A retrospective cohort study of super-refractory status epilepticus in a tertiary neuro-ICU setting

Bellami Kerin[a], Sanjeev Rajakulendran[ade], Dimitri M. Kullmann[a], Aidan Neligan[abc], Matthew C.Walker[a]

[a]UCL Queen Square Institute of Neurology, London, WC1N 3BG, UK
[b]Homerton University Hospital NHS Foundation Trust, Homerton Row, London, E9 6SR, UK
[c]Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Queen Mary University, UK
[d]The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK
[e]The North Middlesex University Hospital, Sterling Way, London, N18 1QX, UK

Abstract

Purpose

Over the last decade, the range of treatments available for the management of super-refractory status epilepticus (SRSE) has expanded. However, it is unclear whether this has had an impact on its high mortality and morbidity. The aim of this study was to investigate whether there has been a change in the outcome of SRSE over time in a neurological intensive care unit (ICU) within a tertiary centre.

Methods

Analysis of a retrospective cohort of 53 admissions from 45 patients to the neurological ICU at the National Hospital for Neurology and Neurosurgery, Queen Square, London, between January 2004 and September 2018.

Results

Significant reductions were observed in both duration of SRSE over time and in the time spent in ICU, suggesting that treatment quality has improved over time. A median of four antiseizure drugs (ASDs) were given prior to seizure resolution. In 23 % resolution of SRSE occurred following optimisation of current treatment rather than introduction of a new ASD. The mortality rate was very low at 11 % by 6 months; however, there was no indication of improvement in outcome as all surviving patients had a modified Rankin scale score of 3–5 upon discharge from ICU, classified as moderate-to-severe disability.

Conclusion

Neither the survival rate nor the outcome score changed significantly over time, suggesting that changes in the treatment of SRSE have had no impact on patient outcome.

Keywords: SRSE, outcome, mortality, morbidity

Introduction:

Super-refractory status epilepticus (SRSE) is defined as status epilepticus which continues for 24 hours or more after the initiation of anaesthesia (Shorvon and Ferlisi, 2012) and includes those cases which recur upon reduction or withdrawal of anaesthetic agents. Evidence suggests that approximately 15% of all cases of status epilepticus enter super-refractoriness. Despite its high mortality, it remains poorly understood with only a few published studies on treatment and prognosis (Kantanen et al., 2017; Kantanen et al., 2015).

Treatment remains largely unguided with no evidence-based protocols for the use of anti-seizure or disease-modifying interventions, aside from the standard protocol of progressing to anaesthesia following the failure to achieve seizure cessation despite the use of benzodiazepines and typically one (or occasionally two) parentally administered anti-seizure drugs (ASDs). This is largely due to a lack of evidence for the efficacy of SRSE treatments, or indeed any pre-eminence of one therapy over another, as research is typically limited to small series as a consequence of the rarity of the condition (Shorvon and Ferlisi, 2011; Shorvon and Ferlisi, 2012). Most evidence points to aetiology as the main determinant of prognosis, where SE occurring in the setting of metabolic disorders, acute neurological insult, meningitis or cerebrovascular disease have been associated with worse prognoses than low AEDs or alcohol abuse (Neligan and Shorvon, 2010; Novorol et al., 2007). Hence, if true, it would be postulated that the advent of newer ASD treatments would not result in a significant change in the prognosis of SRSE.

We aimed to determine if this is the case in a retrospective cohort study of the treatment and outcome of SRSE in a specialist neurological intensive care unit at a tertiary referral unit over >14 years. We investigated whether the prognosis of SRSE has changed over time and if any single treatment has had an impact on prognosis.

Methods:

Data were extracted from the medical records (IntelliVue Clinical Information Portfolio, Clinical Data Repository) and paper medical records of all patients who were admitted to the neurological intensive care unit (ICU) at the National Hospital for Neurology and Neurosurgery (NHNN) between January 2004 and September 2018 for SE. Only cases of SRSE were included, defined as SE that continues for 24 hours or more after the onset of anaesthetic therapy or that recurs on withdrawal of the anaesthetic agent (thiopental or propofol with or without midazolam). Patients not in SE on admission, not sedated on admission, or sedated for agitation rather than SE were excluded.

Patients were also excluded if admission and discharge dates could not be found, data on ASDs could not be found or the duration of SE could not be determined.

Data included dates of ICU admission and discharge (includes date of death for patients who died at NHNN), aetiology if known, and prior history of seizures. The severity of SE was recorded for each patient using the Status Epilepticus Severity Score (STESS) (Rossetti et al., 2008). The time of seizure resolution was taken as time of decision to wean anaesthesia, provided SE did not subsequently reoccur whilst in ICU.

All ASDs given during ICU stay before SE resolution were recorded with start and stop dates and times as well as maximum dosage. ASDs administered on the day of arrival in the ICU were assumed to be drugs initiated prior to transfer, unless a drug was given several hours after other drugs were given. Outcomes at discharge from ICU and at final discharge from the NHNN either home or to the referring hospital were rated using the modified Rankin Scale (mRS) for Neurological Disability (Banks and Marotta, 2007). Outcome data on discharge from the referring hospital was not available. Survival rates were ascertained up to May 2019.

Statistics:

The cohort was split into two groups for analysis: patients with prior history of seizures and patients with no prior history of seizures because previous studies have indicated different outcomes for these two groups. Patient characteristics, ASD usage and patient outcome were analysed separately, with a comparison made between the two groups for each using either Mann Whitney U test or Pearson's chi-square test. Linear and logistic regression analyses were conducted to analyse factors affecting the duration of SE and the duration of admissions to the ICU over time as well as factors influencing survival and mRS score over time. The analysis was performed using IBM SPSS Statistics software.

Results:

There were 86 admissions to the ICU in the given time frame. 33 admissions were excluded because the patients did not have SRSE (9) or because admission data could not be retrieved (24). Thus, 53 admissions from 45 patients were included. Patient characteristics are contained in Table 1, divided into those with (n=25) and without (n=28) prior history of seizures. All but one patient with a prior history of seizures were chronic epilepsy patients; however, some had other suspected SRSE causes

such as stroke, sepsis, NMDA encephalitis, primary brain/meningeal tumour. One patient was 10 years seizure-free and the cause of SRSE was unknown.

No significant differences were found between these two groups for age, gender, time in SE before admission, number of ASDs started before arrival or number of ASDs given overall. A significant difference was found between the two groups for STESS score (U=63.5, p<0.001); however, this is mainly explained by a prior history of seizures being part of the STESS score calculation.

Table 1. Patient Characteristics

Characteristic	Overall (n=53)		Prior history of seizures (n=25)		No prior history of seizures (n=28)		*p* value
Age (years; mean, SD)	40	15.4	39	16.0	41	15.1	0.544[a]
Female gender (n, %)	35	64	17	68	18	63	0.776[b]
STESS score (mean, SD)	4	0.64	3	0.37	4	0.33	**<0.001[a]**
Time in SE before admission (days; median, IQR)*	4	3-8	4	2-6.5	6	3-7	0.479[a]

Bold *p* values are considered significant.

*n=21 overall, n=11 with history of seizures, n=10 with no history of seizures

[a] Mann Whitney *U* test

[b] Chi-square test

The range of aetiologies of SRSE is illustrated in Figure 1. The most common aetiology was encephalitis, with epilepsy of unknown cause as the second most common diagnosis.
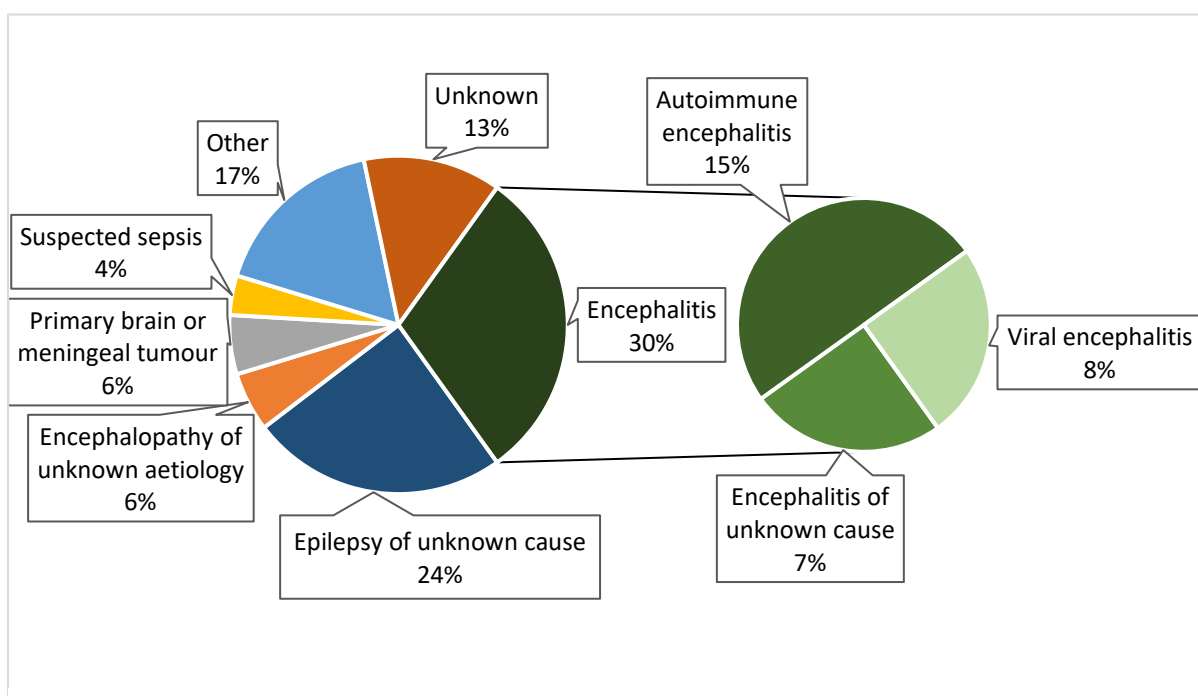
Figure 1. A pie chart displaying the proportion of aetiologies recorded in the sample.

All patients were on ASDs on admission to ICU (Table 2). There were 12 (23%) admissions in which no drugs were started in the ICU, for which the median duration of SE was 3 days. In those patients, dosage alterations to existing ASDs were sufficient to resolve SRSE without introduction of new ASDs. Changes in dosage tended to be made to drugs other than levetiracetam which was usually given at maximum dosage from initiation. Of the other 41 admissions, SRSE resolved in 22 within 3 days of starting a new drug (supplementary table 1). Overall, approximately 10% of new drug administrations resulted in resolution of the SRSE within 3 days with no specific ASD being more effective than others.

Table 2. ASD Usage Summary

	Overall (n=53)		Prior history of seizures (n=25)		No prior history of seizures (n=28)		*p* value
Number of ASDs started before arrival (median, IQR)	3	2-4	3	2-4	4	3-5	0.138[a]

Number of ASDs started in ICU (median, IQR)	1.0	1-2	1.5	0.75-2	1.0	1-2	0.904[a]
Number of ASDs given overall (median, IQR)	4.0	3-5	4.0	3.75-5.25	4.0	3-5	0.371[a]

Bold *p* values are considered significant.

[a] Mann Whitney *U* test

Stepwise multiple regression analyses were performed to determine whether either the duration of SE or length of stay in ICU can be predicted by the date of admission, age, STESS score, gender or seizure history. Of these factors, the date of admission was the only significant predictor of the duration of SE (β=-0.273, $p<0.05$) and the only significant predictor of length of stay in ICU (β=-0.444, $p<0.001$). These results suggest that there was a significant decrease in the duration of SE and length of ICU stay over time but that other factors are very likely to account for these changes.

Usage of immunotherapies is summarised in Table 3. Both steroids and plasma exchange were employed in cases with a suspected inflammatory aetiology.

Table 3. Immunotherapies

Treatment	Number of times given (n, % of total admissions)	Median duration of SE in ICU (days)	Median duration of stay at ICU (days)	Number of times SE resolution was attributable to treatment (n, %)
Steroids	15 (28%)	6	20	10 (67%)*
Methylprednisolone	3 (6%)	25	103	0 (0%)*
Prednisolone	8 (15%)	6	41	6 (75%)*
Dexamethasone	4 (8%)	4.5	19	4 (100%)*
Plasma exchange	4 (8%)	8	61	3 (75%)**

*for SE resolution within 10 days of treatment initiation

**for SE resolution within 2 weeks of treatment initiation

Table 4 shows the results for patient outcome including survival rates and Rankin Outcome Scale scores at discharge. Of the patients who died at the NHNN, half died on ICU. All the Rankin scores at unit discharge were classified as moderate to severe disability. No significant differences were found between patients with prior history of seizures and without prior history of seizures for ICU mortality ($X^2(1)=0.007$, $p=0.935$), NHNN mortality ($X^2(1)=0.014$, $p=0.906$), mortality at 6 months following discharge ($\chi^2(1)=0.520$, $p=0.471$) or current mortality ($\chi^2(1)=0.04$, $p=0.842$). Similarly, no differences were found for mRS scores at ICU discharge ($U=323.5$, $p=0.806$) nor for duration of SE in ICU ($U=0.303$, $p=0.398$) or for duration of ICU stay ($U=339.5$, $p=0.852$).

Table 4. Patient Outcome

	Overall (n=53)		Prior history of seizures (n=25)		No prior history of seizures (n=28)		*p* value
NHNN mortality	8%		8%		8%		0.906[b]
Mortality at 6 months following discharge	11%		8%		14%		0.471[b]
Mortality as of May 2019	19%		20%		18%		0.842[b]
Median Rankin scale score at unit discharge	4		5		4		0.806[a]
Duration of SE in ICU (days; median, IQR)	4	1-8	3	2-7	5	1-11.5	0.398[a]
Duration of stay in ICU (days; median, IQR)	23	10-58	29	10-51	20	8.5-62.5	0.852[a]

*overall n=39 because 6 patients were readmitted to the ICU, and data for outcome at hospital discharge of 8 patients were unavailable, prior history of seizures n=20, no prior history of seizures n=19

[a] Mann Whitney *U* test

[b] Chi Square test

Discussion:

A principal finding of this study is a very low mortality rate of SRSE for NHNN of 8% (11% at 6 months following discharge), compared to published reports citing 17-35%. This is a positive but surprising finding, even taking into account the highly specialised setting in which the patients were managed (Logroscino et al., 2005; Shorvon and Ferlisi, 2012; Neligan et al., 2019). There are a number of explanations for this including: first, NHNN represents a significant outlier, with management of cases occurring in the setting of a dedicated neurological ICU with specialist epilepsy input and availability of continuous EEG monitoring along with specific interventions such as immunotherapy; second, the higher mortality reported in the medical literature may be due to a combination of variability in care settings, expertise and resources, a retrospective selection bias and also in how the definition of SRSE is applied; third and most probably, the cases transferred to the NHNN are generally more likely to survive having negotiated the risk of early demise indicating a degree of selection bias.

Our data indicate both a gradual reduction in the duration of SE among patients in ICU and a decrease in the length of time spent in ICU in the time interval analysed (2004 – 2018) with no patient characteristic identified as influencing either outcome. The former observation would suggest that the treatment of SRSE within the ICU has improved over time resulting in more rapid resolution, whereas improvements in the overall management of these patients, who almost invariably develop medical complications and comorbidities, are likely to account for the latter finding. A possible confounder is that the duration of SE recorded for patients in this study was influenced by when the decision was taken to wean. This was often delayed by either the need to wait for instruction from a senior physician or the need to wait for other medical problems such as sepsis to resolve. Consequently, it was often difficult to determine the exact time point of SE resolution. The decreasing trend in both duration of SE and ICU stay could be a result of either better drug choices, more confidence in dosage changes or better use of anaesthetics.

Nevertheless, whilst the decreasing trend in duration of SE and low overall mortality rate suggest there is a good and improving quality of care for patients at NHNN, it is important to note that there has been no change over time in the mortality of patients, consistent with the findings in a recent meta-analysis of mortality in convulsive status epilepticus (Neligan et al., 2019), nor mRS scores, with all patients discharged from ICU having moderate to severe disability (mRS score of 3-5). Of course, given the fact that pre-admission global functional status (mRS) was not routinely recorded at transfer, it is not certain that this represents a significant deterioration from baseline (pre-admission mRS). Nevertheless, given that patients in this cohort tended to be younger (median age

40), it can be reasonably expected that pre-admission mRS scores were low for many (mRS 0-2). This suggests that any improvement in quality of care has not translated into improved functional outcome of patients. Indeed, we would argue that in future studies, a greater emphasis ought to be placed on functional status following discharge, which unfortunately continues to be poor.

Other findings in this cohort include no differences in prognosis between patients with and without a prior history of seizures in any patient characteristics other than STESS score which indicated, as expected, that the severity of SE was higher for patients without a prior history of seizures. There was no difference in duration of SE in the ICU between the two patient groups nor was seizure history predictive of the outcome measures (survival and mRS outcome score). This suggests that prognostic factors for SRSE may differ from SE in general. Whilst aetiology and prior history of epilepsy have a prognostic value in SE, particularly in terms of the risk of developing refractory SE (and SRSE) (Neligan and Shorvon, 2010; Holtkamp et al., 2005), this may no longer hold true once the SE has progressed to SRSE. The corollary to this is that patients with epilepsy who develop SRSE are a different group from the easily treated group and raises the question of the validity of the STESS score in this context. In keeping with other studies (Jayalakshmi et al., 2014; Rai and Drislane, 2018; Lu et al., 2018; Neligan and Shorvon, 2010; Novorol et al., 2007), it seems likely that aetiology could be the major, indeed possibly the only determinant of outcome at the super-refractory level since no other patient characteristic was a significant predictor. This, together with our findings regarding the success (albeit with limited sample size) of immunotherapies argues perhaps for increased or earlier consideration of immunomodulatory treatments. These may not only target the underlying cause but also pathogenic mechanisms of status epilepticus itself.

A wide range of ASDs was used in the ICU, with levetiracetam and phenytoin highly favoured (almost all commenced these prior to transfer to NHNN) with phenobarbital, clobazam, sodium valproate, and lacosamide also frequently used (see Supplementary Table 1). Whilst the pattern of drugs used here reflects common practice supported by findings in previous studies (Dalziel et al., 2019; Lyttle et al., 2019; Kapur et al., 2019), there was no evidence in our study to indicate that levetiracetam and phenytoin were the most efficacious. Indeed, the findings from the recent ESETT study indicate no significant differences in terms of efficacy and side-effects between the three most used ASDs in established SE (Phenytoin, Levetiracetam and Sodium Valproate) as second-line treatments (Kapur et al., 2019). Although numbers were small, the three most successful ASDs associated with resolution of SRSE within 3 days of administration were perampanel, carbamazepine and lacosamide, possibly supporting the use of some of the newer ASDs in SRSE. However, this did not translate into improvements in morbidity or mortality. Perhaps, more importantly, was the large number (23%) whose SRSE resolved with optimisation of existing ASD treatment. This further

supports the contention that the successful treatment of SE is possibly more dependent on adequate dosing of ASDs rather than using specific ASDs.

Limitations of this study include the small sample size, lack of pre-ICU admission mRS data and absence of long-term follow-up data as consequences of the retrospective nature of this study. The variability in the information recorded in the medical records limited both the quality of the data analysed and the time period for which data were available. The large number of excluded admissions is likely to have biased the results towards a worse prognosis, as admissions excluded for lacking detailed records were likely to have been easily resolved with a short duration in ICU.

In conclusion, this retrospective cohort study has revealed two key findings. The first is that the survival rate of SRSE at NHNN is higher than that typically seen in SRSE cohort studies (Neligan et al., 2019) suggesting that the risk of death from the condition may not be as high as previously thought. Associated morbidity, however, remains very high and indications of improvements in the quality of care over the last 15 years have not been translated into improved functional outcomes. Hence there remains a pressing need to determine what can be done to reduce the level of disability associated with SRSE. The second key finding is that there is little or no evidence to suggest that ASDs have a significant impact on SRSE, and hence the exceedingly recognised notion that aetiology is the dominant determinant of outcome in SRSE seems increasingly likely. Perhaps then, the most important recommendation is that addressing the underlying aetiology is the highest priority for treatment of this condition.

References:

Banks, J. L. & Marotta, C. A. 2007. Outcomes validity and reliability of the modified Rankin scale: Implications for stroke clinical trials - A literature review and synthesis. *Stroke,* 38(3)**,** pp 1091-1096.

Dalziel, S., Borland, M., Furyk, J., Bonisch, M., Neutze, J., Donath, S., Francis, K., Sharpe, C., Harvey, A., Davidson, A., Craig, S., Phillips, N., George, S., Rao, A., Cheng, N., Zhang, M., Kochar, A., Brabyn, C., Oakley, E., Babl, F. & ., P. r. n. 2019. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. *Lancet,* 393(10186)**,** pp 2135-2145.

Holtkamp, M., Othman, J., Buchheim, K. & Meierkord, H. 2005. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry,* 76(4)**,** pp 534-9.

Jayalakshmi, S., Ruikar, D., Vooturi, S., Alladi, S., Sahu, S., Kaul, S. & Mohandas, S. 2014. Determinants and predictors of outcome in super refractory status epilepticus--a developing country perspective. *Epilepsy Res,* 108(9)**,** pp 1609-17.

Kantanen, A. M., Reinikainen, M., Parviainen, I. & Kälviäinen, R. 2017. Long-term outcome of refractory status epilepticus in adults: A retrospective population-based study. 133(13-21.

Kantanen, A. M., Reinikainen, M., Parviainen, I., Ruokonen, E., Ala-Peijari, M., Bäcklund, T., Koskenkari, J., RuutLaitio, R. & Kälviäinen, R. 2015. Incidence and mortality of super-refractory status epilepticus in adults.

Kapur, J., Elm, J., Chamberlain, J. M., Barsan, W., Cloyd, J., Lowenstein, D., Shinnar, S., Conwit, R., Meinzer, C., Cock, H., Fountain, N., Connor, J. T., Silbergleit, R. & Investigators, N. a. P. 2019. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. *N Engl J Med,* 381(22)**,** pp 2103-2113.

Logroscino, G., Hesdorffer, D. C., Cascino, G., Hauser, W. A., Coeytaux, A., Galobardes, B., Morabia, A. & Jallon, P. 2005. Mortality after a first episode of status epilepticus in the United States and Europe. *Epilepsia,* 46(46-48.

Lu, W. Y., Weng, W. C., Wong, L. C. & Lee, W. T. 2018. The etiology and prognosis of super-refractory convulsive status epilepticus in children. *Epilepsy Behav,* 86(66-71.

Lyttle, M. D., Rainford, N. E. A., Gamble, C., Messahel, S., Humphreys, A., Hickey, H., Woolfall, K., Roper, L., Noblet, J., Lee, E. D., Potter, S., Tate, P., Iyer, A., Evans, V., Appleton, R. E. & collaborative, P. E. R. i. t. U. K. I. P. 2019. Levetiracetam versus phenytoin for second-line

treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. *Lancet,* 393(10186)**,** pp 2125-2134.

Neligan, A., Noyce, A., Gosavi, T., Shorvon, S., Köhler, S. & Walker, M. 2019a. Change in Mortality of Generalized Convulsive Status Epilepticus in High-Income Countries Over Time: A Systematic Review and Meta-analysis. *JAMA Neurol*, 76, pp897-905

Neligan, A. & Shorvon, S. D. 2010. Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. *Arch Neurol,* 67(8)**,** pp 931-40.

Novorol, C. L., Chin, R. F. M. & Scott, R. C. 2007. Outcome of convulsive status epilepticus: a review. *Archives of Disease in Childhood,* 92(11)**,** pp 948-951.

Rai, S. & Drislane, F. W. 2018. Treatment of Refractory and Super-refractory Status Epilepticus. *Neurotherapeutics,* 15(3)**,** pp 697-712.

Rossetti, A. O., Logroscino, G., Milligan, T. A., Michaelides, C., Ruffieux, C. & Bromfield, E. B. 2008. Status Epilepticus Severity Score (STESS). *Journal of Neurology,* 255(10)**,** pp 1561-1566.

Shorvon, S. & Ferlisi, M. 2011. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain,* 134(2802-2818.

Shorvon, S. & Ferlisi, M. 2012. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain,* 135(2314-2328.

Appendix:

Supplementary Table 1. Individual ASD administration

Drug	Total admissions given (n, %)		Number of admissions in which SRSE resolved whilst on drug (n, %)		Number of admissions in which ASDs were started in ICU (n, %)		Number of admissions in which SRSE resolved within 3 days for ASDs started in ICU (n, %)	
Phenytoin	45	85%	35	81%	8	18%	5	11%
Levetiracetam	43	81%	36	88%	6	14%	4	9%
Phenobarbital	25	47%	19	76%	9	36%	2	8%
Clobazam	22	42%	15	75%	2	9%	1	5%
Sodium valproate	18	34%	12	75%	2	11%	2	11%
Topiramate	14	26%	10	77%	5	36%	0	0%
Lacosamide	12	23%	7	58%	4	33%	2	17%
Carbamazepine	9	17%	6	75%	3	33%	2	22%
Clonazepam	9	17%	8	89%	2	22%	1	11%
Perampanel	9	17%	6	67%	4	44%	3	33%
Diazepam	8	15%	4	57%	1	13%	0	0%
Lamotrigine	7	13%	5	83%	1	14%	0	0%
Tiagabine	1	2%	1	100%	1	100%	0	0%
Zonisamide	1	2%	1	100%	0	0%	0	0%
Pregabalin	1	2%	1	100%	0	0%	0	0%