Refractory Status Epilepticus in Glasgow 1995-2013
A longitudinal audit and the Need for Action

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Abstract

This study looked at incidence and outcome of refractory Status Epilepticus (RSE) admitted to ITU facilities in Glasgow between 1995 and 2013.

Results

Eight hundred cases were identified, with adequate information available in 633. Cases were separated depending on whether there had been previous epilepsy (SEPE, n=214) or De Novo Status Epilepticus (DNSE, n=419).

The rising rates of RSE between 1995 and 2013 mirrors that seen in previous studies, and occurs in both SEPE and DNSE. There was no association of incidence of SEPE with any particular AED. Causes in both groups were listed, with 52% of those with DNSE having some contribution from substance misuse. In SEPE, this was felt to play a role in 33.7%.

Duration of stay in both groups was similar, but the longest in-patient stays were in the DNSE group. Admission mortality in both groups was significantly higher in DNSE than in SEPE (13.8% versus 7.5%). This mortality risk was most closely associated with substance misuse in the group with DNSE.

Conclusion

Status Epilepticus is a medical emergency, but even after the acute phase is over, the risk of mortality stays high. De Novo Status Epilepticus has a worse prognosis than SE complicating previous epilepsy. The sustained rise in the risk of mortality should cause us to adopt a holistic method of care for our patients wit Refractory Status Epilepticus, particularly where there is a background of substance abuse.

Introduction

Status epilepticus (SE) is defined as continuation of seizures for more than 5 minutes (Trinka et al 2015) and is a medical emergency that requires immediate assessment and treatment (SIGN 2015). Subdivision of stages of SE have been defined depending on the degree of response to treatment and duration of treatment needed. Refractory status epilepticus (RSE) is 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 (Trinka e Kälviäinen, 2017).

Preclinical studies show that persisting epileptic activity leads to changes in GABAergic function, increased glutamatergic stimulation, as well as changes in mitochondrial function and receptor trafficking, leading to a rapid escalation of epileptogenicity with persisting epileptic activity (Chen and Wasterlain 2006, Kapur and Macdonald 1997, Shorvon et al 2007). Such SE-related changes may underly the morbidity and mortality of prolonged seizures.

There are many recognised causes of status epilepticus (Trinka 2012, Tan et al 2010) and in approximately 50% of cases, this will be the first presentation of seizures or epilepsy .

The risk factors for morbidity and mortality related to SE have not previously been well-defined, although small cohort studies (Shorvon e Ferlisi, 2011), (Sutter *et al.*, 2013), (Novy *et al.*, 2010), (Kämppi *et al.*, 2013) 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.

Several studies (Novy *et al.*, 2010), (Logroscino *et al.*, 1997), (Kantanen *et al.*, 2017) have shown an immediate mortality of SE of between 7 and 39%, while long term mortality has been shown to be higher at 35-43% (Shorvon e Ferlisi, 2011) Logroschino 2002, (Kantanen *et al.*, 2017).

It has been suggested that RSE has a higher short-term and long-term mortality than SE, although this is not invariably replicated (Kantalen 2017). The increased 1-year mortality in SRSE has been associated with older age, or poorer neurological status on discharge from hospital (Kantalen 2017)

Other studies have looked at incidence of SE, but we wanted to look at patients with SE which had been sustained enough to merit admission to an ITU setting, each one thereby fulfilling the definition of RSE, and in some cases SRSE. This study looked at the incidence of RSE spanning the decades following the introduction of newer AEDs. We aimed to consider the effect of different baseline

AEDs and assess the management and outcome of SRSE lasting for very extended periods (this will be discussed in a subsequent paper).

We had hypothesised that increasing use of newer antiepileptic drugs (AEDs), with their more predictable pharmacokinetics, would reduce the incidence of RSE in the population of patients with treated epilepsy.

Methods

The NHS GGC Research Ethics Committee 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 of the hospitals in Glasgow. Local records from the ITU in the Institute of Neurological Science provided additional data.

Coding for admission depended on the international methods. ICD9 codes, which were until 31st March 1996, had no specific code for Status Epilepticus. From April 1996, ICD 10 codes were used, and we sought admissions to ITU, HDU and CCU with primary diagnosis of ICD10 codes G40 ('Epilepsy'), G41 ('Status Epilepticus') & R568 ('Other & Unspecified Convulsions').

Patients with a final diagnosis of Pseudostatus Epilepticus or prolonged dissociative attacks are exclude from this audit but will be presented separately in a later paper. Separate publications will outline the treatments used and their effects.

Demographic information was collected in each case. The outcome after admission was recorded, and for each case we recorded death during admission, at 1 years 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 would have been destroyed, leaving only electronic records available. Where necessary, demographic and admission data was collected from the NHS GGC audit department (n=280) (Table 1 shows the minimum data available for every patient).

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). The causes, treatments, and outcomes (including short-term and long-term mortality) of those with DNSE and SEPE 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 (eg previous admission for detoxification, deranged LFTs before admission, ongoing treatment with methadone, or treatment required for alcohol withdrawal syndrome).

The Glasgow incidence of SE-related admissions per 100,000 was calculated using population estimates for Greater Glasgow from the census nearest the mid point 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 in groups was carried out using a Two Tailed Z test, producing a p value and 95% confidence intervals.

Results

A total of 800 admissions to ITU with relevant diagnostic codes were identified. We excluded 167 cases with insufficient information available, or with no supportable diagnosis of RSE. Six hundred and thirty-three admissions to ITU with RSE were identified, with 214 (34%) patients having experienced prior seizures or a diagnosis of epilepsy (Status Epilepticus with Previous Epilepsy – SEPE). 419 (66%) patients were admitted to an ITU for an index seizure (De Novo Status Epilepticus - DNSE).
The nature of the SE was assessed: 590 (93.20%) being convulsive SE, and 24 (3.79%) were focal SE. Thirteen cases (2%) 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. 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 2b) show increased rates related solely to addiction and abuse in the group with DNSE compared to SEPE (41% versus 18%). A more detailed breakdown of cause is shown later.

Annual Incidence

The annual number of cases of RSE (both SEPE and DNSE) in Glasgow is shown in Table 3. The wide variation is noted, and we have for clarity formed 3-year cohorts (Figure 1). 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 by a slight drop.

Baseline AED Treatment

Among 191 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. Of these, 93 (57%) were receiving only established AEDs, with 24 (14.7%) solely on new AEDs and 46 (28%) on a mixture of established and new AEDs.
Table 4 and Figure 3 show 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 5). Enzyme inducing AEDs (EIAEDs - Carbamazepine, phenytoin, phenobarbitone and primidone) were being prescribed in 104 (63.8%) at the time of admission. Valproate (Figure 3) was the single most commonly prescribed AED, used in 68 patients (41.7%). Phenytoin was the second most commonly prescribed (n=53, 32.5%) and levetiracetam the 3rd most common AED 31 (19%).

Identified Causes of SE
Where specific causes were identified, these are listed in Table 6. As expected, SEPE and DNSE have a different spread of contributory and causative factors. 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 13.8%.

Outcomes of RSE – Admission to ITU and Total Hospital Stay
The median duration of stay in ITU (ie time to discharge or death) was similar in both groups, with more than half staying in for 2 days or less (Table 7). While the median stay is similar across SEPE and DNSE groups, 10.5% and 13% 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 0.31% 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.

Outcomes of RSE – Death, Residual Neurological Deficit, or Full Recovery
As can be seen in Table 8 and 9, the admission mortality rate was higher in DNSE than SEPE (14% versus 7.5%) (p=0.0195 CI 1%-11.59%). At one-year, 5 years and 10 years post admission post- admission, this significant difference in mortality had persisted, (Table 8+9).
Where information was available (Table 10), we looked at the discharge status, showing incidence of full recovery in those with DNSE (31.3%) and SEPE (24.4%). Among those surviving the admission, the percentages with and without neurological deficit were very similar in both DNSE and SEPE, with one third in each group surviving without neurological deficit.

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 seen as 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

Discussion

We believe this is one of the largest studies of incidence and outcome of refractory SE (Misra et al 2017, Strzelczyk et al 2017, Kantanen 2017). Using available records we attempted to assess the longitudinal incidence of SE in a single city over a period of almost two decades.

The criteria for recruitment (ie requiring treatment in an ITU setting) ensures that these cases are at least Refractory SE (rSE) with 303 (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.

We have separated out the 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.
A male preponderance is common to both groups which appears unusual in studies of SE (Knake et al 2001, Strzelczyk et al 2017,). The study by Strzelczyk et al (2017) 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 (Nelligan and Walker 2016, Wu et al 2002, Dham et al 2014), and it has been postulated that it is increasing identification and treatment that explains the decreasing mortality from SE in England and Wales (Nelligan and Walker 2016). 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 later 2015 (SIGN 1997, SIGN 2003, SIGN 2015) emphasising the need for emergency care.
Studies of SE (Knake 1997, Hesdorffer 1998, Coeytaux 2000, Jallon 1999) 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 (Kantanen 2017). Our data would suggest a similar incidence of SRSE, at 2.7/100,000, to that described by Kantanen (2017).

The pattern of SE noted in our population was similar to other studies of adults (Knake 2001), with the majority of cases comprising convulsive SE. In those with SEPE, there was no particular emergent pattern of AED use when looking at individual AEDs or when grouping by effect on hepatic enzymes. The increasing use of newer AEDs in SEPE was unsurprising, and is in keeping with the contemporaneous change in prescribing pattern across the country.

Mortality of refractory Status Epilepticus

As can be seen in Table 8 and 9, the admission mortality rate was higher in DNSE than SEPE (14% versus 7.5%). The other large study of RSE suggested an admission mortality of around 15% across all cases of RSE (Strzelczyk et al 2017). 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 then 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).

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 said (Neligan and Shorvon 2011), to depend on the duration of seizures and the underlying cause. 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 (ie alcohol and / or drugs) would reduce mortality, but our data does not reflect this. Table 10 and 11 show the contribution of addiction and abuse to deaths in the group with DNSE and SEPE. At each time point, alcohol and drugs comprise the largest contributor to mortality. In those with SEPE (Table 11) 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

Despite the longer admission with DNSE, the rate of full neurological recovery was similar in those with DNSE and SEPE. This risk of residual neurological deficit despite 'milder' RSE may reflect the cause of the underlying epilepsy in SEPE, whether that be a primary lesion, vascular event, or prior trauma or neurosurgery.

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 (Marson 2005).

Neurological Disability

Previous studies of SE among adults (Cascino 1998) 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 (Nelligan and Shorvon 2011). While the rates of neurological deficit are raised in both DNSE and SEPE, in neither does the level of disability approach that in another larger study where only 23% were able to be discharged back to their home (Kantanen 2017).

Conclusion

We think the study of this group of similarly and consistently severe status epilepticus is important. Firstly we think that 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 significantly 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, and that such episodes should spark off a chain of multispecialty care in order to address this recurring and persisting public health disaster which is comprised of too many personal tragedies.

Figures and Tables

Table 1
minimum data set
CHI number or hospital ID
AGE
SEX
Year of SE
Prior epilepsy or DNSE
Length of ITU STAY
Date of hospital admission
Date of ITU admission
Date of ITU discharge
Date of hospital discharge
Date of death
Death after number of days from ITU d/c

Table 2 Demographic Data:

	Total n=633 (100%)	De Novo SE n=419 (66%)	SEPE n=214(34%)
Age (years) Mean, Range	48 15-91	50 15-91	44 15-90
Female :Male	249:384 1:1.54	162:257 1:1.58	87:127 1:1.46
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 (6.4%)	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	303 (47.86%)	220 (52.5%)	83(38.7%)
Deaths during admission	74 (11.69%)	58 (13.8%)	16(7.47%)
Deaths before 1-year post Admission (%age died / FOLLOW UP @1 YEAR)	141 (22%)	106(25%)	35(16%)

Table 2b Nature of Status Epilepticus and Identified Causes

	Total cohort n=633 (100%)	De Novo SE n=419 (66%)	SEPE n=214(34%)
Type of status:			
Focal	24 (3.8%)	10 (2%)	14 (6%)
GTCS	590 (93%)	395 (94%)	195 (91%)
Not Known	6 (0.9%)	6 (1.5%)	0
NCSE	13 (2%)	8 (2%)	5 (2.3%)
Cause of Status:			
Alcohol & Drugs	210 (33.17%)	171 (41%)	39(18.2%)
Multiple including alcohol and drugs	82 (13%)	48 (11.5%)	34 (15.2%)
Others non-alcohol and drugs related causes	308 (48.65%)	179 (42.7%)	129 (65.9%)
No information	33 (5.2%)	21 (5%)	12(5.6%)
Continued AED	310 (55.45%)	134 (37%)	176 (89%)

Table 3 – Annual No Of Cases of Status Epilepticus in Glasgow 1995-2013

Year	Total Number	SEPE	DNSE
1995	13	2	11
1996	1	0	1
1997	24	8	16
1998	12	1	11
1999	23	5	18
2000	29	8	21
2001	34	12	22
2002	43	15	28
2003	29	7	22
2004	34	14	20
2005	41	16	25
2006	51	17	34
2007	55	21	34
2008	55	22	33
2009	59	18	41
2010	28	13	15
2011	49	17	32
2012	35	9	26
2013	18	9	9

Figure 1
Average Incidence of Status Epilepticus by Cause
(/100,000/year)

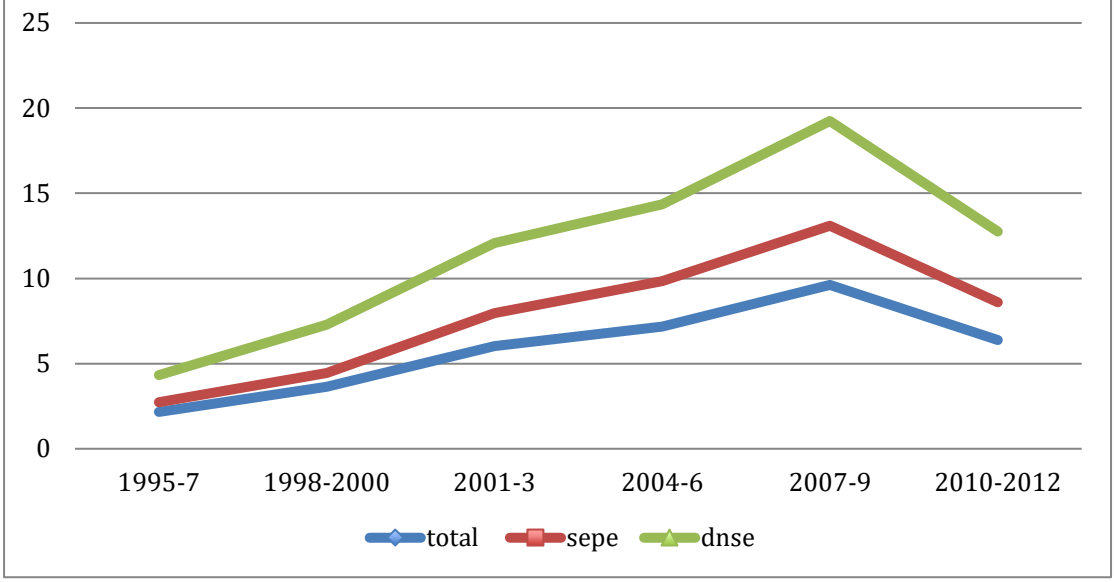
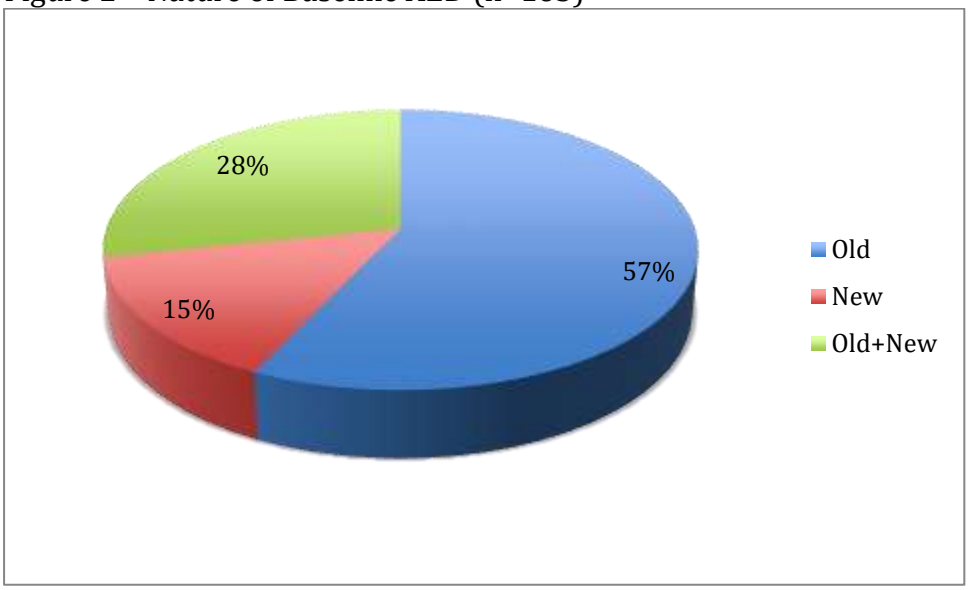


Figure 2 – Nature of Baseline AED (n=163)



Old AEDs =Phenytoin, Carbamazepine, Sodium Valproate
New AEDs = Lamotrigine, Levetiracetam, Gabapentin, Vigabatrin

Table 4 – Nature of Baseline AED in SEPE Group by Year of Admission

	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

CBZ=Carbamazepine, VPA=Valproate, PHT=Phenytoin, GBP=Gabapentin, LTG=Lamotrigine, TPM=Topiramate , LEV=Levetiracetam, VGB=Vigabatrin,

Table 5 – AED use grouped by Hepatic Enzyme Activity

	1995-2002	2003-2013
AED Use		
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 6 - Causes of Status Epilepticus

	DNSE (n=419) N, (%)	SEPE (n=214) N, (%)
Sole Contributor = Alcohol +/or drugs	171 (40.8%)	39 (18%)
Cerebrovascular / trauma	55 (13.1%)	0
Alcohol +/or drugs + Other contributors	48 (11.5%)	34 (15.7%)
Metabolic (eg renal / hepatic failure)	27 (6.5%)	3 (1.4%)
CNS Lesion	17 (4.1%)	15 (6.9%)
CNS infection	17 (4.1%)	3 (1.4%)
Idiopathic	16 (3.8%)	30 (13.8%)
CNS inflammation	11 (2.6%)	3 (1.4%)
Post Op	10 (2.4%)	6 (2.8%)
Systemic Sepsis	9 (2.1%)	17 (7.8%)
Medication	6 1.4%)	3 (1.4%)
Cardiovascular	4 (1%)	2 (0.9%)
Pregnancy	3 (0.7%)	0
Electroconvulsive Therapy	2 (0.5%)	0
Neurodegenerative	2 (0.5%)	1 (0.5%)
Progressive epilepsy syndrome	n/a	24 (11.1%)
Poor adherence or loss of drug levels	n/a	25 (11.5%)
No Information Available	21 (5%)	12 (5.6%)
	419	214

Table 7 – Duration of Hospital and ITU Admission for SE

	Total	DNSE	SEPE
ITU Stay (days)			
Median	1.0	1.0	2.0
Mean	3.6	3.7	3.7
Range	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	8.0	10.0	6.0
Mean	21.4	28.0	8.7
Range	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 8 - Year of Death After SE Admission

Years	DNSE Deaths	SEPE Deaths
0 year	58	16
1 year	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 9 - **Cumulative Mortality Over 10 years**

	Total Cohort	DNSE	SEPE	p-value CI for Difference between DNSE and SEPE
Deaths same admission	74 (11.69%)	58 (13.8%)**	16(7.47%)**	P=0.02 1%-11.6%
Deaths at 1-year post SE	141 (22%)	106(25%)**	35 (16%)**	P=0.011 2.1%-15.8%
Deaths at 5-year post SE	236 (37.3%)	174 (41.5%)***	62 (27.6%)***	P=0.0014 5%-21%
Deaths at 10 - year post SE	285 (45%)	206 (49%)**	79 (37%)**	P=0.0033 4.1%-20.5%

Figure 4 – Date of Death After Admission for SE

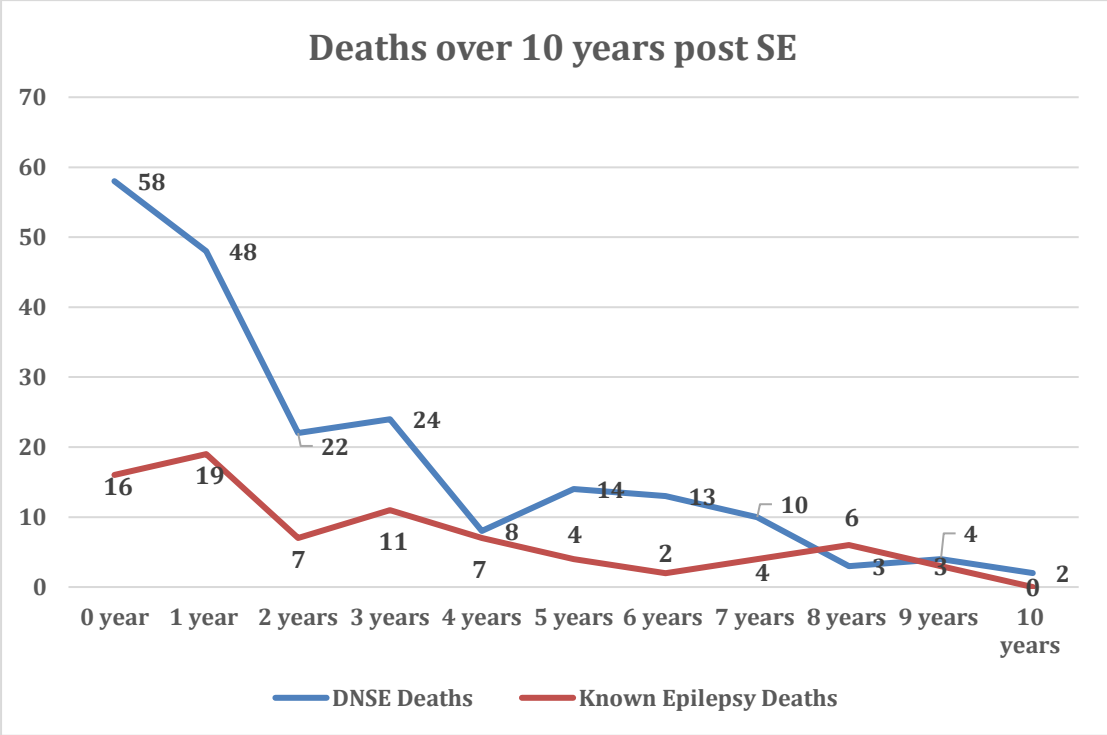


Table 10 – Outcome after SE in DNSE and SEPE

	Total Group (n=430)	DNSE (n=265)	SEPE (n=164)
Death during admission	73 (17%)	58 (21.9%)	16 (9.8%)
Recovery with Neurological Deficit	232 (54%)	124 (46.8%)	108 (65.9%)
Full recovery no neurological deficit	124 (28.8%)	83 (31.3%)	40 (24.4%)

Table 11 **Main Causes of Death in Each Epoch Post-Admission in DNSE**

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

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

Table 12 – SEPE Group - Main Causes of Death in Each Epoch Post-Admission

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

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

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