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Infections in status epilepticus: A retrospective 5-year cohort study

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ABSTRACT

Purpose: Status epilepticus (SE) has attracted renewed interest lately, and efforts are made to optimize every treatment stage. For refractory SE, optimal supporting care involves mechanical ventilation and intensive care unit (ICU) admission. Infections often complicate SE and recently a single-centre observational study demonstrated an association between infections and poor short-term outcome of SE in a cohort of severely ill patients. We have here attempted to replicate those findings in a different cohort.

Method: We performed a retrospective observational study and included all patients with a diagnosis of SE during 2008–2012 at a Swedish tertiary referral centre.

Results: The cohort consisted of 103 patients (53% female, 47% male, median age 62 years, range 19–87 years). In house mortality was less than 2 and 70% of the patients' were discharged home. The most common aetiologies of SE were uncontrolled epilepsy (37%) and brain tumours (16%). A total of 39 patients suffered infections during their stay. Presence of infection was associated with mechanical ventilation (OR 3.344, 95% CI 1.44–7.79) as well as not being discharged home (OR2.705, 95% CI 1.14–6.44), and duration of SE was significantly longer in patients with infection (median 1 day vs. 2.5 days, $p < 0.001$).

Conclusion: We conclude that the previously described association between infections, a longer SE duration, and an unfavourable outcome of SE seems valid also in SE of less severe aetiology.

1. Introduction

Status epilepticus (SE) is a neurological emergency requiring rapid treatment. Over the last years, SE has attracted renewed interest and several studies have addressed important aspects of initial management, particularly first- or second-line antiepileptic medication.[1–3] In addition to the efforts concerning early management of SE, there is also substantial interest in the management of patients that fail to respond to initial treatment. There is little evidence from randomized trials to guide clinicians in this scenario, but fundamental to all treatment strategies is optimal supporting care pending resolution of seizure activity.[4–7] SE is frequently complicated by infections, which can be present either at onset of SE or are acquired during hospital stay. The risk of nosocomial infection is probably enhanced in medically refractory cases of SE, since such patients are often in need of general anaesthesia and consequently subject to ICU-associated risks and complications.[6]

In a recent study, Sutter et al. described infections during the course of SE and found an association between clinical short-term outcome and infections.[8] The occurrence of infections in that study was high; 35.6%, and infections were associated with longer duration of SE, greater risk of refractory SE, and higher mortality. In the discussion, the authors prudently noted that the results might be confounded by a high proportion of the cohort suffering from acute symptomatic SE due to hypoxic-ischaemic encephalopathy, a condition with detrimental prognosis. As this study was performed in a single tertiary centre, it needs to be replicated in another population. In Sweden, neurologists are typically not responsible for the care or patients with hypoxic-ischaemic encephalopathy, which presented an opportunity to investigate the incidence of infections in a cohort with aetiologies of SE different to the cohort described by Sutter et al. The aim of our study was therefore to assess if these findings were valid also in a cohort of patients with SE of less catastrophic aetiology, where optimal supporting care is very important, since the prognosis of SE itself is substantially better.

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2. Materials and methods

2.1. Design and setting

The study design was a retrospective observational cohort study. All patients with SE during 5 consecutive years were included. The study was performed at Uppsala University Hospital in Sweden, a tertiary epilepsy centre, serving a population of 300,000 people for secondary care and 2,000,000 people for tertiary care. The study was approved by the local ethics committee in accordance with the standards laid down in the 1964 Declaration of Helsinki and waived the requirement for informed consent.

2.2. Patients and data collection

We performed a search for all patients with a diagnosis of SE at the Department of neurology at Uppsala University Hospital (ICD-10 code G41) between 2008 and 2012. The initial search yielded 118 hits. The inclusion criteria were patients over 18 years that had suffered SE according to the diagnosis made by the treating physician. Exclusion criteria were insufficient or inaccessible medical records. Eight patients did not meet the inclusion criteria due to erroneous coding (had not suffered SE or were under 18 years of age), three patients were excluded because of restricted access to their medical records, and four record entries were duplicates. The included cohort consisted of 103 patients. The medical records were reviewed according to a predefined template. Data were anonymized prior to analysis.

2.3. Definitions

Assumed aetiology of SE, administered treatment, and presence of infections were all based on the entries made in the medical records by the treating physician. At our centre, we use an operational definition of SE as seizures lasting more than 5 min, or recurrence of seizure activity without recovery of consciousness after a seizure. Refractory SE was defined as continuous seizure activity or relapse of seizure activity within 24 h after two medications. Super-refractory SE was defined as SE refractory to 24 h of general anaesthesia. Duration of SE was counted as the time from onset to the first day without seizure activity. If patients were sedated without EEG-monitoring, the time was counted until awakening from general anaesthesia without recurrence of seizure activity. EEG was performed in 44/59 patients with medically refractory SE and 5/5 patients with NCSE. Regarding infections, we used the time limit specified by the Centre for disease control and prevention (CDC) for surveillance purposes. Presence of an infection was determined based on laboratory values and notes in the medical records. Community-acquired infection was defined as an infection presenting within 48 h of admission. Nosocomial infection was defined as an infection presenting after 48 h after admission.

2.4. Statistical analysis

Demographic and clinical characteristics were described as continuous or categorical variables as appropriate. Fisher's exact test was used for categorical correlations. Correlation between infection and duration of SE was assessed using both Spearman's rank correlation and linear regression. In the correlation analyses, we excluded patients with missing values rather than extrapolating data points. Duration of SE in patients with and without infection was compared using the non-parametric Mann–Whitney test. p-Values <0.05 were considered statistically significant. Statistical analysis was performed in GraphPad Prism version 5 for Mac (Graphpad Software Inc.).

3. Results

We first characterized the cohort (Table 1). A total of 103 patients were included, with a slight female predominance. The average age was 55 years and the two most common types of SE were generalized convulsive SE or focal motor SE with impaired consciousness. Seventy per cent of the patients had a history of epilepsy, and all but two patients with such a history were on antiepileptic drugs at the time of admission (69%).

The aetiology of SE was acute symptomatic in 30% of the patients and remote in 70%. The two most common aetiologies in the remote group were uncontrolled epilepsy (37%) and brain tumours (16%). None of the cases in the cohort was attributed to hypoxic-ischaemic encephalopathy. Considering severity, 57% of the patients had medically refractory SE, and 25% of the cases were super-refractory. A total of 47% received mechanical ventilation. Regarding short-term outcome, only two patients (1.9%) in the cohort died. The vast majority, 69%, were discharged home, whereas the other patients were discharged to regional hospitals or other care providers (e.g. nursing homes, rehabilitation facilities, etc.). The standard treatment at our facility is a benzodiazepine followed by phosphenytoin, and in refractory cases sedation with propofol. This was followed in the majority of cases (Table 2).

We then determined the incidence of infections in our cohort (Table 3). A total of 23 patients (22%) suffered community-acquired infections. The most common infections were pneumonia and urinary tract infections (UTI). We detected a total of 29 cases

Table 1
Clinical features of SE and treatment. GCSE, generalized convulsive SE, FCSE, focal convulsive SE, NCSE, non-convulsive SE. Refractory SE = continued or relapse within 24 h of seizure activity after two medications. Super-refractory SE = SE refractory to 24 h of anaesthesia.

Demographics		
Gender	*n*	%
Female	55	53
Male	48	47
Age	Years	±SD/range
Mean	55	±19.5
Median	62	19–87
Clinical features	*n*	%
History of epilepsy	73	71
On AED at time of admission	71	69
Type of SE		
GCSE	58	56
FCSE with impaired consciousness	33	32
FCSE without impaired consciousness	7	6.7
NCSE	5	4.8
Aetiology		
Acute symptomatic	31	30
Brain trauma/surgery	6	5.8
CNS-infection	4	3.8
Cerebrovascular	3	2.9
Alcohol	3	2.9
Cryptogenic/other	15	15
Hypoxic-ischaemic	0	0
Remote	71	69
Uncontrolled epilepsy	38	37
Brain tumour	16	16
Cerebrovascular	13	13
Neurodegenerative	1	<1
Other/unknown	3	2.9
Severity of SE		
Refractory SE	59	57
Super-refractory SE	26	25
Mechanical ventilation	48	47
Short-term outcome		
Discharge home	71	69
Discharge to other provider	30	29
Death	2	1.9

Table 2
Anti-epileptic drugs administered. Out of all 103 patients, 6 patients with convulsive focal SE without impaired consciousness (epilepsia partialis continua) were admitted from the outpatient clinic for dose-adjustment of the pre-existing oral AEDs. For one patient that was transferred from another hospital information regarding initial therapy was not available in the medical records.

Total population (n = 103)	*n*	%
Specific treatment for SE	*96*	93
Only altered dose of oral AED	*6*	5.8
Information missing	*1*	*0.97*
1st drug (n = 96)		
Diazepam	78	81
Lorazepam	8	8.3
Phosphenytoin	5	5.2
Clonazepam	2	2.1
Propofol	1	1.1
Levetiracetam	1	1.1
Sodium valproate	1	1.1
2nd drug (n = 85)		
Phosphenytoin	68	80
Alternative BZP	7	8.2
Levetiracetam	6	7.1
Sodium valproate	2	2.4
Carbamazepine	1	1.2
Propofol	1	1.2
1st anaesthetic agent (n = 49)		
Propofol	49	100
2nd anaesthetic agent (n = 3)		
Thiopental	3	100

(28%) of nosocomial infections. Some of these cases affected patients with a community-acquired infection, so in total 39 patients (38%) suffered any infection. The most common foci of nosocomial infections were also the respiratory or urinary tracts. About half of the total cohort received intravenously administered antibiotics during their stay in hospital.

Finally, we analyzed statistical associations between presence of any infection and clinical features of the SE. Patients that were not discharged home and patients that had received mechanical ventilation were significantly more likely to have suffered an infection (OR 2.705, 95% CI:1.14–6.44 and 3.344, 95% CI: 1.44–7.79) respectively).The duration of SE was significantly longer in patients with an infection compared to those without an infection (median SE duration of 1 and 2.5 days, respectively), and presence of infection was statistically correlated to SE duration in a linear regression analysis ($p = 0.0071$). Patients with super-refractory SE were significantly more likely to have suffered an infection (OR 4.722, 95% CI: 1.831–12.18), but no significant association could be detected between infections and medically refractory SE.

Table 3
Infections, administered antibiotics and statistical analysis of association between infection and clinical features.

Infections		*n*	%
Infection, any		39	*38*
Community-acquired		23	22
Respiratory tract		8	7.7
Urinary tract		7	6.8
Unclear septicaemia		5	4.9
Meningitis		3	2.9
Nosocomial		29	28
Respiratory tract		13	13
Urinary tract		11	11
Unclear septicaemia		4	3.9
Gastrointestinal tract		1	<1
Treatment			
Antibiotics, any		52	50
Antibiotics, iv		52	50
Antibiotics, oral		9	8.7
Correlation analysis	OR (infection)	95% CI	*p*-Value
Not discharged home	2.705	1.14–6.44	0.028
Mechanical ventilation	3.344	1.44–7.79	0.0071
Medically refractory	1.879	0.822–4.30	ns
Superrefractory	4.722	1.83–12.2	0.0019
Duration of SE (days)	*Median*	*Range*	*p-Value*
No infection	1	1–17	
Infection	2.5	1–56	0.0021

4. Discussion

We here characterized the incidence of infections in a cohort of patients suffering SE at a tertiary referral centre for neurology in Sweden. A previous study on this issue demonstrated an association between infections and more complicated SE in a cohort with high mortality, including patients with SE due to hypoxic-ischaemic brain injury.[8] We report that infections, both community-acquired and nosocomial, in our cohort occurred at a rate that was very similar to Sutter et al.[8] The short-term outcome in our cohort was substantially better, which most likely reflects the different aetiologies of SE. Nonetheless, we could detect statistically significant associations between prolonged SE with poor short-term outcome and presence of infection.

In Sweden, neurologists do typically not handle SE due to hypoxic-ischaemic encephalopathy, and as expected our cohort of patients differed substantially to that of Sutter et al. regarding aetiologies. Uncontrolled epilepsy accounted for 37% of the cases in our cohort (15% in Sutter et al.[8]) and we had no cases of hypoxic-ischaemic encephalopathy (15% in Sutter et al.[8]). Accordingly, the short-term outcome for our cohort was favourable in comparison, with a mortality of only 1.9% (25.6% in Sutter et al.[8]).

Out of all patients, 38% had an infection during their stay. Community-acquired infections occurred in 22% of the cases in our cohort, and nosocomial infections in 28%; figures very similar to those presented in Sutter et al.[8] (35.6% in total, 22.5% infections during SE). As expected, the respiratory and urinary tracts were dominant foci. We also assessed the association between infections and clinical characteristics of SE. Infections were more common in patients that were ultimately not discharged home, in patients that received mechanical ventilation, and in patients with super-refractory SE. Similarly, patients with a long duration of SE were also more likely to have infections. Our findings indicate that the association between severe cases of SE and infections described by Sutter et al.[8] are generalizable among SE patients.

Importantly, the retrospective nature of the study results in important limitations. First of all, the diagnosis of SE relies on the diagnosis made by the treating physician. At our centre, there is a high availability of EEG; the vast majority of patients with medically refractory SE (44 out of 59) underwent EEG, as did all patients with a diagnosis of non-convulsive SE ($n = 5$). Nonetheless, the inclusion of patients in the study rests heavily on the diagnosis made by the treating physician. Additionally, SE duration had to be extrapolated from the medical records and approximated to the first day without general anaesthesia. It would have been very interesting to perform multivariate analyses and search for predictors of infections, such as age, type of SE, etc. However, since data were not prospectively collected for the purpose of research, we could only extract data, which are reasonably reliable also in retrospect (infections, pre-existing epilepsy, drugs administered). Important variables that might affect both SE and infections, such as a pre-existing neurological deficit is not always noted in the medical records in an acute setting, so in absence of such important variables, multivariate analysis was deemed inappropriate. Identifying clinical variables that can predict a high risk of infections in SE should be a priority for future prospective studies.

The setting is probably also important for our study. The rate of NCSE in our cohort was low, which reflects the nature of our neurology service. Neurologists in Sweden are typically not responsible for patients with hypoxic-ischaemic encephalopathy after cardiac arrest. The cohort did therefore not consist of ICU patients with continuous EEG-monitoring, which would most likely have resulted in a much higher number of NCSE, but rather patients admitted from regional hospitals or the local emergency department with a clinical suspicion of seizure activity.

There are differences between our data and Sutter et al.[8] that are worth highlighting. In their statistical analyses, Sutter et al.[8] differentiated between patients whose infections were present before SE and those that were diagnosed during SE regarding short-term outcome. Because of the limited size of our material – only 10 patients had community acquired infections without suffering a later nosocomial infection – and because of the retrospective nature of our data which did not clearly allow for an exact time of SE cessation, we did not differentiate between the two groups in our analysis. In Sutter et al.[8], significant differences in short-term outcome and SE duration were demonstrated between patients without infections and patients with infections diagnosed during SE. The majority of our patients with infections (29/38) suffered from nosocomial infections, so our findings are well in line with those of Sutter et al[8]. The findings in our study are also congruent with previous reports of an association between ventilation and higher in-hospital death rate in patients with SE and a fourfold increase in nursing resources and significant prolongation of ICU stay.[9]

The implications of the association demonstrated in this and previous studies are complex, as causation regarding the severity of SE aetiology and infection is probably not unidirectional. Infections and fever can exacerbate seizures, but hypoventilation, aspiration, ICU-care, and a number of other factors in patients with SE of more severe aetiology might plausibly enhance their vulnerability for infections. It is also likely that severe neurological deficits that prevent independent living affect both our short-term outcome measure and susceptibility to infection, so our data must be interpreted in a purely observational rather than causative manner. The most important findings in our study is not the association between infections and duration or short-term outcome of SE, which has already been established, but rather that this association seems to extend also to patients with SE of less severe aetiology than those described in the previous studies.

The findings highlight the need for vigilant preventive measures and prompt treatment of nosocomial infections in patients with SE, especially in the ICU. The association between mechanical ventilation and infections also raises the important question of optimal use of ICU resources in SE. Future studies will hopefully determine which cases of SE are likely to benefit from general anaesthesia and mechanical ventilation and the optimal length of that therapy, so that other patients might be spared associated risks of infection.

Conflict of interest statement

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References

1. Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. *Epilepsia* 2011;**52**:1292–6. http://dx.doi.org/10.1111/j.1528-1167.2011.03056.x.
2. Shorvon S. The treatment of status epilepticus. *Curr Opin Neurol* 2011;**24**:165–70. http://dx.doi.org/10.1097/WCO.0b013e3283446f31.
3. Silbergleit R, Durkalsk Vi, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012;**366**:591–600. http://dx.doi.org/10.1056/NEJMoa1107494.
4. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain* 2012;**135**:2314–28. http://dx.doi.org/10.1093/brain/aws091.
5. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 2005;**76**:534–9. http://dx.doi.org/10.1136/jnnp.2004.041947.
6. Sutter R, Kaplan PW, Ruegg S. Outcome predictors for status epilepticus – what really counts. *Nat Rev Neurol* 2013;**9**:525–34. http://dx.doi.org/10.1038/nrneurol.2013.154.
7. Sutter R, Marsch S, Fuhr P, Ruegg S. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. *Epilepsia* 2013;**54**:502–11. http://dx.doi.org/10.1111/epi.12064.
8. Sutter R, Tschudin-Sutter S, Grize L, Fuhr P, Bonten MJ, Widmer AF, et al. Associations between infections and clinical outcome parameters in status epilepticus: a retrospective 5-year cohort study. *Epilepsia* 2012;**53**:1489–97. http://dx.doi.org/10.1111/j.1528-1167.2012.03576.x.
9. Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. *Neurology* 2007;**69**:886–93. http://dx.doi.org/10.1212/01.wnl.0000269791.96189.70.