Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit

M Holtkamp, J Othman, K Buchheim, H Meierkord

Objective: To assess risk factors and prognosis in patients with refractory status epilepticus (RSE).

Methods: We retrospectively analysed all episodes of status epilepticus (SE) treated between 1993 and 2002 on the neurological intensive care unit (NICU) of the Charité-Universitätsmedizin Berlin. The predictive and prognostic features of RSE were compared with non-RSE (NRSE). All patients with “de novo” SE were followed up to identify the possible development of post-SE symptomatic epilepsy.

Results: A total of 83 episodes fulfilled our criteria of SE. Of these 43% were refractory to first line anticonvulsants. The mean age of patients with SE was 53.3 (SD 19) years, with only two patients younger than 18 years. Encephalitis was significantly more often the primary cause in RSE (p<0.05), whereas low levels of antiepileptic drugs were significantly more often associated with NRSE (p<0.001). Hyponatraemia within the first 24 hours after onset of status activity was significantly more often associated with RSE (p<0.05). In RSE, compared with NRSE, significantly longer duration of seizure activity (p<0.001), more frequent recurrence of epileptic activity within the first 24 hours after the end of seizure activity (p<0.001), longer stay in the NICU and in hospital (p<0.001 and p<0.01, respectively), and more frequent development of symptomatic epilepsy (p<0.05) were seen.

Conclusions: SE treated in the NICU is frequently refractory to first line anticonvulsant drugs. Encephalitis is a predictor for RSE, which is associated with markedly poor outcome, in particular, the development of post-SE symptomatic epilepsy. Thus prevention of this most severe form of SE should be the primary target of treatment of SE.
as a major part of the definition does not appear to be very helpful since treatment escalation after failure of first line anticonvulsants in other than generalised convulsive forms of SE is usually not done instantly.22 First line anticonvulsant drugs have to be given in the appropriate form and in adequate dosages. An acute anticonvulsant treatment regimen with first line drugs was considered adequate if it included intravenous administration of 10 mg diazepam, 1 mg clonazepam, 6 mg lorazepam, or 5 mg midazolam followed by 750 mg phenytoin or an analogue dosage of fosphenytoin. SE of patients who did not receive phenytoin or fosphenytoin was defined as refractory with continuing epileptic activity after a dosage of benzodiazepines double that described above.

In comatose patients with none or only subtle motor phenomena, SE was defined by the presence of repetitive generalised or focal epileptiform discharges (spikes, sharp waves, and spike waves) whereas periodic lateralised epileptiform discharges alone were not regarded as diagnostic.

- **Pre-existing epilepsy:** This was defined as two or more unprovoked epileptic seizures that had occurred at least more than four weeks before the onset of SE.
- **Post-SE symptomatic epilepsy:** In patients with “de novo” SE—that is, without pre-existing epilepsy, the development of symptomatic epilepsy after SE was defined as the occurrence of at least one unprovoked epileptic seizure occurring not earlier than four weeks after termination of SE.

The term “anticonvulsant” is used to describe drugs administered for the treatment of SE and the term “antiepileptic” is used to describe drugs administered in existing epilepsy.

We used the criteria of the International League against Epilepsy (ILAE) for the clinical classification of SE.10 In a first step the causes of SE were subsumed into broader categories, along the lines suggested by Hauser et al13 and Hesdorffer et al14 with some modifications:

- central nervous system (CNS) disease (acute symptomatic, progressive, and remote)
- substance associated (intoxication, withdrawal, and low levels of antiepileptic drugs (AEDs))
- idiopathic/cryptogenic.

SE was considered to be caused by “acute symptomatic” CNS disease if it occurred within one week after an acute brain insult. “Progressive” CNS disease was defined as the presence of a non-static CNS condition such as tumour, multiple sclerosis, or a neurodegenerative disease. “Remote” CNS disease was defined as presence of a history of CNS insult, and the time between the SE and the neurological insult had to be more than one week. SE was classified as idiopathic/cryptogenic in the absence of acute, progressive, or remote CNS disease as well as absence of any substance association.9 If the SE could be assigned aetiologically to more than one of the subgroups described above, it was assigned to the most probable group after considering the overall clinical picture.

**Encephalitis** was defined as encephalopathy (depressed or altered level of consciousness lasting >24 hours, lethargy, or change in personality) and one or more of one of the following symptoms: fever, focal neurological findings, cerebrospinal fluid (CSF) pleocytosis, or electroencephalogram (EEG) or neuroimaging findings consistent with encephalitis.24 Encephalitis was classified as infectious, non-infectious, or of unknown aetiology. Infectious brain diseases caused by bacteria or parasites were not included in the diagnosis of encephalitis but were itemised separately. In our NICU, all patients with encephalitis are tested for neurotropic viruses including serological and polymerase chain reaction examinations. They are also tested for enteroviruses, arboviruses, Bartonella species, *Chlamydia* species, and *Mycoplasma pneumoniae* including serological examination of serum and CSF.

SE was terminated in patients not treated with anaesthetics on the basis of clinical description and in patients treated with anaesthetics with cessation of seizure activity and absence of burst suppression patterns in the EEG.

**Patients**

We retrospectively analysed all episodes of SE treated over a period of 10 years (January 1993 to December 2002) in the NICU at the Charité University Hospital (Charité-Universitätsmedizin Berlin). To ensure identification of all possible episodes we conducted a computer assisted search of patient files using the keywords “SE”, “seizure clustering”, and “prolonged epileptic seizures”. Episodes were included if SE commenced after admission to the NICU, before admission but still continuing after admission to the NICU, and SE terminated near-term before admission to the NICU, if the admission was causally related to the SE. Episodes were excluded if the records of the patient were not retrievable, if impairment of consciousness between two seizures within five minutes was iatrogenic, or if the episode classified as SE was retrospectively a paroxysmal incident of non-epileptic origin—that is, psychogenic non-epileptic seizure, prolonged convulsive syncope, transient ischaemic attack, etc.

By these criteria we identified 140 episodes in 131 patients, suitable for SE. The records of five patients with six episodes were not located in the archives of the hospital. From the remaining cases, 83 episodes in 79 patients fulfilled our definition of SE. The patients with “de novo” SE were followed up by telephone interview with regard to the development of symptomatic epilepsy after SE. Before the telephone interview patients were contacted by mail giving them the choice to refuse the interview. The local ethics committee of the Universitätsklinikum Charité approved the procedure and informed consent was obtained from the patients taking part in the follow up study.

**Clinical data**

To analyse the clinical variables we employed a structured data collection grid that was used by two independent reviewers. For each episode of SE, the patient’s demographic data (age, sex) and medical history (acute/chronic, neurological/non-neurological) were documented. Data on one-on-one aetiology, semiology, and clinical course were evaluated. In addition, paraclinical data from the first 24 hours after the onset of SE including serum sodium and glucose levels, rectal temperature, and CSF variables were analysed. Finally, we analysed outcome measures including duration of SE, short term recurrence of epileptic activity within 24 hours after termination of SE, length of stay in hospital and in the NICU, inhospital mortality, and, in patients with “de novo” SE, development of symptomatic epilepsy. As the prognosis of complex partial SE (CPSE) and generalised convulsive SE (GCSE) may differ, subgroup analysis of these two types of SE with regard to outcome measures was performed.

**Statistical analysis**

Data were collected with the help of the database program Microsoft Access 2000. Statistical calculations were performed with SPSS 11.0. Frequency distributions of predictive and prognostic features of RSE and NRSE were compared in order to identify characteristics of RSE and were calculated using the χ² test. The t test was used for analysis of continuous data with normal distribution and the Mann–Whitney U test for data with non-normal distribution. Where
applicable, Pearson’s correlation coefficient was calculated. Differences were considered significant at \( p < 0.05 \).

RESULTS

Study population

A total of 83 episodes in 79 patients (51/83 (61.4%) female) treated in the NICU fulfilled our diagnostic criteria for SE. The mean age was 53.3 (SD 19) years (range 11–94) with one peak in the fourth decade and another one in the seventh. The vast majority of patients included in this study were adults, with only two patients 11 and 16 years of age. Following our definition, 36 episodes (43.4%) complied with refractory SE (RSE). Distribution of age and sex was not significantly different between the two study groups. In 8.4% (7/83) of cases SE occurred while patients were treated in the NICU for other reasons.

Comorbidity

The most common pre-existing diseases in the patients were epilepsy (33/83, 39.8%), arterial hypertension (20/83, 24.1%), cardiovascular disease, chronic alcohol abuse, and manifest stroke (19/83, 22.9%). Pre-existing epilepsy was seen significantly more often in patients with NRSE (24/47, 51.1%) than in patients with RSE (9/36, 25%; \( p < 0.05 \)). Cardiovascular disease and stroke were seen more often in RSE, and arterial hypertension and chronic alcohol abuse were seen more often in NRSE, but the differences were not significant.

Aetiology

SE was caused by diseases affecting primarily the CNS in 88.9% of refractory cases and 51.1% of non-refractory cases (\( p < 0.001 \)). This finding can mainly be attributed to acute symptomatic CNS diseases, which were the cause in 50% of episodes with RSE and 14.9% of episodes with NRSE (\( p < 0.01 \)). Progressive and remote CNS diseases causing SE were not significantly different in the two study groups. In contrast, substance associated SE was seen significantly more often in NRSE (36.2%) compared with RSE (11.1%; \( p < 0.05 \)). Similarly, idiopathic/cryptogenic SE caused NRSE in 14.9% of cases and RSE in none (\( p < 0.05 \)) (table 1).

The individual aetiologies are listed in table 2. In 3/10 cases with encephalitis, neurotrope viruses were proved to be the causative agents, and in 7/10 the aetiology remained unknown. Encephalitis was causative significantly more often in RSE (22.2%) compared with NRSE (4.3%; \( p < 0.05 \)). In contrast, insufficient levels of AEDs was the main aetiological factor in NRSE (27.7%) but not at all in RSE (\( p < 0.01 \)). In the subgroup of patients with pre-existing epilepsy low levels of AEDs were significantly more often causal for NRSE (34.2%) compared with RSE (0%) as well (\( p < 0.001 \)).

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>NRSE (n = 47)</th>
<th>RSE (n = 36)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS disease</td>
<td>23 (48.9%)</td>
<td>22 (88.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute symptomatic</td>
<td>7 (14.9%)</td>
<td>18 (50%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>16 (34%)</td>
<td>14 (38%)</td>
<td>0.65 (NS)</td>
</tr>
<tr>
<td>Remote</td>
<td>10 (21.3%)</td>
<td>8 (22.2%)</td>
<td>1.0 (NS)</td>
</tr>
<tr>
<td>Progressive</td>
<td>6 (12.8%)</td>
<td>6 (16.7%)</td>
<td>0.76 (NS)</td>
</tr>
<tr>
<td>Substance associated</td>
<td>17 (36.2%)</td>
<td>4 (11.1%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Idiopathic/cryptogenic</td>
<td>7 (14.9%)</td>
<td></td>
<td>0.017</td>
</tr>
</tbody>
</table>

NRSE, non-refractory status epilepticus; RSE, refractory status epilepticus; CNS, central nervous system; NS, not significant.

Paraclinical factors

Serum sodium was measured in 73 episodes within the first 24 hours after onset of SE. Hyponatraemia with serum sodium of less than 135 mmol/l was seen significantly more often in episodes of RSE (10/29; 34.5%) compared with episodes of NRSE (6/44, 13.6%; \( p < 0.05 \)). Low serum sodium did not correlate with aetiology or semiology of SE. Data for serum glucose were available for 68 episodes in the first 24 hours of SE. Hyperglycaemia with serum glucose levels of more than 10 mmol/l was seen in 3/25 episodes of RSE and in 11/43 episodes of NRSE, the difference was not significant. Temperature was documented in 48 episodes, in a quarter of cases patients had fever with rectal temperatures of more than 38.5 °C. Fever was seen significantly more often in RSE (9/24, 37.5%) compared with NRSE (3/24, 12.5%; \( p < 0.05 \)). However, fever correlated significantly positively with acute encephalitis (\( r = 0.66; p < 0.05 \)) and thus was not an independent factor. CSF was examined in 46 cases (55.4%). Pleocytosis was seen slightly more often in RSE (8/22, 36.4%) than in NRSE (7/24, 29.2%), and white cell count in the CSF was higher in NRSE compared with RSE, but differences were not significant (fig 1).

Semiology

The most common form of SE was complex partial SE (CPSE; 41/83, 49.4%), followed by generalised convulsive SE (GCSE) with partial onset (16/83, 19.3%) and GCSE without partial onset (15/83, 18.1%). Simple partial SE was seen in 8.4% (7/83) of patients. Absence status and myoclonic status were exhibited by two patients each (2.4%), the former was seen in NRSE and the latter in RSE. No form of SE was seen significantly more often in either of our study groups. Taking all forms of focal and focal onset SE together (64/83, 77.1%), focal forms amounted to 77.8% (28/36) in RSE and 76.6% (36/47) in NRSE.

Outcome measures

The duration of seizures was significantly longer in RSE (median 92 hours) compared with NRSE (median 24 hours; \( p < 0.001 \)). In those patients surviving SE, recurrence of epileptic activity within 24 hours after termination of SE was seen significantly more often with RSE (15/33, 45.4%) compared with NRSE (3/46, 6.5%; \( p < 0.001 \)) (fig 2). The length of stay in the NICU was significantly longer in RSE (median 16.5 days) compared with NRSE (median 2 days; \( p < 0.001 \)). The length of stay in hospital was also significantly longer in RSE (median 30 days) compared with NRSE (median 10.5 days; \( p < 0.01 \)). Inhospital mortality was higher in RSE (6/36, 16.7%) compared with NRSE (4/47, 8.6%), but the difference was not significant. Three patients with RSE and one patient with NRSE died in persisting seizures. The other patients died due to medical complications exclusively.

In 50/83 episodes patients had “de novo” SE and thus were eligible for the follow up telephone interview about development of post-SE symptomatic epilepsy. Seven patients were not followed up because either the current address and telephone number were not ascertainable or the patient refused the interview. Another 26 patients had already died. Thus 17 patients were available for the interview. Nine of these patients had developed symptomatic epilepsy after SE. Symptomatic epilepsy occurred significantly more often after RSE (7/8, 87.5%) compared with NRSE (2/9, 22.2%; \( p < 0.05 \)).

Subgroup analysis of outcome measures with regard to CPSE and GCSE showed that the duration of seizures was significantly longer in CPSE (205.2 hours) compared with GCSE (46.8 hours; \( p < 0.05 \)) whereas all other measures were not significantly different between the groups.
DISCUSSION

Status epilepticus (SE) represents one of the most frequent emergency situations in neurology associated with significant morbidity and mortality. If such status is refractory to first line anticonvulsants the condition becomes even more critical and requires management in an intensive care unit.

Unfortunately, the definition of refractoriness in SE as yet has been subject to much controversy and confusion. In some studies, besides failure of anticonvulsants, a minimum time span that has elapsed since seizure onset has been used as the cornerstone of the definition. However, in others the requirement has been the failure of a number of anticonvulsants regardless of duration of seizure activity. In the current study, failure of two anticonvulsants—a benzodiazepine and phenytoin/fosphenytoin—in adequate dosages defined RSE; the duration of status activity was not considered. We focused on refractoriness towards anticonvulsants because the time point to escalate anticonvulsant treatment of SE including the administration of anaesthetics is rather variable, with more hesitancy in CPSE compared with GCSE. Thus a fixed description of status duration as major part of the definition of refractoriness is not convincing, in particular for those cases treated late after the onset of symptoms.

To identify predictive and prognostic characteristics associated with RSE, we analysed data of all patients treated for SE in the NICU at the Charité University Hospital Berlin over a period of 10 years. In addition, patients without preexisting epilepsy were followed up about development of symptomatic epilepsy. Our main findings were: (a) SE was refractory to first line anticonvulsants in 43% of cases; (b) encephalitis is a major risk factor for RSE; (c) SE caused by

<table>
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<th>Table 2 Individual aetiologies of status epilepticus</th>
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<tr>
<td>Aetiology</td>
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<td>Inflammatory CNS diseases</td>
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<td>Encephalitis</td>
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<td>Meningitis</td>
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<td>Multiple sclerosis</td>
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<td>Cerebral toxoplasmosis</td>
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<td>Cerebrovascular CNS diseases</td>
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<td>Acute stroke</td>
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<td>Remote stroke</td>
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<tr>
<td>Intracerebral haemorrhage</td>
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<td>Sinus venous thrombosis</td>
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<td>Infantile brain damage</td>
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<td>Cortical dysplasia</td>
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<td>Encephalopathy</td>
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<td>Hypertensive encephalopathy</td>
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<tr>
<td>Substance associated</td>
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<tr>
<td>Low levels of AEDs</td>
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<tr>
<td>Alcohol-associated</td>
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<tr>
<td>Drug associated</td>
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<tr>
<td>Unknown</td>
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</table>

AEDs, antiepileptic drugs; CNS, central nervous system; NRSE, non-refractory status epilepticus; RSE, refractory status epilepticus.

Figure 1  Paraclinical factors measured in the first 24 hours after seizure onset in non-refractory status epilepticus (NRSE) and refractory status epilepticus (RSE). Data are presented as the rate of episodes in each subgroup with the particular feature. Hyponatraemia and fever were seen significantly more often in episodes of RSE. *p<0.05.

Figure 2  Short term recurrence of epileptic activity in the first 24 hours after seizure termination and development of post status epilepticus symptomatic epilepsy. Data are presented as the rate of episodes in each subgroup (non-refractory status epilepticus (NRSE) and refractory status epilepticus (RSE)) with the particular feature. Short term recurrence of epileptic activity and development of symptomatic epilepsy were seen significantly more often after RSE. *p<0.05; **p<0.001.
insufficient levels of AEDs is usually not refractory; and (d) symptomatic epilepsy develops significantly more often following RSE.

The general demographic features of the population included in this study were similar to a previous retrospective NICU based study on RSE. As almost all patients were older than 18 years, the clinical features discussed here cannot be considered representative for all age groups. In the present study, the rate of refractory cases was 43% which is slightly higher than the 31% reported by Mayer et al. The differences are most likely due to the definitions used and also perhaps due to differences in the study population. There is a paucity of data on the overall figures of refractory cases and a selection bias might be assumed since patients only from the NICU were considered. Clearly, a number of patients with NRSE will not have entered the NICU. Thus, this series of patients may not be representative of patients with SE in general. It is therefore interesting to note that in a large hospital based trial a very similar rate of 35–44% of patients did not respond to common initial anticonvulsants. Thus, the number of refractory cases in the current population does not greatly differ from the hospital based population.

The clinical characteristics of refractory status and risk factors of the condition are poorly understood, therefore current management approaches are still unsatisfactory. The current study identified acute symptomatic CNS diseases and particularly encephalitis as etiological predictors for RSE. Encephalitis seems to be notably epileptogenic and has been described in previous retrospective case series to cause RSE requiring long term treatment with anticonvulsant anaesthetics, sometimes up to several weeks. Pathogenetically, the multifocal distribution of the cortical epileptogenic lesions as caused by encephalitis is likely to represent an important factor predisposing to refractoriness in SE. Furthermore, some causative agents such as herpes virus, predominantly affect the temporal lobe, a structure well known for low seizure threshold. The current data suggest an aggressive therapeutic approach with rapid escalation of treatment in SE associated with encephalitis. This may prevent functional and structural neurological deficits resulting from continuing seizure activity itself which add to the deficits emerging in the course of encephalitis.

In contrast, insufficient levels of AEDs in patients with pre-existing epilepsy were not seen at all in the RSE group, but this was the most common cause of NRSE. It has been shown previously that patients with SE caused by insufficient levels of AEDs have better prognosis with lower mortality. Our current findings are important as various authors have shown that low levels of AEDs is one of the most common aetiologies in SE in general. With respect to therapeutic management in clinical practice, treatment escalation in SE caused by insufficient levels of AEDs should be used reluctantly.

Clinical and experimental data have shown the proconvulsive properties of hyponatraemia. In the study, hyponatraemia measured in the first 24 hours after onset of SE was significantly associated with refractoriness. These patients had not been exposed to carbamazepine, oxcarbazepine, or other drugs possibly causing low serum sodium levels significantly more often compared with patients with NRSE. Furthermore, hyponatraemia did not correlate with the primary cause of SE. As SE is not known to cause low serum sodium levels, the current results may support previously reported proconvulsive properties of hyponatraemia maintaining SE. Although the causal relationship between hyponatraemia and RSE is as yet unclear, the current findings suggest balancing hyponatraemia in all patients with SE with due consideration of the risk of severe neurological deficits when reloading serum sodium too rapidly.

The overall clinical outcome is poor in RSE. Similar findings have been described before in the general condition of SE of long duration. However, the specific clinical consequences of RSE episodes compared with NRSE, as shown in the current study, reveal a significant association with poor outcome and post-SE symptomatic epilepsy.

Symptomatic epilepsy frequently follows SE in patients who have previously not had epileptic seizures. The development of epilepsy in such circumstances is usually associated with the cerebral damage that has taken place. However, in most cases it is difficult to determine if such damage is related to the underlying pathology, to the status as such, or to a combination of both. Experimental animal data indicate that symptomatic epilepsy in the wake of status is not necessarily associated with major structural lesions but may also result from plastic changes of the brain that may not be detected with current imaging modalities.

To our knowledge, the effects of NRSE and RSE on the development of symptomatic epilepsy have not yet been analysed. The current data clearly show that refractory status is significantly more often followed by symptomatic epilepsy. This finding was independent of the type of SE. The current data suggest at least a prominent contribution of SE itself to the process of epileptogenesis. The influence of continuing epileptic activity on development of symptomatic epilepsy is also supported by the finding that the 10 year cumulative incidence of later unprovoked seizures is 13% after acute symptomatic seizures and 42% after acute symptomatic SE. However, it has to be considered that the neuronal lesions caused by severe acute symptomatic CNS diseases rather result in RSE and in more frequent unprovoked seizures. More than half of the patients in the current study who had been followed up for possible development of symptomatic epilepsy died. Most of these patients died in other hospitals and the causes of death remain obscure. Follow up studies looking specifically into mortality and causes of death following RSE will be of great interest.

In summary, SE is a frequent condition and patients with encephalitis as primary cause of SE are at special risk of developing RSE. Our data suggest treatment escalation early in the course of SE in these patients. Hyponatraemia early in the course of SE may facilitate the development of refractoriness, thus cautious balancing of serum sodium levels may be recommended. Prevention of the refractory type of SE is vital as this condition is associated with markedly poor prognosis including frequent short term recurrences of seizure activity, increased length of stay in the ICU and in hospital, and frequent development of post-SE symptomatic epilepsy.

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