Original article

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Prognostic factors of status epilepticus in adults

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ABSTRACT – *Aim*. Status epilepticus (SE) can lead to sequelae or even death. Identifying characteristics associated with poor outcome is crucial in guiding patient treatment. Based on our retrospective patient cohorts, potential prognostic factors were analysed.
Methods. Patients consecutively treated for refractory convulsive status epilepticus (CSE) between 2001 and 2010 and non-convulsive status epilepticus (NCSE) between 2004 and 2009 were studied. Outcome was compared to prognostic variables. Index SE episodes were used for the statistical analyses. Crosstabs and independent samples t-test were applied. Due to sample size, logistic regression was performed for the combined groups.
Results. In total, 50% (9/18) of index refractory CSE and 42% (16/38) of index NCSE episodes led to sequelae. Refractory CSE requiring narcosis for >20 hours was associated with poor outcome (p=0.05). *De novo* presentation (p=0.0001), long-lasting SE (>2 hours) (p=0.014), age >65 years (p=0.002), and refractory SE (p=0.047) were predictors of poor outcome following NCSE. Based on logistic regression for combined refractory CSE and NCSE, *de novo* presentation was identified as the strongest predictor of sequelae.
Conclusions. Older age and *de novo* SE are predictors of sequelae following NCSE. Prolonged SE is a risk factor for poor outcome, both for refractory CSE and NCSE. Aggressive initial treatment to terminate seizures during the early phase is therefore essential.

Key words: epilepsy, status epilepticus, prognostic factors, aetiology, outcome

Status epilepticus (SE) can be fatal or lead to serious sequelae. The incidence of SE, traditionally defined as seizures lasting for more than 30 minutes, is 10-40 patients/year/100,000, with up to 60 episodes/year/100,000 (DeLorenzo *et al*., 1996; Coeytaux *et al*., 2000; Knake *et al*., 2001; Vignatelli *et al*., 2003). The incidence according to the more recent operational definition of five minutes duration, formerly referred to as "impending SE" (Brophy *et al*., 2012), is unknown. This shorter time limit aids the clinician with regards to when to initiate anticonvulsive treatment. The 30-minute limit will more reliably identify patients with a substantial risk of sequelae and death unless

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the seizures are terminated (Trinka *et al*., 2015). The mortality associated with SE lasting for more than 30 minutes has been estimated to be 19%, compared to only 2.6% for SE lasting 10 to 29 minutes (DeLorenzo *et al*., 1999). When studying morbidity and mortality, the definition of 30 minutes is the most relevant. Whether this also applies to cognitive sequelae remains unanswered, as systematic neuropsychological studies following SE are lacking.

Several factors affect the risk of a poor outcome, many of which are often identifiable at patient admission. Additional factors may become evident during treatment and are potentially modifiable. Convulsive SE (CSE), long SE duration, therapy resistance, old age, and acute symptomatic seizures have all been linked to a poor outcome (Towne *et al*., 1994; Claassen *et al*., 2002a; Rossetti *et al*., 2006; Drislane *et al*., 2009; Neligan and Shorvon, 2010). Benzodiazepines remain the primary choice in first-line treatment (Meierkord *et al*., 2010). The type of benzodiazepine used and mode of administration varies in different clinical centres. Nasal and buccal midazolam or rectal diazepam are often used, with no established difference in efficacy (Brigo *et al*., 2015). Furthermore, there is no consensus regarding the choice of second-line agent (Alvarez *et al*., 2011; Yasiry and Shorvon, 2014). Most epileptologists argue the importance for all centres to have an unambiguous treatment protocol (Shorvon *et al*., 2008; Aranda *et al*., 2010; Meierkord *et al*., 2010). However, some authors have questioned the impact of such protocols on patient prognosis (Rossetti *et al*., 2013).

We have previously shown differences between the outcome of SE arising *de novo* and SE in patients with previous seizures (Power *et al*., 2011; Power *et al*., 2015). Establishing variables associated with a poor outcome is essential for treatment optimisation. In this study, we focus on prognostic variables with particular reference to the challenging subgroups of refractory convulsive SE (CSE) and non-convulsive SE (NCSE). No solid evidence-based treatment guidelines are available for these groups. Factors predicting outcome are consequently of the utmost interest.

Methods and patients

Adult patients consecutively treated for SE at the Department of Neurology, Haukeland University Hospital, Norway, were studied retrospectively. The unit serves as the primary and only unit for 511,000 inhabitants of Hordaland County. The patient population is therefore unselected. The regional committee for medical and health research ethics accepted the study terms.

Episodes of refractory CSE were identified from a clinical data base of all patients treated at the ICU with therapeutic propofol narcosis during 2001-2010. Eighteen patients with 27 refractory CSE episodes were identified. Propofol has been our first-line anaesthetic for refractory CSE since 2001. Forty-eight episodes of NCSE in 39 patients were identified from a clinical data base including all patients with an ICD-10 diagnosis of SE between 2004 and 2009. Inclusion and exclusion criteria are documented in our previous articles on refractory CSE and NCSE (Power *et al*., 2011; Power *et al*., 2015).

Definitions and outcome measures

The current operational definition of SE is ≥5 minutes of continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness. This timeframe applies to convulsive or tonic-clonic SE. For focal seizures with impaired consciousness and absence seizures, the timeframe is 10 (-15) minutes (Trinka *et al*., 2015). These operational definitions have time limits chosen to guide emergency treatment. The older definition of SE, using 30 minutes as the time limit, corresponds to a cut-off beyond which a continuation of the SE represents a clear risk of sequelae (Meldrum and Horton, 1973). For the purpose of this article, we have chosen to include only SE lasting for more than 30 minutes. NCSE was defined as SE without major motor symptoms or convulsions (Walker *et al*., 2005; Shah *et al*., 2009). Refractory SE was defined as SE episodes requiring three or more antiepileptic drugs (AEDs) for termination (Hocker *et al*., 2014). The patients with refractory CSE received propofol as the third-line agent in accordance with our protocol. SE was classified as either *de novo* (no prior seizures) or as occurring in patients with previous seizures. For the NCSE group, the outcome alternatives were death, severe sequelae (permanent and greatly affecting daily living), moderate sequelae (severe, lasting for >one month, but not permanent or permanent with a mild or moderate effect on daily living), mild sequelae (slight and transient or more serious lasting for <one month, without any permanent adverse outcome), and full restitution. For the refractory CSE group, the alternatives were death, severe sequelae (permanently affecting daily living), mild sequelae (lasting for a short period or moderately transient), and full restitution. Death was defined as hospital mortality during the SE-associated hospitalisation. The classification of sequelae was based on clinical evaluation by a neurologist. Neurological, cognitive, and somatic sequelae were all evaluated. The grading of sequelae is described in detail in our previous reports (Power *et al*., 2011; Power *et al*., 2015).

A 24/7 EEG service is not available in our hospital. SE events, including NCSE with a clinically overt

semiology, were consequently included without EEG confirmation. The clinical diagnosis of SE was, in such cases, determined by a neurologist. For index refractory CSE episodes, 8/18 were confirmed by EEG during the ictal phase. An additional 2/18 patients had postictal EEG recordings showing epileptic activity. For patients with no EEG recordings during the ictal or postictal phase, 6/8 had previous or subsequent EEGs with epileptic activity. For index NCSE episodes, 20/39 were confirmed by EEGs during the ictal phase. An additional 8/39 had EEG recordings shortly after termination, showing focal slowing or focal functional disturbances consistent with the semiology. Among the remaining, eight had previous recordings with epileptic activity.

STESS (Status Epilepticus Severity Score) was applied retrospectively. STESS is a prognostic score based on four outcome predictors (Rossetti *et al*., 2008): age (<65 years=0; ≥65 years=2), history of previous seizures (yes=0; no=1), worst seizure type (simple focal, complex focal, absence, and myoclonic seizures=0; generalized convulsive=1; NCSE in coma/subtle SE=2), and extent of impairment of consciousness (alert or somnolent/confused=0; stuporous or comatose=1), as determined before the start of treatment. We used a cut-off of ≥3 and calculated the negative predictive value (NPV) for not dying or suffering severe sequelae in the group with a negative test (*i.e*. value <3) and the positive predictive value (PPV) for dying or suffering severe sequelae with a positive test (*i.e*. value of ≥3).

Statistics

Sequelae and death after SE were examined in order to identify any correlation with the following variables: history of previous epileptic seizures, age, gender, duration of SE, duration of narcosis (refractory CSE), time to narcosis (refractory CSE), and number of antiepileptic agents required to terminate NCSE.

For statistical purposes, we only included each patient's index SE in order to avoid bias of repeated measurements for a particular subject. For 1/39 index NCSE episodes, we could not evaluate sequelae other than death due to a further SE during the initial phase of the follow-up.

Crosstabs and two-sided Fischer's exact test or Pearson's chi square test were used to analyse the dichotomous categorical variables. Independent samples t-test were used for continuous variables after testing for normal distribution, and Levene's test for equality of variance.

For the total group of SE, the variables were examined using a binary logistic regression model. This was performed for refractory CSE and NCSE combined due to the small sample sizes. The factors included were *de novo vs*. previous seizures, >2 hours duration *vs*. <2 hours duration, >65 years of age *vs* <65 years of age, and refractory CSE *vs* NCSE. Refractoriness was not included in this model as all SE episodes in the refractory CSE group, by definition, were refractory.

Results

Refractory convulsive status epilepticus

All refractory CSE episodes were secondary generalized tonic-clonic seizures. The SE episodes were remote or acute (three) symptomatic due to acquired causes in 17/18; 1/18 had focal epilepsy of unknown cause. The most common cause was a cerebrovascular event; six cerebral infarctions and two cerebral haemorrhages (Power *et al*., 2011). Mean age was 49.2 years (20-86 years). Sequelae were identified following 9/18 (50%) index SE events. There was a trend for *de novo* SE to be more often followed by sequelae than SE in patients with previous seizures (*table 1*). There was also a trend for a longer duration of narcosis required to treat *de novo* SE (*table 2*).

SE with narcosis >20 hours was more often followed by sequelae than SE with narcosis <20 hours (*table 1*). The mean time of narcosis for SE with sequelae was 65.7 hours (median: 56.0 hours; range: 136 hours), compared to 20.4 hours for SE with no sequelae (median: 14.0 hours; range: 51.7 hours), *i.e*. a mean difference of 45.3 hours (CI: 11.0-79.6; *p*=0,015).

There were two deaths and three with severe sequelae. The mean time of narcosis for these five SE episodes was 86.8 hours (median: 86.2 hours; range: 112.5 hours), compared to a mean of 26.2 hours (median: 19.0 hours; range: 69 hours) for SE with no or mild sequelae; a mean difference of 60.7 hours (CI: 92.6-28.8; *p*=0.001). Outcome was unrelated to gender. There was a tendency for a higher frequency of sequelae in patients over 65 years and when SE was complicated with pneumonia.

For refractory CSE episodes, 5/18 continued or recurred after more than 24 hours of narcosis (*i.e*. super-refractory) (Shorvon and Ferlisi, 2011). Both deaths and two out of three severe sequelae belonged to this subgroup.

For refractory CSE episodes, 3/6 with a STESS ≥3 died or had severe sequelae, *i.e*. a positive predictive value (PPV) of 50%. 10/12 with a score <3 on STESS had no or mild sequelae, *i.e*. a negative predictive value (NPV) of 83%. These results were not significant (*p*=0.27).

Table 1. Sequelae following RCSE according to various potential predictors*.

	Sequelae (*n*)	Sequelae (%)	*p* value
***De novo* SE**	4/5	80%	0.29
SE after previous seizures	5/13	38%	
Narcosis >20 hours	8/11	73%	0.05
Narcosis <20 hours	1/7	14%	
Age ≥65 years	3/3	100%	0.21
Age <65 years	6/15	40%	
Age ≥50 years	4/8	50%	1.0
Age <50 years	5/10	50%	
Male	7/14	50%	1.0
Female	2/4	50%	
Complicated by pneumonia	5/7	71%	0.34
Not complicated by pneumonia	4/11	36%	

*Pairwise, presumed risk factor listed first.
Results from crosstabs and Fischer's exact or Pearson's chi square test.

Table 2. Duration of *de novo* SE compared to SE after previous seizures*.

RCSE	**>2 hours SE before narcosis**	**>20 hours of narcosis**	
De novo (%)	4/5 (80)	5/5 (100)	
Previous seizures (%)	9/13 (69)	6/13 (46)	
Total (%)	13/18 (72)	11/18 (61)	
p value	1	0.1	
NCSE	**>2 hours duration SE**	**>24 hours duration SE**	**Refractory**
De novo (%)	14/16 (88)	11/16 (69)	9/16 (56)
Previous seizures (%)	18/23 (78)	8/23 (35)	6/23(26)
Total (%)	32/39 (82)	19/39 (49)	15/39(38)
p value	0.68	0.05	0.059

*Results from crosstabs and Fischer's exact or Pearson's chi square test

Non-convulsive status epilepticus

For NCSE episodes, 28/39 were complex focal, 9/39 were simple focal, 1/39 was an atypical absence, and 1/39 was a myoclonus SE (progressive myoclonic epilepsy, type Unverricht-Lundborg disease). Three of 39 NCSE episodes occurred in patients with cryptogenic epilepsy. In 36/39, the NCSE represented symptomatic epilepsies or seizures; 5/36 genetic and 31/36 acquired (7/31 acute symptomatic). The main aetiology was a cerebrovascular event; 10 cerebral haemorrhages and seven cerebral infarctions (Power *et al.*, 2015). Mean age was 63.3 years (18-97 years).

Three of the 39 index NCSE episodes led to death (7.7%); 16/38 (42%) NCSE episodes led to sequelae.

De novo NCSE lasted longer, was more refractory to treatment, and more often led to sequelae than NCSE in patients with previous seizures (*tables 2, 3*). In patients with SE >2 hours, the outcome was worse compared to those with shorter-lasting SE (*table 3*).

Seven of the 16 sequelae were categorised as serious; three deaths and four severe sequelae. All seven SE episodes were seizures lasting for more than two hours, and five of them exceeding 24 hours. In comparison, 14/32 (44 %) NCSE episodes lasting longer than

Table 3. Sequelae following NCSE according to potential predictors*.

	Sequelae (*n*)	Sequelae (%)	*p* value
***De novo* SE**	12/15	80%	0.0001
SE after previous seizures	4/23	17%	
>2 hours	16/31	52%	0.014
<2 hours	0/7	0%	
>24 hours	11/18	61%	0.047
<24 hours	5/20	25%	
Age ≥50 years	15/29	52%	0.052
Age <50 years	1/9	11%	
Age ≥65 years	14/22	64%	0.002
Age <65 years	2/16	13%	
Male	9/22	41%	1.0
Female	7/16	44%	
Refractory	9/14	64%	0.047
Non-refractory	7/24	29%	

*Pairwise, presumed risk factor listed first.
Results from crosstabs and Fischer's exact or Pearson's chi square test.

24 hours were followed by either moderate or mild sequelae, or no sequelae (p=0.31). Older age was a predictor of sequelae in the NCSE group (*table 3*).

Refractory NCSE

Fifteen of 39 NCSE episodes were refractory, and 14/15 were symptomatic seizures or epilepsies (five acute symptomatic). The main cause was a cerebrovascular event; four haemorrhages and three infarctions. Mean age was 66.7 years (18-89 years). Mortality occurred in 2/15 (13.3 %), and 14/15 NCSE episodes were evaluated for sequelae other than death (*see section on Statistics*). For patients with refractory NCSE, the risk of sequelae was twice as much, compared to those responding to first-line treatments. Eight refractory NCSE episodes were *de novo* seizures and seven of these led to sequelae. In comparison, only two of the six refractory NCSE episodes in patients with previous seizures led to sequelae (p=0.091).
All refractory NCSE episodes lasted >2 hours, and 12 refractory NCSE episodes lasted >24 hours.
Age over 65 years correlated with sequelae; sequelae were present in 9/10 patients over 65 years versus 0/4 patients below 65 years (p=0.005).
Three of seven refractory NCSE episodes with a high STESS were associated with poor outcome (PPV: 43%) and 7/8 with a low STESS with good outcome and no or mild sequelae (NPV: 88%) (p=0.28).

Recurrent SE

Only the first SE per person was used in the analyses in order to avoid inclusion of statistically dependent events. However, whether outcome differed between patients with single SE episodes and those with recurrent SE episodes within the observation period remains an interesting point. For the overall number of recurrent SE events, both the first and the following episodes in the study period were included for patients with multiple SE episodes.
Among the 27 refractory CSE episodes, 9/15 (60%) single SE episodes led to sequelae, compared to 4/12 (33%) in the recurrent SE group. The 12 recurrent refractory CSE episodes occurred in three patients, and sequelae occurred in one of these.
Among the 48 NCSE episodes, 15/32 (47%) single SE episodes were followed by sequelae, compared to 3/16 (19%) for recurrent SE episodes. The 16 recurrent SE episodes occurred in seven patients, with sequelae occurring in three of them.

Prognostic variables for refractory CSE and NCSE combined

Table 4 shows unadjusted risks of sequelae according to different prognostic factors for NCSE and refractory CSE combined.
Binominal logistic regression was applied in order to evaluate the relative importance of the predictor

Table 4. Sequelae following SE according to potential predictors*.

	Sequelae (*n*)	Sequelae (%)	*p* value
***De novo* SE**	16/20	80%	0.0001
SE after previous seizures	9/36	25%	
>2 hours	23/44	52%	0.028
<2 hours	2/12	17%	
Age ≥65 years	17/25	68%	0.002
Age <65 years	8/31	26%	
Male	16/36	44%	0.968
Female	9/20	45%	
Refractory	18/32	56%	0.044
Non-refractory	7/24	29%	

*Pairwise, presumed risk factor listed first.
Results from crosstabs and Fischer's exact or Pearson's chi square test.

variables (*de novo vs*. previous seizures, >2 hours duration *vs*. <2 hours duration, >65 years of age *vs* <65 years of age, and refractory CSE *vs* NCSE) on the outcome variable sequelae *vs* no sequelae. *De novo* SE was the strongest predictor of sequelae with an OR of 12.43 (CI: 2.38-64.97), *p*=0.003. The other factors had the following predictive values: duration >2 hours: OR=6.12 (CI=0.82-45.90), *p*=0.078; age >65 years: OR=9.74 (CI=1.45-65.24), *p*=0.019; and refractory CSE *vs* NCSE: OR=9.40 (CI=1.24-71.13), *p*=0.03.

In total, SE was caused by a cerebrovascular event in 18/25 SE episodes in patients >65 years, but in only 7/32 SE episodes in patients <65 years (Pearson's Chi-Square test; *p*=0.0001).

Discussion

NCSE, presenting as the first epileptic manifestation, has a significantly worse outcome than NCSE in patients with previous seizures. This is probably explained by the nature of the underlying conditions, as *de novo* seizures more often represent acute current medical and neurological disorders. No significant difference could be proven for the subgroups, refractory NCSE or refractory CSE, however, *de novo* seizures were associated with a trend towards a poorer prognosis. Previous studies have shown this correlation for SE in general, whereas the findings for refractory SE have been inconsistent (Drislane *et al*., 2009; Novy *et al*., 2010; Canoui-Poitrine *et al*., 2011; Hocker *et al*., 2013). A possible explanation is that refractoriness by itself is a marker of a severe event, and that the damage caused by the SE overshadows the prognostic value of a *de novo* situation. We found that old age is a predictor of negative outcome for NCSE, including refractory NCSE, but refractory CSE outcome did not depend on age. Former studies on SE have found a worse prognosis among older patients (Claassen *et al*., 2002b; Rossetti *et al*., 2006). Other reports focusing on refractory SE (Hocker *et al*., 2013), and specifically refractory CSE (Lai *et al*., 2015), have shown no difference. *De novo* presentation and older age may be connected to poorer outcome because these patients more often have comorbidities and acute neurological conditions. A vulnerable or compromised brain is likely to be more susceptible to damage from a seizure. Based on our data, old age was highly correlated to an underlying aetiology of cerebrovascular events.

There was no relationship between gender and outcome. A recent, large epidemiological study of convulsive SE found a slightly higher mortality in men (Dham *et al*., 2014).

Refractoriness is a risk factor for poor NCSE outcome. This could partly be explained by the association between long seizure duration and poor outcome, as all refractory NCSE episodes lasted for more than two hours. It is well known that seizure duration and refractoriness are inter-related with respect to epileptic seizures, which is illustrated by seizure-induced reduction of benzodiazepine sensitivity (Lowenstein and Alldredge, 1993; Kapur and Macdonald, 1997). This demonstrates the negative impact of initial treatment failure and the need for urgent and effective SE therapy. For refractory CSE, the duration of narcosis was a marker of total SE duration. Refractory CSE episodes were more frequently associated with sequelae when more than 20 hours of narcosis was required to terminate them, compared to a shorter period of narcosis. A relationship between SE duration and poor outcome has also been found in previous studies (Towne *et al*., 1994; Sagduyu *et al*., 1998; Drislane *et al*., 2009). A recent

study connected poor SE outcome with the use of narcosis, and advocated caution when using this line of treatment (Marchi *et al*., 2015). However, such an association does not necessarily imply that the narcosis is unfavourable *per se*. It is used to treat a refractory subgroup of SE, mainly convulsive SE, with a duration long enough to pose a risk of brain damage. Interestingly, none of the patients with refractory NCSE in our study were treated with narcosis, and yet they had a worse outcome compared to those with refractory CSE. This observation contrasts the recently published data (Marchi *et al*., 2015).

An interesting finding in our study is that SE recurring in the same person led to less sequelae than SE occurring only once during the observation time. This is in accordance with previous findings, and is most likely explained by the presence of a less severe medical condition, as recurrent SE is usually unrelated to acute symptomatic events (Tsetsou *et al*., 2015).

This study is hampered by its retrospective design and a limited number of cases. The inclusion periods for the refractory CSE and NCSE groups only partly overlapped and this might potentially affect results. As treatment protocols remained unchanged during this time, this should not have influenced the study outcome. We believe that the patients included in our study represent an unselected cohort, as our centre serves as a primary referral unit. Hence, our findings should be valid for the SE population in general.

Conclusions

SE occurring *de novo* has a poorer outcome than SE in patients with previous seizures, especially for patients presenting with NCSE. Older age is a predictor of less favourable outcome following NCSE. Refractoriness and long duration of SE is associated with more frequent and worse sequelae. This underlines the need for a well-structured treatment protocol and aggressive treatment in order to terminate seizures during the early phase. □

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References

Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. *Epilepsia* 2011; 52(7): 1292-6.

Aranda A, Foucart G, Ducasse JL, *et al*. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. *Epilepsia* 2010; 51(10): 2159-67.

Brigo F, Nardone R, Tezzon R, Trinka E. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: a systematic review with meta-analysis. *Epilepsy Behav* 2015; 49: 325-36.

Brophy GM, Bell R, Claassen J, *et al*. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012; 17(1): 3-23.

Canoui-Poitrine F, Bastuji-Garin S, Alonso E, *et al*. Risk and prognostic factors of status epilepticus in the elderly: a case-control study. *Epilepsia* 2011; 52(10): 1849-56.

Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002a; 43(2): 146-53.

Claassen J, Lokin JK, Fitzsimmons BF, Mendelsohn FA, Mayer SA. Predictors of functional disability and mortality after status epilepticus. *Neurology* 2002b; 58(1): 139-42.

Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 2000; 55(5): 693-7.

DeLorenzo RJ, Hauser WA, Towne A, *et al*. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996; 46(4): 1029-35.

DeLorenzo RJ, Garnett LK, Towne AR, *et al*. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. *Epilepsia* 1999; 40(2): 164-9.

Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. *Neurocrit Care* 2014; 20(3): 476-83.

Drislane FW, Blum AS, Lopez MR, Gautam S, Schomer DL. Duration of refractory status epilepticus and outcome: loss of prognostic utility after several hours. *Epilepsia* 2009; 50(6): 1566-71.

Hocker SE, Britton JW, Mandrekar JN, Wijdicks E, Rabinstein AA. Predictors of outcome in refractory status epilepticus. *JAMA Neurol* 2013; 70(1): 72-7.

Hocker S, Tatum WO, LaRoche S, Freeman WD. Refractory and super-refractory status epilepticus-an update. *Curr Neurol Neurosci Rep* 2014; 14(6): 452.

Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. *J Neurosci* 1997; 17(19): 7532-40.

Knake S, Rosenow F, Vescovi M, *et al*. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. *Epilepsia* 2001; 42(6): 714-8.

Lai A, Outin HD, Jabot J, *et al*. Functional outcome of prolonged refractory status epilepticus. *Crit Care* 2015; 19(1): 199.

Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. *Neurology* 1993; 43(3): 483-8.

Marchi NA, Novy J, Faouzi M, *et al*. Status epilepticus: impact of therapeutic coma on outcome. *Crit Care Med* 2015; 43(5): 1003-9.

Meierkord H, Boon P, Engelsen B, *et al*. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010; 17(3): 348-55.

Meldrum BS, Horton RW. Physiology of status epilepticus in primates. *Arch Neurol* 1973; 28(1): 1-9.

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

Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia* 2010; 51(2): 251-6.

Power KN, Flaatten H, Gilhus NE, Engelsen BA. Propofol treatment in adult refractory status epilepticus. Mortality risk and outcome. *Epilepsy Res* 2011; 94(1-2): 53-60.

Power KN, Gramstad A, Gilhus NE, Engelsen BA. Adult nonconvulsive status epilepticus in a clinical setting: semiology, aetiology, treatment and outcome. *Seizure* 2015; 24: 102-6.

Rossetti AO, Hurwitz S, Logroscino G, Bromfield EB. Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry* 2006; 77(5): 611-5.

Rossetti AO, Logroscino G, Milligan TA, *et al*. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 2008; 255(10): 1561-6.

Rossetti AO, Alvarez V, Januel JM, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. *J Neurol* 2013; 260(2): 421-8.

Sagduyu A, Tarlaci S, Sirin H. Generalized tonic-clonic status epilepticus: causes, treatment, complications and predictors of case fatality. *J Neurol* 1998; 245(10): 640-6.

Shah AM, Vashi A, Jagoda A. Review article: convulsive and non-convulsive status epilepticus: an emergency medicine perspective. *Emerg Med Australas* 2009; 21(5): 352-66.

Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011; 134(10): 2802-18.

Shorvon S, Baulac M, Cross H, Trinka E, Walker M. The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London Colloquium on Status Epilepticus. *Epilepsia* 2008; 49(7): 1277-85.

Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia* 1994; 35(1): 27-34.

Trinka E, Cock H, Hesdorffer D, *et al*. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; 56(10): 1515-23.

Tsetsou S, Novy J, Rossetti AO. Recurrence of status epilepticus: prognostic role and outcome predictors. *Epilepsia* 2015; 56(3): 473-8.

Vignatelli L, Tonon C, D'Alessandro R. Incidence and short-term prognosis of status epilepticus in adults in Bologna, Italy. *Epilepsia* 2003; 44(7): 964-8.

Walker M, Cross H, Smith S, *et al*. Nonconvulsive status epilepticus: Epilepsy Research Foundation workshop reports. *Epileptic Disord* 2005; 7(3): 253-96.

Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. *Seizure* 2014; 23(3): 167-74.

TEST YOURSELF

(1) What is the most recently defined timeframe for status epilepticus and the rationale behind this choice? For which purpose is the older timeframe more useful?

(2) How does the prognosis of status epilepticus in patients with previous seizures compare to status epilepticus presenting as the first seizure?

(3) What are the relevant prognostic factors for outcome following non-convulsive status epilepticus?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".