE groups. There was a male preponderance in both groups, which may reflect the incidence of causative factors seen in subsequent tables. Patients in known epilepsy group were slightly younger with mean age 45.54 compared to De novo group with mean age 53. The incidence of alcohol-related problems was higher in SRDNSE than among SREPE patients. Analysis of addiction issues and other risk

factors (Table 3.3) show increased rates related solely to addiction and abuse in the group with SRDNSE compared to SRSEPE (43.53% versus 33.33%). Out of total cohort of 231 patients 92 (39.82%) has some sort of direct or indirect contribution from alcohol and drugs as causative factor for status epilepticus.

	Total n=231	SRDNSE n= 147 (63.63%)	SRSEPE n= 84 (36.36%)
Age (years) Mean, Range	 53.02 17-83	 53.03 17-83	 45.54 18-89
Female: Male	93:138	60:87	33:51
Previous ITU with neurological condition	41 (17.74%)	12 (8.16%)	29 (34.52%)
Days in hospital Mean, Median (Range) Interquartile range	 20.71 13 (2-200) 17	 24.52, 15 (2-200) 20.5	 14.06, 11 (2-155) 12.25
Days in ITU Mean, Median (Range) Interquartile range	 3.39 3 (2-7) 2	 3.49 3 (2-7) 3	 3.22 3 (2-7) 2
Number of Deaths over 10 years from total cohort of 231	121(52.38%)	87 (59.1%)	34(40.47%)
Deaths during same admission	30(12.98%)	22(14.96%)	8 (9.5%)
Deaths within 1-year post Admission	54 (23.37%)	36 (24.48%)	18 (21.42%)

Table 3.1: Demographic Data supra refractory status epilepticus cases**.** Patient staying in ITU between 2 and 7 days. Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

Type of status:	Total n=231	SRDNSE n=147	SREPE n=84
Focal	10 (4.3%)	6 (4%)	4 (4.7%)
GTCS	213 (92%)	136 (92.5%)	77 (91.6%)
Not Known	1 (0.4%)	1 (0.68%)	0
NCSE	7 (3%)	4 (27.2%)	3 (3.5%)
Long Term AED Treatment among survivors on discharge (N on AED / N of survivors)	110 (47.61%)	46 (31.29%)	65 (77.38%)

Table 3.2 Status Classification and Subsequent Use of AED

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

Identified Causes of SRSE

Where specific causes were identified, these are listed in Table 3.3a, 3.3b and Figure 3.1. As expected, SRSEPE and SRDNSE have a different spread of contributory and causative factors. Provocation by alcohol +/or drug misuse with or without other associated factors (metabolic, infective or trauma) is significant in 43.53% of those with SRDNSE and 33.33% of those with SRSEPE. 26% cases out of total cohort of 231 have substance abuse as only causative factor, with majority from SDNSE group 32.65%. In the SRSEPE group a wide range of causes was found. In those with a prior diagnosis of epilepsy, the progressive nature of the epilepsy syndrome and incomplete adherence or loss of effect of AED made up the majority of the SRSEPE. No cause was identified in 6%.

	SRDNSE N=147	**SRSEPE N=84**
Alcohol and drugs in isolation or with other associated factors	64 (43.53%)	28 (33.33%)
CVD, ICH, SDH, SAH, HI	23 (15.64%)	3 (3.5%)
Metabolic	14 (9.5%)	1 (1.19%)
Encephalitis	10 (6.8%)	2 (2.38%)
No information	8 (5.44%)	6 (7.14%)
Post op	6 (4.08%)	2 (2.3%)
CNS structural problem	4 (2.72%)	1 (1.19%)
Idiopathic	4 (2.72%)	11 (13.09%)
Malignancy	4 (2.72%)	2 (2.3%)
Sepsis	4 (2.72%)	6 (7.14%)
CNS inflammation	2 (1.36%)	0
CVS	1 (0.68%)	0
Medication	1 (0.68%)	0
Neuro degenerative	1 (0.68%)	2 (2.3%)
Pregnancy	1 (0.68%)	0
AED's issues, non-compliance	0	10 (11.90%)
Poorly controlled epilepsy and progressive	0	10 (11.90%)

Table 3.3 Causes of supra refractory Status Epilepticus

Supra refractory SE with Prior Epilepsy (SRSEPE).

Supra refractory De Novo Status Epilepticus (SRDNSE)

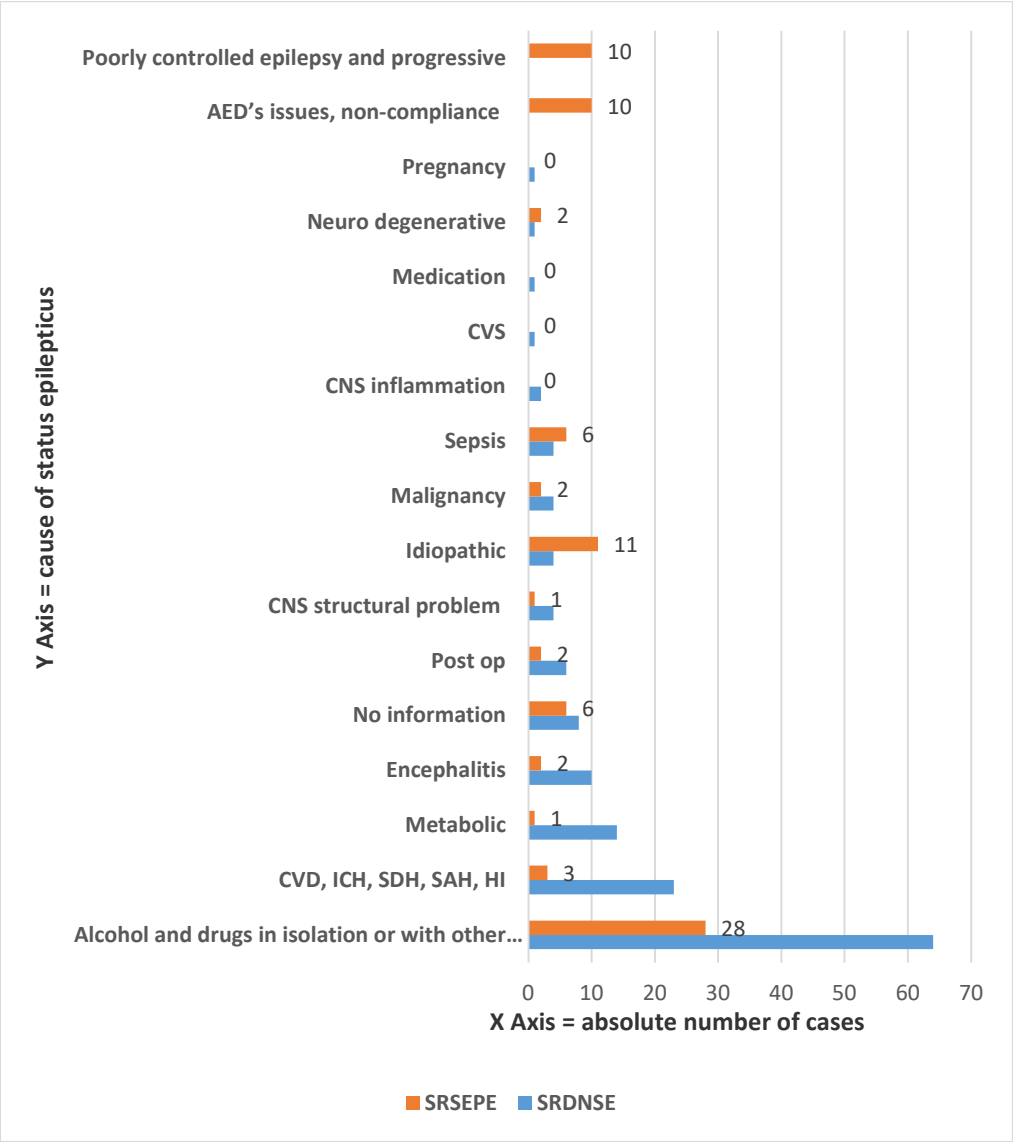

Figure 3.1 a Causes of supra refractory Status Epilepticus

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

Cause of SRDNSE	Cause of SRSEPE
Alcohol and drugs (43.5%)	Alcohol and drugs (33.33%)
CVD, ICH, SDH, SAH, HI (15.6%)	Idiopathic (13 %)
Metabolic (9.5%)	AEDs issue (11.90%)
Encephalitis (6.8%)	Poorly controlled epilepsy (11.90%)

Table 3.3b. Top 4 causes Cause of SE from cohort of 231 Supra refractory cases

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

Outcomes of SRSE – Admission to ITU and Total Hospital Stay

The median duration of stay was 3 days in ITU (i.e., time to discharge or death) it was similar in both groups. Median duration of total in-patient hospital stay was slightly longer in SRDNSE (15 versus 11 days). Range of hospital stay lasted from 2 to 200 days in SRDNSE group compared to 2 to 155 in SRSEPE group. (Table 3.1)

Outcomes of SRSE – Death, Residual Neurological Deficit, or Full Recovery

Outcome data was available in 73% of case (n=168). Table 3.4, Table 3.5, and figure 3.2 the admission mortality rate was higher in SRDNSE than SRSEPE (14.96% versus 9.5%). At 1 year, 5 years and 10 years post-admission, this significant difference in mortality had persisted, (Table 3.4, 3.5, Figure 3.2). Where information was available (Table 3.6, Figure 3.3), we looked at the discharge status, showing incidence of full recovery in those with SRDNSE (29.93%) and SREPE (48.8%). Recovery with neurological deficit and incidence of death during same admission are more in SRDNSE group.

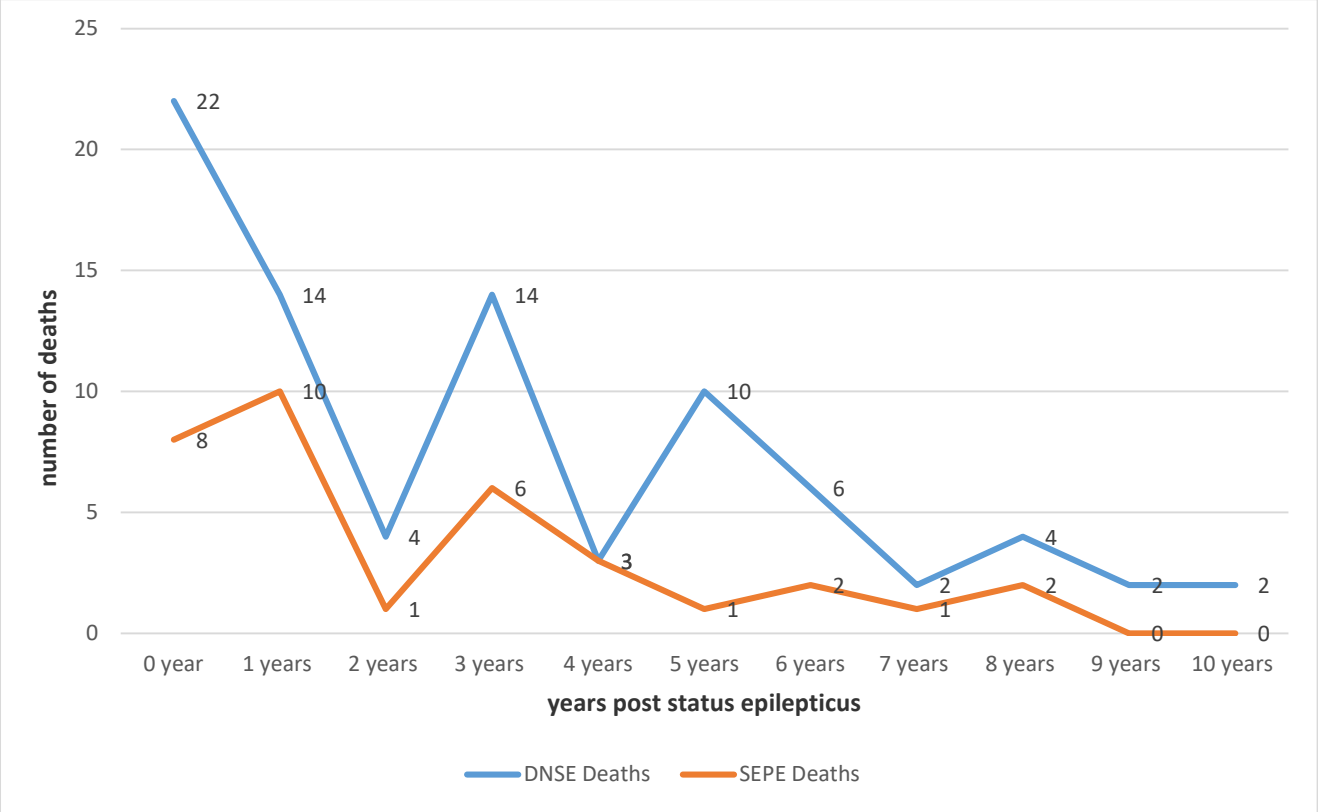

Figure 3.2 Number of deaths over 10 years in both groups

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

	Total Cohort 231	**SRDNSE 147**	**SRSEPE 84**
Total Number of Deaths	121(52.38%)	87 (59.1%)	34(40.47%)
Deaths same admission	30(12.98%)	22(14.96%)	8 (9.5%)
Deaths at 1-year post SE	54 (23.37%)	36 (24.48%)	18 (21.42%)
Deaths at 5-year post SE	96 (41.55%)	67 (45.57%)	29 (34.52%)
Deaths at 10 -year post SE	118 (51.08%)	84 (57.14%)	34 (40.47%)

Table 3.4- Cumulative Mortality Over 10 years

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status

Years		**SRDNSE Deaths =83**	**SREPE Deaths =34**
0 year		22	8
1 years		14	10
2 years		4	1
3 years		14	6
4 years		3	3
5 years		10	1
6 years		6	2
7 years		2	1
8 years		4	2
9 years		2	0
10 years		2	0

Table 3.5- Year of Death after SE Admission absolute numbers

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

	Total Group (n=231)	SRDNSE (n=147)	SRSEPE (n=84)
Death during admission	30 (12.98 %)	22 (14.96%)	8 (9.52%)
Recovery with Neurological Deficit	53 (22.94%)	35 (23.80%)	18 (21.42%)
Full recovery no neurological deficit	85 (36.79%)	44 (29.93%)	41 (48.8%)
No information	63 (27.27%)	46 (31.29%)	17 (20.23%)

Table 3.6 - Outcome after SRSE in SRDNSE and SRSEPE

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

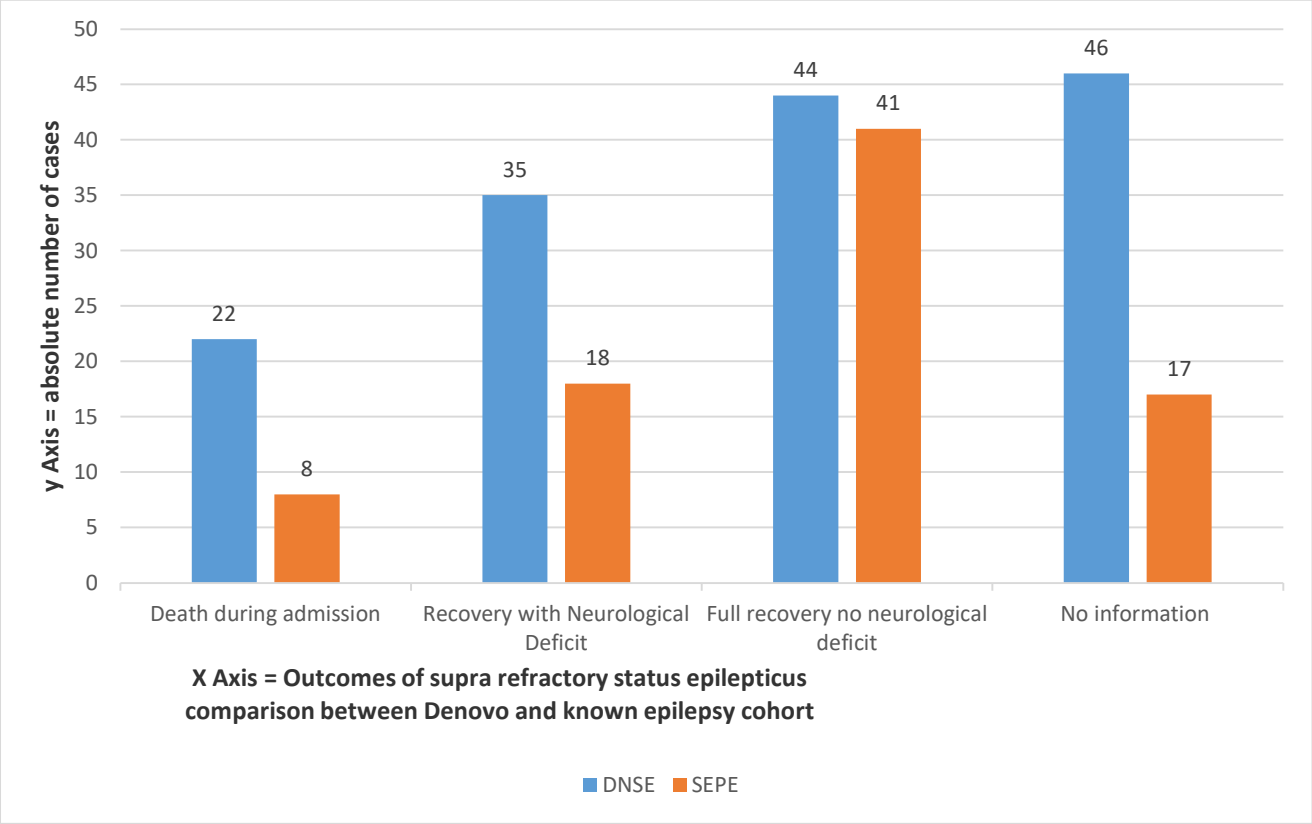

Figure 3.3 Outcomes comparison of 2 groups

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

Outcomes of SRSE - Risk of Subsequent Epilepsy

Forty-six patients with SRDNSE (31.29%) were started on long term AEDs and could be inferred as having developed epilepsy this is compared to sixty-five (77.38%) in SRSEPE. (Table 3.2)

Causes of immediate and long-term mortality

Addiction and substance abuse issues are associated with an increased subsequent mortality in both SRDNSE and SRSEPE. Table 3.7, 3.8 show the contribution of addiction and abuse to deaths in the group with SRDNSE and SRSEPE. Table 3.9 shows comparison of top 3 causes of morality over 4 years post status epilepticus.

Cause of death same admission (n=22)	**N**	**Cause of death 1-year post SE (n=14)**	**N**	**Cause of death 2-year post SE (n=4)**	**N**	**Cause of death 3-year post SE (n=14)**	**N**	**Cause of death 4-year post SE (n=3)**	**N**
Encephalitis	5	Alcohol and drugs	4	Alcohol and drug	2	CVS	4	Alcohol and drugs	1
Seizure	4	Malignancy	2	Seizure	1	Alcohol and drugs	4	Malignancy	2
CVS	4	CVD	2	Malignancy	1	Sepsis	3		
Sepsis	2	SDH	1			CVD	1		
CVD	2	Neuro-degenerative	1			Malignancy	1		
Alcohol and drug	2	Seizure	1			PVD	1		
IIH	1	Sepsis	1						
Malignancy	1	PVD	1						
Anoxic brain injury	1	Spinal problem	1						

Table 3.7 - Main causes of death in each Epoch post-admission in SRDNSE 57 in total

CVD= cerebrovascular disease, ICH= intracerebral haemorrhage, CVS= cardiovascular, PVD= peripheral vascular disease.

Cause of death same admission (n=8)	**N**	**Cause of death 1-year post SE (n=10)**	**N**	**Cause of death 2-year post SE (n=1)**	**N**	**Cause of death 3-year post SE (n=6)**	**N**	**Cause of death 4-year post SE (n=3)**	**N**
Seizure	4	Seizure	6	Malignancy	1	Seizure	4	Seizure	2
Sepsis	2	Sepsis	1			Malignancy	1	Alcohol and drugs	1
Neuro-degenerative	1	Neuro-degenerative	1			Alcohol	1		
Malignancy	1	Alcohol and drugs	1						
		Anoxic brain injury	1						

Table 3.8 Main causes of death in each Epoch post-admission in SRSEPE 28 deaths

CVD= cerebrovascular disease, ICH= intracerebral haemorrhage, CVS= cardiovascular, PVD= peripheral vascular disease.

Cause of death	**SRDNSE** **57 deaths in 4 years**	**SRSEPE** **28 deaths in 4 years**
1	Alcohol and drugs (22.8%)	Seizures (57%)
2	CVS (14%)	Sepsis (10.7%)
3	Seizures (10.5 %)	Malignancy (10.7%) Alcohol and drugs (10.7%)

Table 3.9- Causes of mortality over 4 years in Supra refractory cohort

Supra refractory SE with Prior Epilepsy (SRSEPE). Supra refractory De Novo Status Epilepticus (SRDNSE)

Discussion

An assessment of the outcomes and causes of SRSE in a single region spanning 6 hospitals over a period of almost two decades was performed. Cases selected were supra refractory SE by defined as a duration of ITU stay due to SE was between 2-7 days. 231 patients out of 633

identified patients of SE fulfilled the criteria for Super Refractory SE. We separated out these 231 cases in 2 groups depending on a prior history of seizures and think that the approach has been validated by demonstration of the differences between the groups in causation and outcome. The male preponderance is common to both groups which appears unusual in studies of SE (108,112).

Mortality of Supra refractory Status Epilepticus

Super-refractory status epilepticus is a serious condition. The mortality rate is substantial, reported in various series between 30 and 50% in ICU setting (70,117) but very few studies have reviewed long term outcomes in SRSE. Shovron published (57) an article in 2012, which focused on outcome assessment on the immediate control of seizures as the primary endpoint of each therapy. In total of 596 cases, the long-term outcome could also be ascertained. Overall, 35% of the patients died in this review study with sever neurological deficit in 13%, mild neurological deficit in 13%, unidentified deficit 4% and 35% reached baseline function. Long-term mortality in RSE and SRSE is known to be related not so much to the treatment used as to the underlying aetiology (probably the main determinant) and also the duration of status epilepticus. This study shows the admission mortality rate was higher in SRDNSE than SRSEPE (table 3.4). One-year post admission, this difference in mortality rates in SRDNSE and SRSEPE was maintained, but expanded in subsequent years, such that 5 years after admission 45.57% of SRDNSE had died compared to 34.52% of those with SRSEPE (Table 3.4). It may have been anticipated that SRSEPE would respond better than those with SRDNSE, since many of these would be related to reversible causes. By one-year post-admission, mortality rates in our cohort are considerable with 24.48% of SRDNSE and 21.42% of SSEPE not alive at 1 year mark post SRSE. At 10 year this difference was maintained with death of 57% from SRDNSE versus 40.47 % from SRSEPE group. (Table 3.4 and 3.5). This data suggests that people with known epilepsy prior to status epilepticus do better in term of both, short- and long-term mortality and morbidity.

Causes of SRSE-Associated mortality

Addiction and substance abuse issues are associated with an increased admission and subsequent mortality in both SRDNSE and SRSEPE. Table 3.7, 3.8 and 3.9 show the contribution of addiction and abuse to deaths in the group with SRDNSE and SRSEPE. At each

time point, alcohol and drugs comprise the largest contributor to mortality. In those with SRSEPE alcohol and drug use comprise a less striking contributor to mortality. The causes of the two groups of SRSE are predictably different: in SRSEPE, the better outcome may signal the presence of a reversible cause of epilepsy exacerbation. In SRDNSE, our data suggests that underlying addiction or abuse issues are not a simple reversible cause or exacerbation but are in fact a negative prognostic marker for long term mortality. In the SRDNSE group 22.8% of all deaths within 5 years were related to alcohol and drug-related complications. In the SRSEPE group 57% of all deaths at 5 years were related to seizure complications. There were longer admissions with SRDNSE, the rate of full neurological recovery was less in those with SRDNSE compared to SRSEPE. Mortality was higher rate was higher in SRDNSE group compared to SRSEPE and this difference was maintained throughout 10-year post SE. It is known that outcomes are related to aetiology of status epilepticus.

Subsequent Seizures

In patients with SRDNSE, this index seizure was followed by a need for AEDs in 31%, a level of recurrence which would confirm that an index episode of SRSE is no more liable to lead to a recurrence and need for AEDs than a single shorter seizure (2.3).

Neurological Disability

Previous studies of SE among adults (117) have suggested neurological deterioration in only 3.3% among those surviving at least 30 days. In our study recovery with neurological deficit was similar in both groups SRDNSE 23.8% vs SRSEPE 21.42 % at the same time we saw more patient recovering without neurological deficit in SRSEPE group 48.8% compared to 29.93 % in SRDNSE group. This probably indicates simple nature of SE in epileptic patients ie lack of mediation compliance etc whereas supra refractory De Novo SE patients is usually caused by acute symptomatic causes like trauma, infection, neuro immunological causes, metabolic and intoxication which leads to more complicated recovery more distality and complications.

Conclusion

Supra Refractory status is important and in much need of study. The separation of SRDNSE from SRSEPE is helpful in beginning to delineate prognosis, the need for further investigation, and the role of ineffective or absent AEDs in causation. The mortality and morbidity rate of SRSE are high. The greater admission mortality with SDNSE, which persists in the years following discharge should confirm that SE with a background of addiction or abuse should not simply be considered as a 'provoked seizure' and treated with acute support and encouragement to abstinence. Instead, it suggests that a presentation with SRDNSE is a sign of a system in peril. While public health measures are vital in reducing the disease burden of triggers such as alcohol and addiction, each episode should prompt a chain of multispecialty care in order to address this recurring and persisting public health disaster, which comprises of too many personal tragedies. This study looks at the causes and long plus short-term outcomes of Supra Refractory Status Epilepticus across 18 years in Glasgow. Mortality is increased in short term and the long-term in both supra refractory De Novo Status Epilepticus and supra refractory Status Epilepticus Complicating Epilepsy, but we saw relatively more mortality rate in SRDNSE group. Most important factor determining the outcome of SRSE is aetiology both in short and long term.

Summary of findings

1. Demographic data shows increased rates related solely to addiction and abuse in the group with SRDNSE compared to SRSEPE (43.53% versus 33.33%).

2. Top 3 causes of SRES in De novo group were Alcohol/drugs 43.5%, HI 15.6%, and brain bleeds and metabolic 9.5% respectively.

3. Top 3 causes of SRSE in SEPE group were alcohol and drugs 33%, idiopathic 13%, poorly controlled epilepsy and issues with AED's made 12% contribution each making up to 24%. **2.** The admission mortality rate was higher in SRDNSE than SRSEPE (15% versus 9.5%).

4. By one-year post-admission, mortality rates in our cohort are considerable with 24.48% of SRDNSE and 21.42% of SSEPE not being alive at 1 year mark. 5 years after admission 45.57% of SRDNSE had died compared to 34.52% of those with SRSEP. At 10 year this difference was maintained with death of 57% from SRDNSE versus 40.47 % from SRSEPE group.

5. In the SRDNSE group 22.8% of all deaths within 5 year were related to alcohol and drug-related complications. In the SRSEPE group 57% of all deaths at 5 years were related to seizure complications

6. Incidence of recovery with no deficit was better in SRSEPE group 49% compared to 30% in SRDNSE group.

Chapter 5

Neuro ITU 193 cases of Status Epilepticus in Glasgow 1995-2013

Introduction

Often selected patients with status epilepticus end up being in neuro ITU. These patients are usually consulted for generalised refractory, supra refractory SE and NCSE. We often come across patients having complications from neuro surgical presentations or procedures ending up in SE. Other causes of neuro ITU admission can be acute brain trauma complicating with SE, neuro inflammatory causes, mitochondrial causes and unusual syndromes causing frequent supra refractory status epilepticus. Following adequate resuscitation, the treatment of status epilepticus in the neuro ITU proceeds simultaneously on four fronts: termination of seizures, prevention of seizure recurrence once status is controlled, management of the precipitating causes, and management of the complications. The aim of treatment is to stop SE as soon as possible and to avoid complications while focusing on underlying cause too. Neuro ITU patients may be more susceptible to the ravages of SE because of their pre-existing cerebral injuries. Some previous studies have suggested that even in neuro ITU more patients have acute symptomatic cause for SE than compared to underlying epilepsy. In one study of 80 patients cause of SE was neurological lesion in 75.1%, uncontrolled epilepsy in 20%, and systemic derangements in 4.9% (122).

Objective

To describe incidence of RSE in a neurological intensive care unit (Neuro ITU) and determine predictors of short-term and long-term clinical outcome. We also wanted to evaluate the leading causes of neuro ITU admission with RSE compared to general ITU as we believe cause of SE in neuro ITU might be different than general ITU. We compared cause and outcomes of SE patients admitted to neuro ITU with general ITU. We set out to investigate several aims including causes of RSE and to compare outcomes of neuro ITU admissions by dividing total cohort into 2 groups, 1st neuro ITU refractory status epilepticus with history of prior epilepsy N-RSEPE and 2nd neuro ITU refractory De Novo status epilepticus N-RDNSE. We wanted to determine the predictors of short-term and long-term prognosis. We also wanted to compare neuro ITU cases with general ITU cases in terms of causes of SE and outcomes.

Results

Demographic information

Majority cases were in N-RDNSE group (63% of total cohort). Age range for N-RSEPE group was 15-91 with mean of 48 whereas in N-RSEPE age range was 20-51with mean of 43.7 indicating slightly younger population in N-RSEPE group (table 4.1). Sex ratio was not much different with very slight male predominance. Mean stay in hospital was 38 days for whole cohort but patients with N-RDNSE stayed in hospital longer, with almost double the length of stay of N-RSEPE group. More patients in N-RSEPE group had previous ITU stay (almost 40%) which in most cases was due to status or other neurological illness leading to development of epilepsy. By far huge majority of cases were GTCS with only 3% of total cohort with SCSE (table 4.2). 14% of SEPE group had SE due to AED change, side effects of other meds or due to noncompliance with medications.

	Total n= 193	N-RDNSE n= 122 (63.21%)	N-RSEPE n=71(36.78%)
Age (years) Mean, Range	 46.48 15-91	 48 15-91	 43.74 20-51
Female: Male	94:99	59:63	35:36
Previous ITU with neurological condition	37 (19.17%)	8 (6.55%)	28 (39.43%)
Days in hospital Mean Range	 38.82 0.5-1497	 48.90 0.5-1497	 21.50 1-155
Days in ITU Mean Range	 6.35 0.5-165	 6.43 0.5-165	 6.22 0.5-26
Number of Deaths over 10 years from total cohort of 193 Patient staying in neuro ITU	98 (50.77%)	66 (54.09%)	31 (43.66%)

Deaths during same admission	34 (17.61%)	25 (20.49%)	9 (12.67%)
Deaths within 1-year post Admission	53 (27.46%)	35 (28.68%)	18 (25.35%)

Table 4.1: Demographic Data for neuro ITU SE admissions

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus

Type of status:	Total n=231	N-RDNSE n=147	N-RSEPE n=84
Focal	10 (4.3%)	6 (4%)	4 (4.7%)
GTCS	213 (92%)	136 (92.5%)	77 (91.6%)
Not Known	1 (0.4%)	1 (0.68%)	0
NCSE	7 (3%)	4 (27.2%)	3 (3.5%)
Long Term AED Treatment among survivors on discharge (N on AED / N of survivors)	110 (47.61%)	46 (31.29%)	65 (77.38%)

Table 4.2 Status Classification and Subsequent Use of AED in neuro ITU cases

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus

Cause of status epilepticus

In total cohort of 193 case, alcohol and drugs use in isolation or as an associated cause with another contributor stood out as more prevalent cause of SE with 24.87% of all cases (48 cases). Next most common cause in total cohort was intracranial bleeds of different types 16% (31 cases). CNS inflammation, idiopathic causes, and CNS infection was also, in top 4 causes of SE (table 4.3, 4.4). On comparison of subgroups, N-RDNSE and N-RSEPE it was interesting to note that alcohol and drugs still stood out as number one cause in both groups admitted to neuro ITU for SE, but addiction of these substances was more common in N-RDNSE with 29% patients in this group compared to 18% in N-RSEPE group (Figure 1). CVD, ICH, SDH, SAH, HI, AVM were more prevalent associations in N-RDNSE 23% compared to 4% in SEPE group.

Change in AED medications, noncompliance, and interaction with other medications was noted in 14% of the N-RSEPE group. Progressive epilepsy made 11% of SE in N-RSEPE group. If progressive epilepsy and issue with anti-epileptic medications are combined that makes 25% of N-RSEPE group. No identifiable cause for SE (idiopathic SE) was seen more commonly in N-RSEPE (9.8%) compared to N- RDNSE group (5.7%). Which is an interesting observation as often patients with prior epilepsy end up being in status and despite extensive investigation no cause is found.

Cause of status in N-RDNSE		**Cause of status is N-RSEPE**	
Alcohol and drugs	35 (28.68%)	Alcohol and drugs	13 (18.3%)
ICH, SDH, HI	28 (22.9%)	AED change, noncompliance	10 (14%)
CNS inflammation	12 (9.8%)	Progressive epilepsy	8 (11.26%)
CNS infection	12 (9.8%)	Idiopathic	7(9.85%)

Table 4.3 Compassion of top 4 causes of SE between 2 groups of neuro ITU cases

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus.

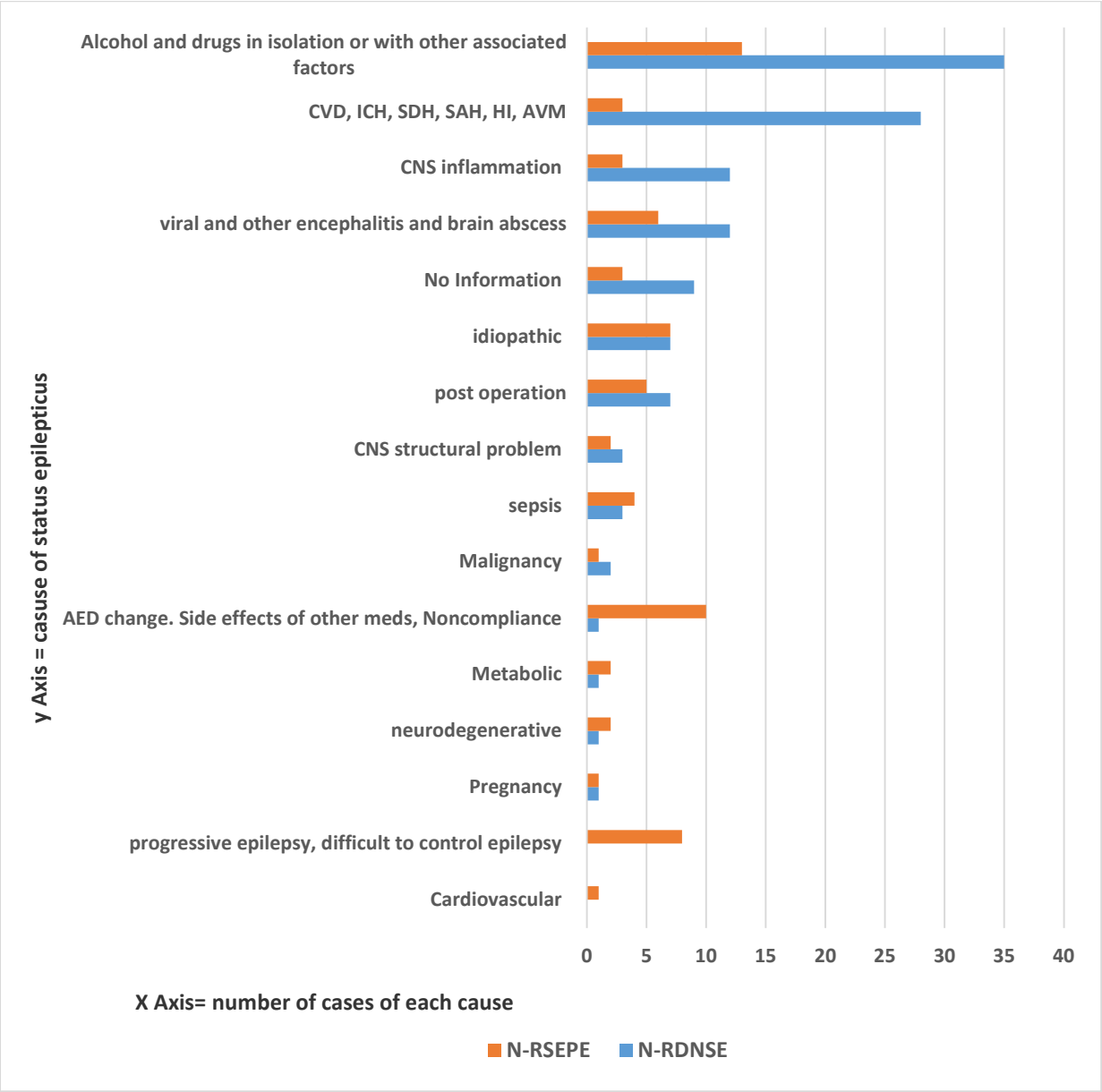

Figure 4.1 Comparison of SE causes in 2 group of neuro ITU cases

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus

Cause of status Epilepticus	**N-RDNSE N=122**	**N-RSEPE N=71**
Cardiovascular	0(0%)	1(1.4%)
progressive epilepsy, difficult to control epilepsy	0(0%)	8(11.26%)
Pregnancy	1(0.81%)	1(1.4%)
Neurodegenerative	1(0.81%)	2(2.8%)
Metabolic	1(0.81%)	2(2.8%)
AED change. Side effects of other meds, Noncompliance	1(0.81%)	10(14%)
Malignancy	2(1.63%)	1(1.4%)
Sepsis	3(2.45%)	4(5.63%)
CNS structural problem	3(2.45%)	2(2.8%)
Post operation	7(5.73%)	5(7.0%)
idiopathic	7(5.73%)	7(9.85%)
No Information	9(7.37%)	3(4.22%)
viral and other encephalitis and brain abscess	12(9.8%)	6(8.45%)
CNS inflammation	12(9.8%)	3(4.22%)
CVD, ICH, SDH, SAH, HI, AVM	28(22.9%)	3(4.22%)
Alcohol and drugs in isolation or with other associated factors	35(28.68%)	13(18.3%)

Table 4.4 Compassion of causes of status epilepticus between 2 groups of neuro ITU cases (patients with prior epilepsy vs De Novo SE)

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus

We also compared causes of SE in 440 cases admitted to Gen ITU with 193 neuro ITU cases. Most common causes of general ITU SE in decreasing order were alcohol 54%, idiopathic 7%, metabolic 6%, sepsis 4.5% and no information 4.5%. Whereas in neuro most common causes were alcohol 34%, brain bleeds/CVD 16%, CNS infection 9.3% and inflammation 7.7%.

Causes of SE	**General ITU N=440**	**Neuro ITU N=193**
neuro degenerative	1 (0.2%)	3 (1.5%)
CNS inflammation	3 (0.65)	15 (7.7%)
ECT	2 (0.45%)	0
Pregnancy	2 (0.45%)	2 (1%)
Post operation	4 (0.9%)	12 (6%)
medication	5 (1%)	1 (0.5%)
CVS	5 (1%)	1 (0.5%)
structural brain pathology	6 (1.3%)	5 (2.5%)
CNS infection	6 (1.3%)	18 (9.3%)
malignancy	9 (2%)	3 (1.5%)
HI. ICH, Subdural, SAH, CVD	32 (7.2%)	31 (16%)
AED change. Side effects of other meds, Noncompliance	15 (3.4%)	11 (5.7%)
progressive epilepsy syndrome	14 (3%)	8 (4.1%)
no info	20 (4.5%)	12 (6.2%)
Sepsis	20 (4.5%)	7 (3.6%)
Metabolic	27 (6%)	3 (1.5%)
Idiopathic	32 (7%)	14 (7%)
Alcohol and drugs	237(54%)	47 (34%)

Table 4.5 Compassion of causes of status epilepticus between general and neuro ITU cases

Cause of SE general ITU	**Cause SE neuro ITU**
Alcohol/ drugs (54%)	Alcohol /drugs (34%)
Idiopathic (7%)	HI. ICH, Subdural, SAH, CVD (16%)
Metabolic (6%)	CNS infection (9.3%) _
Sepsis (4.5%), No info (4.5%)	CNS inflammation (7.7%)

Table 4.6 Top 4 of causes of SE in neuro ITU and general ITU

Outcomes of RSE – Death, Residual Neurological Deficit, or Full Recovery

Table 4.5 and Figure 4.2 demonstrate that the admission mortality rate was higher in RDNSE than RSEPE group (20.49% versus 12.67%). At 1 year, 5 years and 10 years post admission, this significant difference in mortality had persisted, (Table 4.5,4.6), (Figure 4.2). At 1 year post SE nearly quarter of patients in both groups died with slightly more incidence in mortality in N-RDNSE group. By the end of 5-year post SE nearly 40% of patients in N- RDNSE had died compared to 33.8% in N-RSEPE group and by end of 10-year post SE nearly half of patients in N-RDNSE died compared to 42.2% in N-RSEPE group. Causes of mortality is discussed in later paragraph. It is interesting to note that majority of deaths happened in first 3 years post SE (Figure 4.3).

	Total Cohort 193	**N-RDNSE 122**	**N-RSEPE 71**
Total Number of Deaths	98 (50.77%)	67 (54.9%)	31 (43.66%)
Deaths same admission	34 (17.61%)	25 (20.49%)	9 (12.67%)
Deaths at 1-year post SE	53 (24.46%)	35 (28.68%)	18 (25.35%)
Deaths at 5-year post SE	73 (37.82%)	49 (40.16%)	24 (33.80%)
Deaths at 10 -year post SE	90 (46.63%)	60 (49.18%)	30 (42.25%)

Table 4.7- Cumulative Mortality Over 10 years

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus

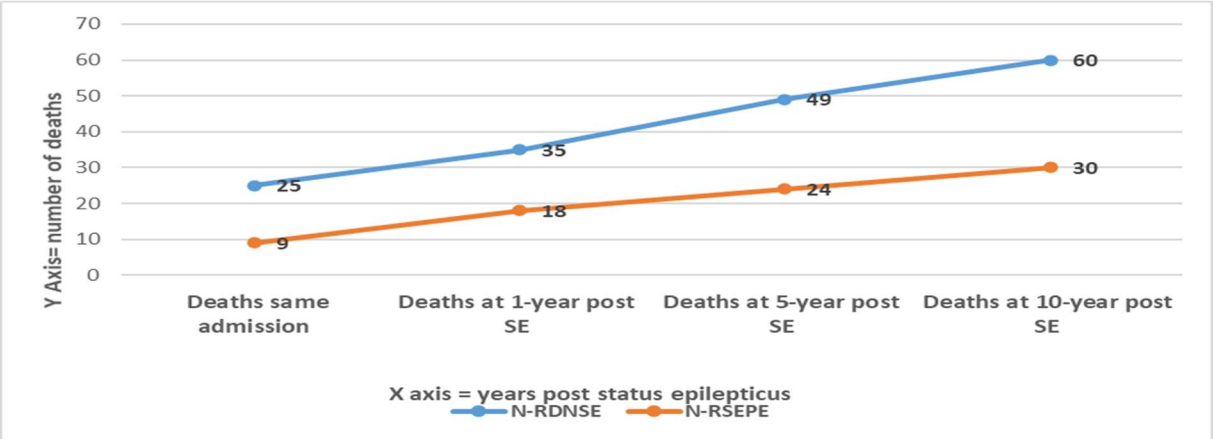

Figure 4.2 Incidence of death over 10 years post SE admission to neuro ITU

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy N-RDNSE Neuro ITU refractory De Novo status epilepticus

Years	N-RDNSE Deaths =122	N-RSEPE Deaths =71
0 year	25	9
1 years	10	9
2 years	7	2
3 years	4	3
4 years	1	1
5 years	4	1
6 years	1	1
7 years	2	2
8 years	5	2
9 years	1	0
10 years	0	0

Table 4.8 - Year of Death after SE Admission to neuro ITU

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy N-RDNSE Neuro ITU refractory De Novo status epilepticus

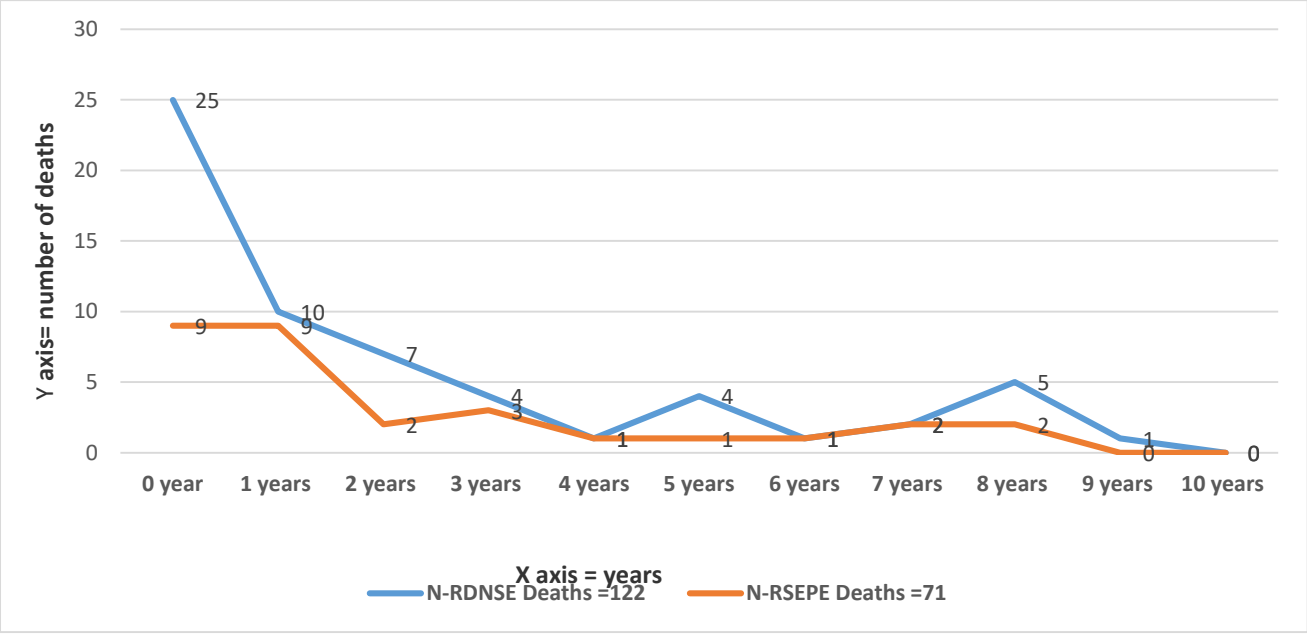

Figure 4.3 Yearly death incidence in both groups of neuro ITU SE cases .Showing more deaths in N-RDNSE group compared to N-RSEPE group with most death within 1-3 years after SE.

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy N-RDNSE Neuro ITU refractory De Novo status epilepticus

It's clear from data that mortality was higher in N-RDNSE group and remains so over period of 10 years, but interestingly significant portion of N-RSEPE had recovery with deficits at the time of discharge (39.43%). At the same time recovery with no deficit was recorded in 26.76% in N-RSEPE group which was more than N-RDNSE group (Table 4.7, Figure 4.4). We do appreciate that up to 40% patient in N-RDNSE had no data available about outcomes which might have affected the outcomes calculations. We also know the fact that patients in N-RSEPE group admitted neuro ITU tend to have drug resistant and more often syndromic type of epilepsy which also likely has impact on overall outcomes.

	Total Group (n=193)	N-RDNSE (n=122)	N-RSEPE (n=71)
Death during admission	34 (17.61%)	25 (20.49%)	9 (12.67%)
Recovery with Neurological Deficit	57 (29.5%)	35 (28.68)	28 (39.43%)
Full recovery no neurological deficit	38 (19.68%)	13 (10.65%)	19 (26.76%)
No information	50 (25.9%)	49 (40.16%)	15 (21.12%)

Table 4.9 Outcomes after SE admission to neuro ITU, comparison between RDNSE and RSEPE groups

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus

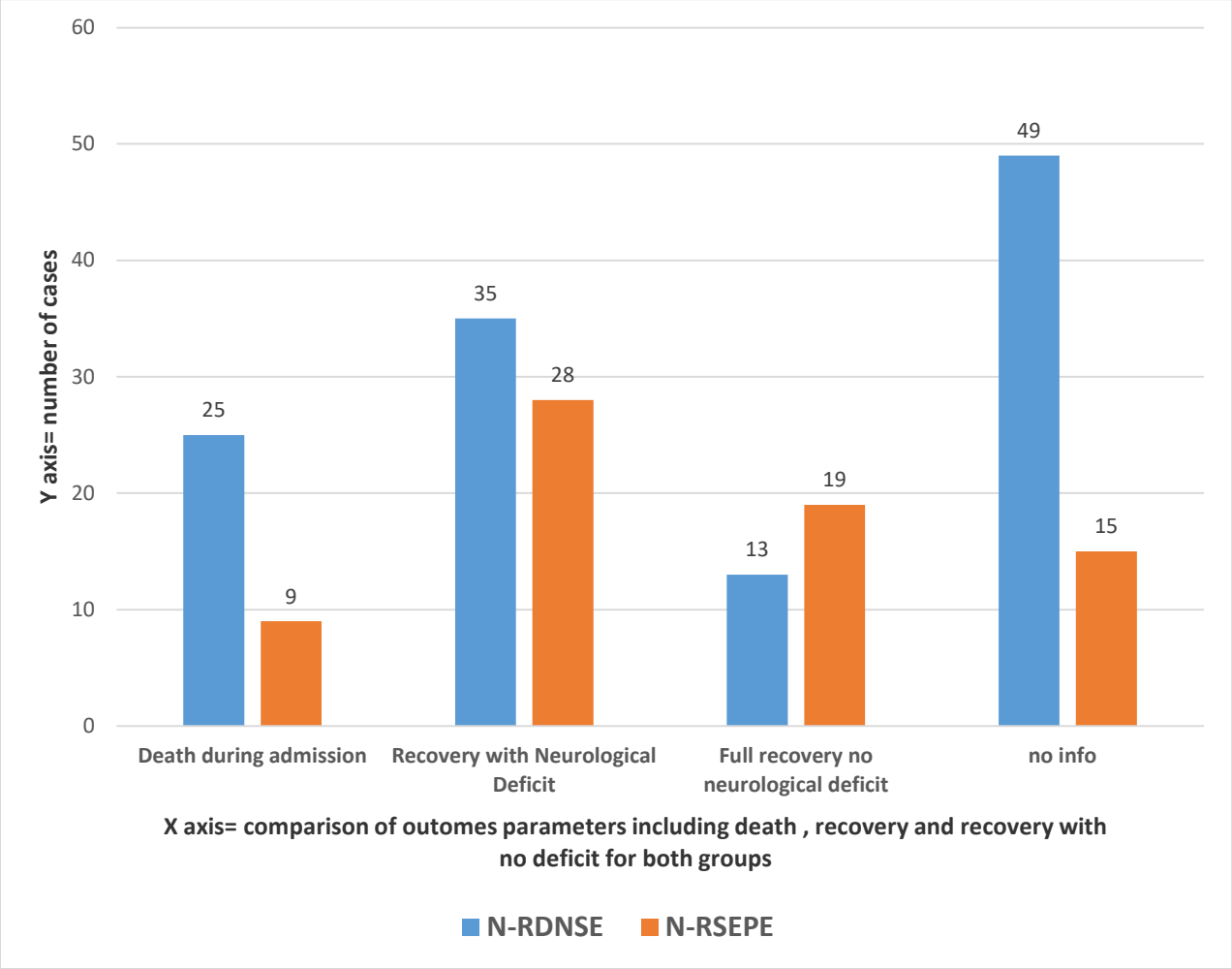

Figure 4.4 comparison of outcomes in both groups of neuro ITU cases

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

N-RDNSE Neuro ITU refractory De Novo status epilepticus

Comparison of outcomes between general and neuro ITU

We compared outcomes of general ITU with neuro ITU cases. It was clear that neuro ITU status epilepticus cases had more mortality than general ITU (17.6 % vs 8.6%). Similarly, recovery with neurological deficit was more in neuro ITU group 29.5% compared to 13.8% in general ITU group.

	General ICU Group (n=440)	Neuro ICU (n=193)
Death during admission	38 (8.6%)	34 (17.61%)
Recovery with Neurological Deficit	61 (13.8%)	57 (29.5%)
Full recovery no neurological deficit	200 (45%)	38 (19.68%)
No information	140 (31%)	50 (25.9%)

Table 4.10 Outcome after SE in general vs neuro ITU

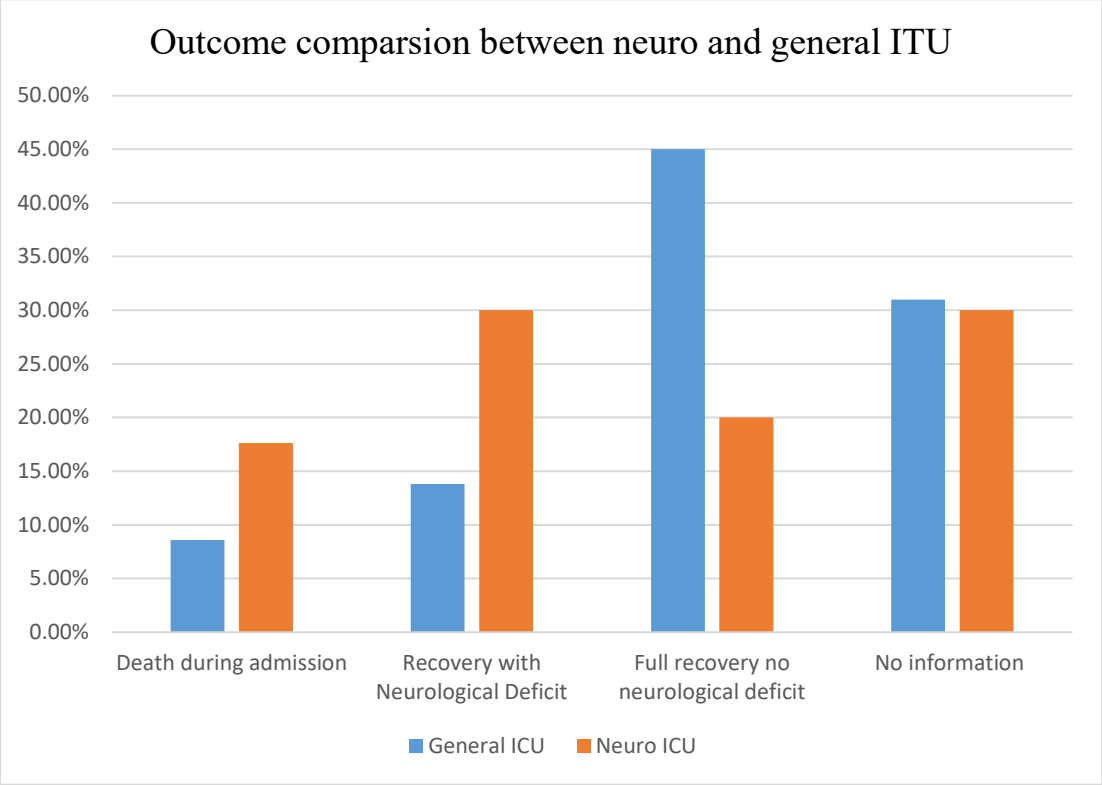

Figure 4.5 comparison on outcomes between neuro and general ITU cases

Cause of mortality in Neuro ITU cohort

Incidence of mortality and cause of mortality during same admission and next 4 years is compared for both groups (table 4.8,4.9,4.10). Table 4.10 shows that in N-RDNSE group a total of 47 patients died over next 4 year. It was interesting to note that CVD, ICH, HI was most common cause of mortality in N-RDNSE group (23.40%). It probably just reflects type of cases admitted to neuro ITU as most are usually admitted for Neurosurgical interventions. Sepsis was 2nd most common cause (15%) and encephalitis was 3rd most common cause of death in N-RDNSE group (12.76%). In N-RSEPE group most common cause of mortality appears to be seizure and its complications (33%). Alcohol and drugs related deaths and sepsis were other most prevalent causes of death in this groups (16.6% each).

Cause of death same admission (n=25)	**N**	**Cause of death 1-year post SE (n=10)**	**N**	**Cause of death 2-year post SE (n=7)**	**N**	**Cause of death 3-year post SE (n=4)**	**N**	**Cause of death 4-year post SE (n=1)**	**N**
CVD, ICH, HI	8	CVS	2	Alcohol and drug	2	CVS	1	COPD	1
Encephalitis	6	Sepsis	3	Seizure	2	Alcohol and drugs	1		
CVS	2	Neurodegenerative	2	ARDS	1	Asphyxia	1		
Sepsis	3	Seizures	2	CVD	1	CVD	1		
Alcohol and drug	2	CVD.SAH	1	Sepsis	1				
Seizures	1								
MS	1								
Malignancy	1								
Neurodegenerative	1								

Table 4.11 –Main causes of death in RDNSE cases in neuro ITU in each epoch post-admission (Death at admission and next 4 years total n= 47)

N-RDNSE Neuro ITU refractory De Novo status epilepticus

Cause of death same admission (n=9)	**N**	**Cause of death 1-year post SE (n=9)**	**N**	**Cause of death 2-year post SE (n=2)**	**N**	**Cause of death 3-year post SE (n=3)**	**N**	**Cause of death 4-year post SE (n=1)**	**N**
Seizure	3	Seizure	3	CVA	1	Alcohol related	1	Malignancy	1
Sepsis	3	Sepsis	1	Seizures	1	Seizures	1		
Alcohol related	2	Neuro-degenerative	2			No info	1		
Malignancy	1	Anoxic brain injury	1						
		CVS	1						
		Alcohol	1						

Table 4.12 Main causes of death in N-RSEPE cases in neuro ITU in each epoch post-admission (Death at admission and next 4 years total n= 24)

N-RSEPE Neuro ITU refractory status epilepticus with history of prior epilepsy

Cause of death	**N-RDNSE** **47 deaths over 4 years**	**N-RSEPE** **24 deaths over 4 years**
1	CVD, ICH, HI (23.40%).	seizures complications (33%)
2	Sepsis (15%)	Alcohol and drugs (16.6%)
3	Encephalitis (12.7%)	Alcohol and drugs (16.6%)

Table 4.13 Top 3 Causes of mortality in neuro ITU, comparison of 2 groups over 4 years post RSE CVD= cerebrovascular disease, ICH= intracerebral haemorrhage, CVS= cardiovascular, PVD= peripheral vascular disease

Discussion

The RSE approach in the Neuro ITU needs a multidisciplinary team with the participation of neurophysiologists, intensive care specialists, neurologists, and in some cases, neurosurgeons. Not much data is available about incidence and mortality and morbidity of RSE in neuro ITU hence studies like this are important.

History of prior ITU admission

In this study neuro ITU cohort had more patients in known prior epilepsy group who had previous ITU stay (almost 40%) which in most cases was due to status or other neurological illness. That is possible indication of more complex form of epilepsy or epilepsy secondary to some prior neurological insult.

Causes of SE in neuro ITU In neuro ITU cohort of 193 case, alcohol and drugs use in isolation or as an associated cause with another contributor stood out as more prevalent cause of SE with 23% of all cases. On subgroup analysis, of neuro ITU group, CVD, ICH, SDH, SAH, HI, AVM caused De novo status epilepticus in 23% compared to 4% in known epilepsy group presenting with status epilepticus. This possibly indicates that in neuro ITU provoked seizures secondary to brain bleeds of different origin or HI are common presentations complicating with RSE. In another study the most common aetiology of RSE in neuro ITU was acute neurological lesion in 75.1% of the patients (122). In our study if we combine progressive epilepsy and issues with anti-epileptic medications as cause of status epilepticus in known epilepsy patients, it makes 25% of total causes of SE in N-RSEPE group. It's obvious from comparison of general ITU and neuro ITU that top causes of SE in neuro ITU were slightly different than general, but alcohol and drugs still played a major role in causation. In neuro ITU we had more cases of SE with neuro surgical complications, CNS inflammation and infection compared to general ITU.

Mortality of SE in neuro ITU

Previous smaller studied of RSE in neuro ITU have suggested the mortality rate was very low at 11 % by 6 months (123). This study looked at long term follow up to try and look at association of cause of SE and cause of mortality over period of time. At 1 year post SE nearly quarter of patients in both groups died with slightly more incidence in mortality in N-RDNSE group. By the end of 5-year post SE nearly 40% of patients in N-RDNSE had died compared to 33.8% in N-RSEPE group. It was interesting to note that CVD, ICH, HI was most common cause of mortality in N-RDNSE group 23.40%. In N-RSEPE group the most common cause of

death was seizure and related complication as mentioned before this possibly represents complicated drug resistant epilepsy or symptomatic epilepsy secondary to a progressive cause as 40% of these patients had prior ITU admission too. Compared to the main N-RDNSE group from original cohort of 633 patient, in this subgroup N-RDNSE of neuro ITU cases the association of alcohol and drugs with cause of mortality was less. In the original cohort 35% of all death over 4 years post SE in N-RDNSE were related to substance abuse. In neuro ITU subgroup only 10.67% deaths were related to alcohol and drugs. On further comparison between neuro and general ITU its obvious that neuro ITU had more mortality and disability compared to general ITU status epilepticus cases.

Subsequent use of AED

31% patients in N-RDNSE ended up with long term AEDs which is possible reflection of that fact that, majority of them got treated as epilepsy in long term. ILAE defines epilepsy as having 2 or more unprovoked seizures 24 hours apart or one seizure with high risk of having 2nd seizure over time, ie abnormal EEG, abnormal brain scan etc

Conclusion

Our data suggest that patients with SE admitted to neuro ITU have high mortality and morbidity compared to general ITU. Most De Novo cases in neuro ITU were in relation to brain trauma or insults from different form of bleeds. Mortality in N-RDNSE group remains high both in long term and short term compared to N-RSEPE group admitted to neuro ITU. Patients maintain higher rate of mortality even at 1–5-year mark post SE. We also saw more patients in N-RSEPE group had prior ITU admission due to neurological cause compered to N-RDNSE group which is an indication of complexity of these cases possibly adding towards less recovery compared to N-RDNSE group. More publications and randomized-controlled trials are required to explore above mentioned facts.

Summary of findings

1. In our study of neuro ITU cohort (193 cases) more patients in known prior epilepsy group had previous ITU stay (almost 40%) which in most cases was due to prior status epilepticus or other neurological Illness.

2. Even in neuro ITU cohort of 193 case, alcohol and drugs use in isolation or as an associated cause with another contributor stood out as more prevalent cause of SE with 23% of all cases.

3. In neuro ITU group, CVD, ICH, SDH, SAH, HI, AVM caused De novo status epilepticus in 23% compared to 4% in known epilepsy group presenting with status epilepticus.

4. If we combine progressive epilepsy and issues with anti-epileptic medications as cause of status epilepticus in known epilepsy patients, it makes 25% of this group. Which is $1/4^{th}$ of total causes of SE in this group. Most patient with prior epilepsy had poor recovery outcomes compared to general cohort possibly due to complicated drug resistant/Syndromic form of epilepsy with likely complicated background disability prior to admission to ITU.

5. In neuro ITU cohort, at 1 year post SE, nearly quarter of patients in both groups died with slightly more incidence in mortality in N-RDNSE group. By the end of 5-year post SE nearly 40% of patients in N-RDNSE had died compared to 33.8% in SEPE group.

6. It was interesting to note that CVD, ICH, HI was most common cause of mortality in N-RDNSE group 23.40%. In N-RSEPE group most common cause of mortality appears to be seizures and its complications (33%).

7. Comparisons of Refractory DNSE group from original cohort (419 patients) with neuro ITU subgroup of refractory DNSE group ((122 patients) show the association of alcohol and drugs with mortality was less prominent in later group. In original cohort 35% of all death 4 years post RSE were related to substance abuse. In neuro ITU subgroup of N-RDNSE only 10.67% deaths were related to alcohol and drugs over this period of time.

8. Data also reflects that neuro ITU patients with RSE have slightly different causes than general ITU (Table 2.3a chapter 3). Mortality and morbidity in this group is significantly more than general ITU. **1**. Comparison was made between causes of SE in 440 cases from general ITU with 193 neuro ITU cases. Most common causes of general ITU SE in decreasing order were alcohol 54%, idiopathic 7%, metabolic 6%, sepsis 4.5% and no information 4.5%.

Whereas in neuro ITU most common causes were alcohol 34%, brain bleeds/CVD 16%, CNS infection 9.3% and inflammation 7.7%.

9**.** Comparison was made between outcomes of general ITU with neuro ITU cases. It was clear that neuro ITU status epilepticus cases had more mortality than general ITU cases (17.6 % vs 8.6%). Similarly, recovery with neurological deficit was more in neuro ITU group 29.5% compared to 13.8% in general ITU group.

10. Comparison was made between causes of SE in 440 cases from general ITU with 193 neuro ITU cases. Most common causes of general ITU SE in decreasing order were alcohol 54%, idiopathic 7%, metabolic 6%, sepsis 4.5% and no information 4.5%. Whereas in neuro ITU most common causes were alcohol 34%, brain bleeds/CVD 16%, CNS infection 9.3% and inflammation 7.7%.

Chapter 6

Important points and conclusions

Slight male predominance seen throughout all cohort.

Patients in DNSE group were slightly older than compared to SEPE group

Outcomes for refractory status epilepticus (RSE) 633 patients

1. Provocation by alcohol +/ or drug misuse was significant in 54.9% of those with RDNSE and 33.7% of those with RSEPE.

2. The admission mortality rate was higher in RDNSE than RSEPE (13.8% versus 7.5%).

3. One-year post admission, this difference in mortality rates in RDNSE and RSEPE was maintained, but expanded in subsequent years, such that 5 years after admission 41.5% of RDNSE had died compared to 27.6% of those with RSEPE.

4. On subgroup analysis, total death number was 206 over 4 years in RDNSE group. Alcohol and death related causes made 34.46% (n=71) of total deaths over 4 years in this group. 2nd most common cause was malignancy 12% (n=25), 10.67% (n=22) patients had death due to CVD coming up as 3rd most common cause.

5. In RSEPE group total death count over 4 year was 78. Most common cause of death in this group was seizure related complication 73% (n=29), 2nd most common cause was alcohol and drug related complication 12.8% (n=10) and 3rd most common cause of mortality was sepsis 10.25% (n=8).

6. At each time point, alcohol and drugs comprise the largest contributor to mortality in both groups but in those with RSEPE alcohol and drug use comprise a less striking contributor to mortality.

7. In the RDNSE group 28% of all deaths within 1 year were related to alcohol and drug-related complications, increasing to 34.4% of all deaths over 10 years. In the SEPE group, 1-year mortality was 20.2%, with 31.6% dying because of seizures over 10 years.

8. Where information was available, we looked at the discharge status, showing incidence of full recovery in those with RDNSE (19.98%) and RSEPE (50%).

9. The rate of full neurological recovery was more in RSEPE group compared to RDNSE group.

Cause of RDNSE	**Cause of RSEPE**
Alcohol/ drugs (54.9%)	Alcohol /drugs (33.7%)
ICH, SDH, HI (13.1%)	Poor adherence AEDs (11.5%)
Metabolic (6.5%)	Progressive epilepsy syndrome (11.1%)
No Information Available (5.0%)	Idiopathic (14%)

Table 5.1 Top 4 causes Cause of SE in total cohort of 633

RDNSE= Refractory De Novo status epilepticus, RSEPE =Refractory status Epilepticus with prior epilepsy. (Poor adherence with AED was identified from documented lack of compliance in clinical notes).

	Total Group (n=633)	DNSE (n=419)	SEPE (n=214)
Death during admission	74 (11.69%)	58 (13.84%)	16 (7.47%)
Recovery with Neurological Deficit	232 (36.65%)	124 (29.59%)	41 (19%)
Full recovery no neurological deficit	124 (19.58%)	83 (19.98%)	107(50%)
No information	204 (32.22%)	154 (36.75%)	50 (23.36%)

Table 5.2 - Outcome after SE in RDNSE and RSEPE main cohort of 633 cases

RDNSE= Refractory De Novo status epilepticus

RSEPE =Refractory status Epilepticus with prior epilepsy

Cause of death	RDNSE 206 deaths in 4 years	RSEPE 78 deaths in 4 years
1	Alcohol and death related 34.46%	seizure related complication 40%
2	Malignancy 12%	alcohol and drug related complication 12.8%
3	Cerebrovascular disease 10.67%	sepsis 10.25%

Table 5.3 Top 3 Causes of mortality over 4 years in main cohort

RDNSE= Refractory De Novo status epilepticus

RSEPE =Refractory status Epilepticus with prior epilepsy

Supra refractory status epilepticus (SRSE) 231 patients.

1. Demographic data shows increased rates related solely to addiction and abuse in the group with SRDNSE compared to SRSEPE (43.53% versus 33.33%).

2. Top 3 causes of SRES in De novo group were Alcohol/drugs 43.5%, HI 15.6%, and brain bleeds and metabolic 9.5% respectively.

3. Top 3 causes of SRSE in SEPE group were alcohol and drugs 33%, idiopathic 13%, poorly controlled epilepsy and issues with AED's made 12% contribution each making up to 24%.

4. The admission mortality rate was higher in SRDNSE than SRSEPE (15% versus 9.5%).

5. By one-year post-admission, mortality rates in our cohort are considerable with 24.48% of SRDNSE and 21.42% of SSEPE not being alive at 1 year mark. 5 years after admission 45.57% of SRDNSE had died compared to 34.52% of those with SRSEP. At 10 year this difference was maintained with death of 57% from SRDNSE versus 40.47 % from SRSEPE group.

6. In the SRDNSE group 22.8% of all deaths within 5 years were related to alcohol and drug-related complications. In the SRSEPE group 57% of all deaths at 5 years were related to seizure complications.

7. Incidence of recovery with no deficit was better in SRSEPE group 49% compared to 30% in SRDNSE group.

Cause of SRDNSE	**Cause of SRSEPE**
Alcohol and drugs (43.5%)	Alcohol and drugs (33.33%)
CVD, ICH, SDH, SAH, HI (15.6%)	Idiopathic (13 %)
Metabolic (9.5%)	AEDs issue (11.90%)
Encephalitis (6.8%)	Poorly controlled epilepsy (11.90%)

Table 5.4. Top 4 causes Cause of SE in total cohort of 231 Supra refractory case

SRDNSE =Supra Refractory De Novo Status Epilepticus.

SRSEPE =Supra Refractory Status Epilepticus with Previous Epilepsy

	Total Group (n=231)	SRDNSE (n=147)	SRSEPE (n=84)
Death during admission	30 (12.98 %)	22 (14.96%)	8 (9.52%)
Recovery with Neurological Deficit	53 (22.94%)	35 (23.80%)	18 (21.42%)
Full recovery no neurological deficit	85 (36.79%)	44 (29.93%)	41 (48.8%)
No information	63 (27.27%)	46 (31.29%)	17 (20.23%)

Table 5.5 - Outcome after SE in SRDNSE and SRSEPE

SRDNSE =Supra Refractory De Novo Status Epilepticus.

SRSEPE =Supra Refractory Status Epilepticus with Previous Epilepsy

Cause of death	SRDNSE 57 deaths in 4 years	SRSEPE 28 deaths in 4 years
1	Alcohol and drugs (22.8%)	Seizures (57%)
2	CVS (14%)	Sepsis (10.7%)
3	Seizures (10.5 %)	Malignancy (10.7%) Alcohol and drugs (10.7%)

Table 5.6 Top 3 Causes of mortality over 4 years in Supra refractory cohort

RDNSE = Refractory De Novo Status Epilepticus.

RSEPE = Refractory Status Epilepticus with Previous Epilepsy

Refractory Status epilepticus in Neuro ITU 193 cases

Status epilepticus and seizures in the neuro-ICU are often the result of a primary disease of the brain. Patients who are admitted to the neuro-ICU suffer from a variety of traumatic and nontraumatic cerebral disorders that can predispose them to SE. These conditions, among others, include cerebral venous thrombosis, intracranial hemorrhage, large cerebral infarction or intracranial neoplasm, meningitis or encephalitis, post craniotomy, and traumatic brain injury.

1. In our study of neuro ITU cohort (193 cases) more patients in known prior epilepsy group had previous ITU stay (almost 40%) which in most cases was due to prior status epilepticus or other neurological Illness.

2. Even in neuro ITU cohort of 193 case, alcohol and drugs use in isolation or as an associated cause with another contributor stood out as more prevalent cause of SE with 23% of all cases.

3. On subgroup analysis, in neuro ITU group, CVD, ICH, SDH, SAH, HI, AVM caused De novo status epilepticus in 23% compared to 4% in known epilepsy group presenting with status epilepticus.

4. If we combine progressive epilepsy and issues with anti-epileptic medications as cause of status epilepticus in known epilepsy patients, it makes 1/4th of total causes of SE in this group.

5. In neuro ITU cohort, at 1 year post SE, nearly quarter of patients in both groups died with slightly more incidence in mortality in RDNSE group. By the end of 5-year post SE nearly 40% of patients in DNSE had died compared to 33.8% in SEPE group.

6. It was interesting to note that CVD, ICH, HI was most common cause of mortality in N-RDNSE group 23.40%. In N-RSEPE group most common cause of mortality appears to be seizures and its complications (33%).

7. When we compared the refractory DNSE group from original cohort (419 patients) with neuro ITU subgroup of refractory DNSE group ((122 patients) the association of alcohol and drugs with mortality was less prominent in later group. In original cohort 35% of all death 4 years post RSE were related to substance abuse. In neuro ITU subgroup of RDNSE only 10.67% deaths were related to alcohol and drugs over this period of time.

Cause of RDNSE in neuro ITU	**Cause of RSEPE in neuro ITU**
Alcohol and drugs 35 (28.68%)	Alcohol and drugs 13 (18.3%)
ICH, SDH, HI 28 (22.9%)	AED change, noncompliance 10 (14%)
CNS inflammation 12 (9.8%)	Progressive epilepsy 8 (11.26%)
CNS infection 12 (9.8%)	Idiopathic 7(9.85%)

Table 5.7 Neuro ITU, Compassion of top 4 causes of SE between 2 groups

Neuro-Supra Refractory De novo SE = N-SRDNSE

Neuro supra–Refractory SE in known prior epilepsy N- SRSEPE

	Total Group (n=193)	N-RDNSE (n=122)	RSEPE (n=71)
Death during admission	34 (17.61%)	25 (20.49%)	9 (12.67%)
Recovery with Neurological Deficit	57 (29.5%)	35 (28.68%)	28 (39.43%)
Full recovery no neurological deficit	38 (19.68%)	13 (10.65%)	19 (26.76%)
No information	50 (25.9%)	49 (40.16%)	15 (21.12%)

Table 5.8– Neuro ITU, Outcome after SE in RDNSE and RSEPE

Neuro- Refractory De novo SE = N-RDNSE

Neuro –Refractory SE in known prior epilepsy N- RSEPE

Cause of death	**N-RDNSE** **47 deaths over 4 years**	**RSEPE** **24 deaths over 4 years**
1	CVD, ICH, HI (23.40%).	seizures complications (33%)
2	Sepsis (15%)	Alcohol and drugs (16.6%)
3	Encephalitis (12.7%)	Alcohol and drugs (16.6%)

Table 5.9 Top 3 Causes of mortality neuro ITU 2 groups over 4 years post RSE

Neuro- Refractory De novo SE = N-RDNSE

Neuro –Refractory SE in known prior epilepsy N- RSEPE

Comparison of 3 groups

Mortality same admission comparison in 3 groups

Incidence of death was more in De Novo status epilepticus groups in all 3 cohorts as shown in Figure 1 and table 10. Main cohort the rate of admission mortality is almost double in RDNSE group (14 % vs 7.40%). In Supra refractory group the incidence of admission mortality is 5% higher in De Novo status epilepticus (15% vs 10%). In neuro ITU cases incidence of De Novo status epilepticus is 8% higher in De Novo status epilepticus (20% vs 12%).

Groups and subgroups	RDNSE	RSEPE	SRSNSE	SRSEPE	N-SRDNSEN-	N-SRSEPE
Death during same admission	14.00%	7.40%	15%	10%	20%	12%

Table 5.10 Death during same admission comparison btw 3 cohorts and subgroups

Refractory De novo SE main cohort **vs** Refractory De novo SE in known prior epilepsy main cohort RDNSE vs RSEPE 633 cases.

Supra Refractory De novo SE cohort **vs** supra–Refractory De novo SE in known prior epilepsy. SRDNSE vs SRSEPE 231 cases

Neuro-Supra Refractory De novo SE cohort **vs** neuro supra–Refractory De novo SE in known prior epilepsy. N-SRDNSE vs N- SRSEPE 193 cases

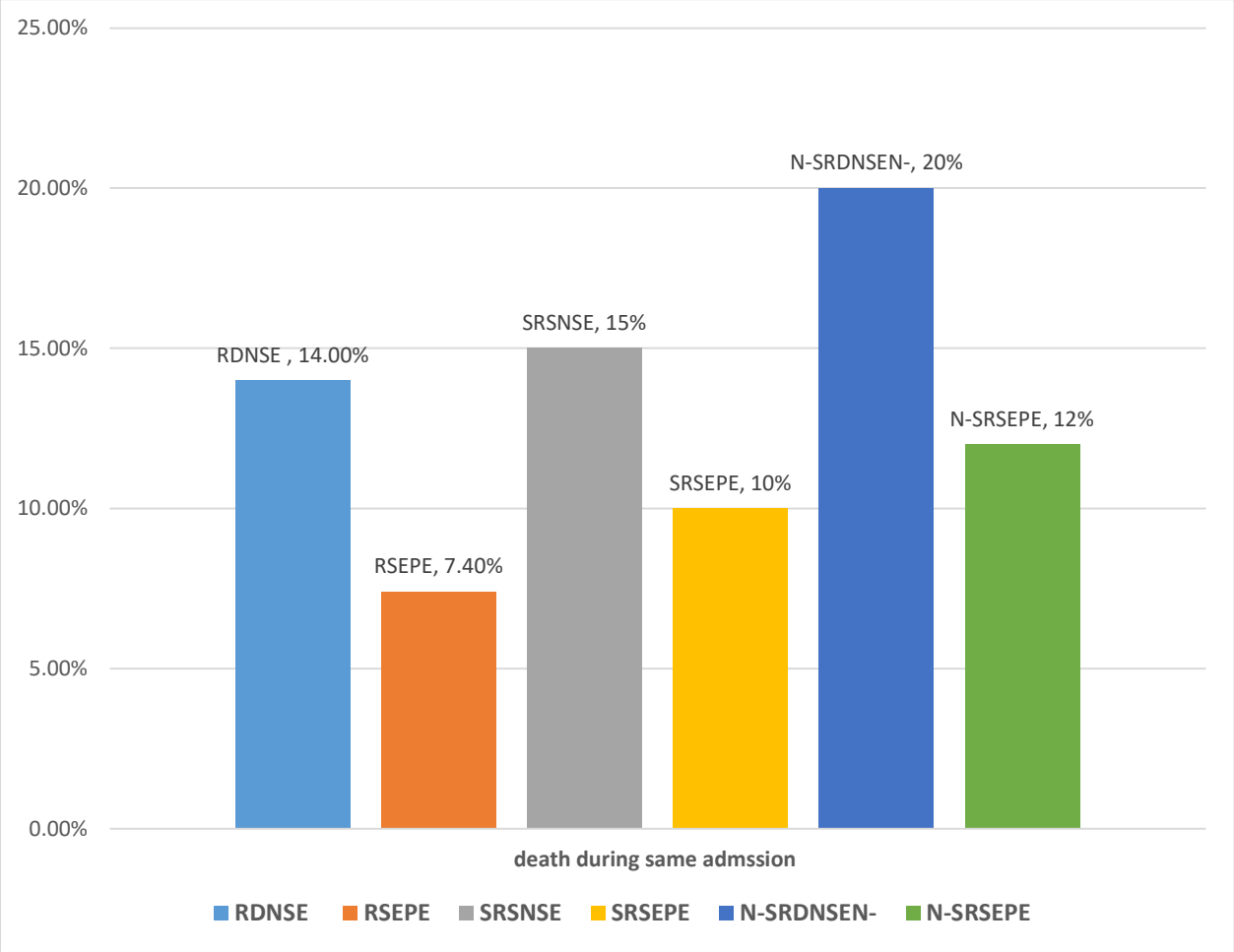

Figure 5.1 Death during same admission comparison btw 3 cohorts and subgroups

Refractory De novo SE main cohort **vs** Refractory De novo SE in known prior epilepsy main cohort RDNSE vs RSEPE 633 cases

Supra Refractory De novo SE cohort **vs** Supra–Refractory De novo SE in known prior epilepsy. SRDNSE vs SRSEPE 231 cases

Neuro-Supra Refractory De novo SE cohort **vs** neuro supra–Refractory De novo SE in known prior epilepsy. N-SRDNSE vs N- SRSEPE 193 cases.

Recovery with deficit after SE comparison in 3 groups

Incidence of recovery with deficit was more in De Novo status epilepticus groups in main cohorts and but not much different in supra refractory group and in fact was worst in neuro ITU group as shown in Figure 2 and table 11. Main cohort the rate recovery with deficit was 30% for De Novo group compared to 19% for SEPE group. In Supra refractory group the incidence of recovery with deficit was not much different between De Novo and known epilepsy group 23% vs 21.42% this probably reflects poorer outcomes from prolong ITU admission, complicated and drug resistant nature of supra refractory status epilepticus. Underlying cause most likely also has association between poor outcomes in supra refractory status epilepticus outcomes. In neuro ITU cohort incidence of recovery with deficit was higher in known epilepsy group 39% vs 28% in De Novo group.

Groups and subgroups	**RDNSE**	**RSEPE**	**SRSNSE**	**SRSEPE**	**N-SRDNSEN-**	**N-SRSEPE**
Recovery with Neurological Deficit	30%	19%	23%	21.42%	28%	39%

Table 5.11 Recovery with deficit comparison btw 3 cohorts and subgroups

Refractory De novo SE main cohort **vs** Refractory De novo SE in known prior epilepsy main cohort RDNSE vs RSEPE 633 cases

Supra Refractory De novo SE cohort **vs** supra–Refractory De novo SE in known prior epilepsy. SRDNSE vs SRSEPE 231 cases

Neuro-Supra Refractory De novo SE cohort **vs** neuro supra–Refractory De novo SE in known prior epilepsy. N-SRDNSE vs N- SRSEPE 193 cases

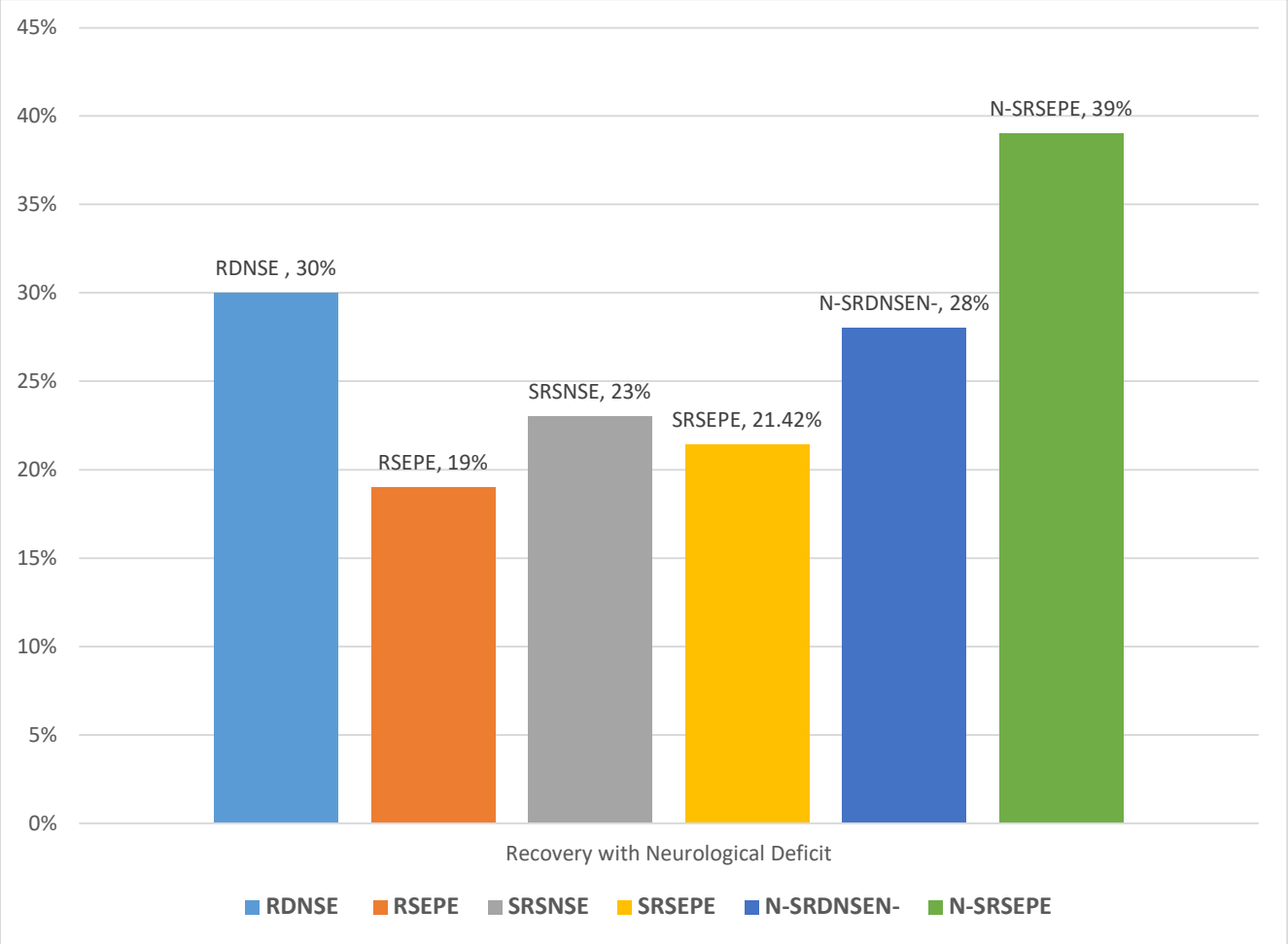

Figure 2 Recovery with deficit after SE, comparison btw 3 cohorts and subgroups

Refractory De novo SE main cohort **vs** Refractory De novo SE in known prior epilepsy main cohort RDNSE vs RSEPE 633 cases

Supra Refractory De novo SE cohort **vs** supra–Refractory De novo SE in known prior epilepsy. SRDNSE vs SRSEPE 231 cases

Neuro-Supra Refractory De novo SE cohort **vs** neuro supra–Refractory De novo SE in known prior epilepsy. N-SRDNSE vs N- SRSEPE 193 cases

Recovery with no deficit after SE comparison in 3 groups

Throughout the cohort recovery with no deficit was more evident in known epilepsy subgroup. This common observation in all 3 cohorts (main cohort, supra refractory status epilepticus and neuro ITU). In main cohort recovery without no deficit rate was almost 30% more in known epilepsy group, in supra refractory group rate of full recovery was 18% more in known epilepsy group and in neuro ITU group rate of full recovery was 17% more in known epilepsy group (table 12 and figure 3)

Groups and subgroups	**RDNSE**	**RSEPE**	**SRSNSE**	**SRSEPE**	**N-SRDNSEN-**	**N-SRSEPE**
Full recovery no neurological deficit	20%	50%	30%	48.80%	10%	27%

Table 5.12 Recovery without deficit after SE, comparison btw 3 cohorts

Refractory De novo SE main cohort **vs** Refractory De novo SE in known prior epilepsy main cohort RDNSE vs RSEPE 633 cases

Supra Refractory De novo SE cohort **vs** supra–Refractory De novo SE in known prior epilepsy. SRDNSE vs SRSEPE 231 cases

Neuro-Supra Refractory De novo SE cohort **vs** neuro supra–Refractory De novo SE in known prior epilepsy. N-SRDNSE vs N- SRSEPE 193 cases

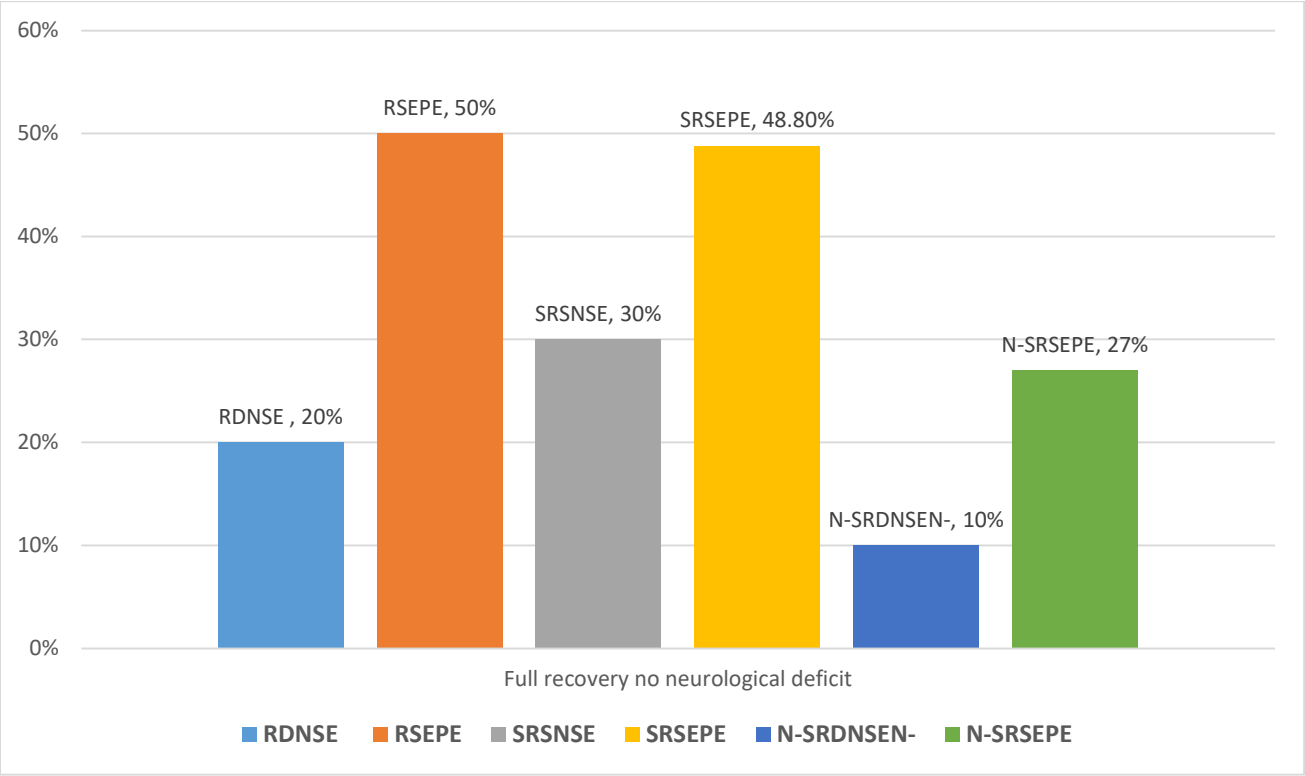

Figure 5.3 Recovery without deficit after SE, comparison btw 3 cohorts

Refractory De novo SE main cohort **vs** Refractory De novo SE in known prior epilepsy main cohort RDNSE vs RSEPE 633 cases

Supra Refractory De novo SE cohort **vs** supra–Refractory De novo SE in known prior epilepsy. SRDNSE vs SRSEPE 231 cases

Neuro-Supra Refractory De novo SE cohort **vs** neuro supra–Refractory De novo SE in known prior epilepsy. N-SRDNSE vs N- SRSEPE 193 cases

Cause of death and causes of status comparison btw 3 group

Most prevalent cause of status epilepticus in main cohort was alcohol and drug provocation but incidence of provocation was more in De novo group 55% compared to known epilepsy group 37%. Same was the case in supra refractory group with alcohol and drugs causing status more in De Novo group 43% compared to 33% in known epilepsy group. In neuro ITU group we noticed significantly less provocation from alcohol and drugs compared to main and supra refractory groups, but substance abuse was still the cause of status in up to quarter of neuro ITU case in De Novo group. Interestingly in neuro ITU known epilepsy group main cause of status was complex epilepsy syndromes, drug resistant epilepsy or issues with anti-epileptic medication failure.

In main cohort most common cause of death for De Novo group was alcohol and drugs (34%) but in known epilepsy group in main cohort most common cause of death was seizure related complications (40%). In supra refractory group most common cause of death in De novo subset was intra cranial bleeds and head injuries (23%) and most common cause of death in supra refractory known epilepsy cohort was seizures related complication (33%). In neuro ITU group the most common cause of death in De Novo group was alcohol and drugs (22.8%) and in known epilepsy group neuro ITU was seizures (57%).

	RDNSE	**RSEPE**	**SRDNSE**	**SRSEPE**	**N-SRDNSE**	**N-SRSEPE**
Most prevalent cause of status	Alcohol/ drugs (55%)	Alcohol/ drugs (37%)	Alcohol and drugs (43.5%)	Alcohol and drugs (33%)	Alcohol and drugs (28.6%)	Progressive epilepsy syndrome and AED failure (25%)
Most common cause of death	Alcohol/ Drug (34%)	Seizure complication (40%)	CVD, ICH, HI (23%)	Seizure complication (33%)	Alcohol and drugs (22.8%)	Seizure complications (57%)

Table 5.13 Comparison of most common cause of status epilepticus and cause of mortality in 3 cohorts and subgroups

Refractory De novo SE main cohort **vs** Refractory De novo SE in known prior epilepsy main cohort RDNSE vs RSEPE 633 cases

Supra Refractory De novo SE cohort **vs** supra–Refractory De novo SE in known prior epilepsy. SRDNSE vs SRSEPE 231 cases

Neuro-Supra Refractory De novo SE cohort **vs** neuro supra–Refractory De novo SE in known prior epilepsy. N-SRDNSE vs N- SRSEPE 193 cases

Comparison of general vs neuro ITU status epilepticus cases

We compared causes of SE in 440 cases of Gen ITU with 193 neuro ITU cases. Most common causes of general ITU SE in decreasing order were alcohol 54%, idiopathic 7%, metabolic 6%, sepsis 4.5% and no information 4.5%. In neuro most common causes were alcohol 34%, brain bleeds/CVD 16%, CNS infection 9.3% and inflammation 7.7%.

Cause of SE general ITU n=440	**Cause SE neuro ITU n=193**
Alcohol/ drugs (54%)	Alcohol /drugs (34%)
Idiopathic (7%)	HI. ICH, Subdural, SAH, CVD (16%)
Metabolic (6%)	CNS infection (9.3%)
Sepsis (4.5%), No info (4.5%)	CNS inflammation (7.7%)

Table 5.14 Top 4 causes of SE in general ITU vs neuro ITU

On further analysis of data for neuro and general ITU its obvious that neuro ITU had higher mortality, immediate and long-term disability compared to general ITU status epilepticus cases. Neuro ITU status epilepticus cases had immediate mortality of 17.6 % compared to 8.6% in general ITU cases. Similarly, recovery with neurological deficit was more in neuro ITU group 29.5% compared to 13.8% in general ITU group.

	General ICU (n=440)	**Neuro ICU (n=193)**
Death during admission	38 (8.6%)	34 (17.61%)
Recovery with Neurological Deficit	61 (13.8%)	57 (29.5%)
Full recovery no neurological deficit	200 (45%)	38 (19.68%)
No information	140 (31%)	50 (25.9%)

Table 5.15- Outcome after SE in general and neuro ITU

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Papers and Presentations

Papers

Refractory Status Epilepticus in Adults Admitted to ITU in Glasgow 1995-2013.

A Longitudinal Audit Highlighting the Need for Action for Provoked and Unprovoked Status Epilepticus

Journal: Seizure: European Journal of Epilepsy Jan 2019

DOI: https://doi.org/10.1016/j.seizure.2019.01.011

Platform Presentation

Franco Scottish epilepsy surgical meeting

Glasgow UK, May 2019

Annual neuro anaesthesia scientific meeting

Strathclyde University Glasgow UK

Status Research Talk

Glasgow neuroscience day Dec 2016

Status Epilepticus Research presentation

Dublin Ireland 2016

Epilepsy surgical case presentation

ABN Brighton UK 2016

Research presentation Status Epilepticus

Edinburgh UK 2014

Presentation Epilepsy futures meeting

London UK 2014

Poster

American Epilepsy society meeting Texas USA Dec 2016

Status Epilepticus Retrospective review

Poster

ILAE annual meeting Nottingham UK September 2014

Incidence and prevalence of status epilepticus 1995 to 2013

Weakness of study

Our study has several limitations. Our analysis was retrospective and as such is subject to bias. In addition, the reported cohort stems from a single city, (although did involve 5 major ITUs in this region), so the results may not be applicable to all patients with RSE. Lastly, we do not have data on quality of life. The latter should be included in future studies. As some of the patient studied were not alive and their data was also destroyed it was hard to be certain about facts. Therefore, there is lack of availability of full information about every case. Not every patient's data was available electronically, as IT system for electronic notes came in place from 2008 onwards, this made it difficult to attain some information for already deceased patients. We accept the limitations of the study in examining patient records. Reliable coding is difficult to guarantee, but we feel that this limitation may lead to reduced sensitivity rather than a reduction in specificity. Such a limitation may explain some of the variability in the incidence across the epochs. Data in relation to SE treatment would have been desirable.