ORIGINAL CONTRIBUTION

Refractory Status Epilepticus

Frequency, Risk Factors, and Impact on Outcome

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Background: Refractory status epilepticus (RSE) is a life-threatening condition in which seizures do not respond to first- and second-line anticonvulsant drug therapy. How often RSE occurs, risk factors that predispose to this condition, and the effect of failure to control seizures on clinical outcome are poorly defined.

Objective: To determine the frequency, risk factors, and impact on outcome of RSE.

Design: Retrospective cohort study.

Setting: Large academic teaching hospital.

Patients: Consecutive sample of 83 episodes of status epilepticus in 74 patients (mean age, 63 years).

Main Outcome Measures: Refractory status epilepticus was defined as seizures lasting longer than 60 minutes despite treatment with a benzodiazepine and an adequate loading dose of a standard intravenous anticonvulsant drug. Factors associated with RSE were identified using univariate and backward stepwiselogistic regression analyses.

Results: In 57 episodes (69%), seizures occurred after treatment with a benzodiazepine, and in 26 (31%), seizures occurred after treatment with a second-line anticonvulsant drug (usually phenytoin), fulfilling our criteria for RSE. Nonconvulsive SE ($P=.03$) and focal motor seizures at onset ($P=.04$) were identified as independent risk factors for RSE. Eleven (42%) of 26 patients with RSE had seizures after receiving a third-line agent (usually phenobarbital). Although mortality was not increased (17% overall), RSE was associated with prolonged hospital length of stay ($P<.001$) and more frequent functional deterioration at discharge ($P=.02$).

Conclusions: Refractory status epilepticus occurs in approximately 30% of patients with SE and is associated with increased hospital length of stay and functional disability. Nonconvulsive SE and focal motor seizures at onset are risk factors for RSE. Randomized controlled trials are needed to define the optimal treatment of RSE.

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STATUS EPILEPTICUS (SE) is a life-threatening condition that affects 120 000 to 200 000 people annually in the United States.[1] In its most severe form, refractory SE (RSE), continuous or repetitive seizures do not respond to first- and second-line anticonvulsant drug (ACD) therapy.[2,3] Little is known about the clinical epidemiologic features of RSE, which may be because of lack of consensus regarding its definition. Proposed criteria for RSE have varied in the number of ACDs failed (2 drugs[2,4-7] or 3 drugs[3,8-10]) and in whether a minimum duration of persistent seizure activity is required (range, none[2,7-10] to 1 hour[5,11] or 2 hours[4,6]).

Estimates of the frequency of RSE in patients with SE have ranged from 9% to 40%,[2,3,12] but few studies have focused specifically on RSE as a clinical problem, to our knowledge. In one hospital series,[12] failure of first- and second-line therapy was associated with delayed treatment and nonstructural causes of SE such as hypoxia-ischemia, metabolic encephalopathy, and central nervous system infection. The results of the Veterans Affairs (VA) Cooperative Study,[13] a randomized trial that compared 4 different first-line interventions for generalized convulsive SE (GCSE), indicate that RSE may be a problem of greater magnitude than is generally appreciated. In this trial,[14] 38% of patients with "overt" SE and 82% of patients with "subtle" SE continued to have seizures after receiving 2 ACDs, and only 2% and 5%, respectively, stopped having seizures after receiving a third agent.

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Many experts believe that SE should initially be treated with intravenous lorazepam (0.1 mg/kg), followed by a loading dose of phenytoin or fosphenytoin (20 mg/kg).[8,10] Although intravenous phenobarbital (20 mg/kg) has conventionally been

PATIENTS AND METHODS

STUDY POPULATION

We retrospectively identified all adults with SE admitted to the neurological intensive care unit (NICU) at Columbia-Presbyterian Medical Center between January 1, 1994, and March 31, 1998. Because of the retrospective nature of this study, the need for written informed consent was waived by the hospital institutional review board. Patients were identified using (1) the department of neurology admission log; (2) the NICU admission log; and (3) a computerized search of the hospital clinical information system for patients with a discharge diagnosis of SE (*International Classification of Diseases, Ninth Revision,* codes 345.2 and 345.3), partial seizures with decreased level of consciousness (code 345.7), epilepsia partialis continua (code 345.7), and convulsions (code 780.39). A complete list of all patients with possible SE was compiled by cross-referencing the 3 sources.

The diagnosis of SE was established when either of the following criteria was met: (1) continuous tonic-clonic or electrographic seizure activity for at least 10 minutes or (2) intermittent seizure activity without recovery of consciousness for at least 30 minutes. We equated these criteria because continuous SE carries a worse prognosis than intermittent SE[17] and because intermittent SE of more than 30 minutes' duration has a worse prognosis than seizure episodes lasting 10 to 29 minutes.[18] Using these criteria, we identified 132 hospital admissions for possible SE in 122 patients. Medical records were retrieved for 85% of these episodes (112/132), which were reviewed independently by 2 reviewers (J.L., F.M., L.J.D., or B.-F.F., and S.A.M.), with disagreements resolved by consensus. The diagnosis of SE was confirmed in 85 hospital admissions. Because our goal was to determine how often RSE occurs in patients who receive standard treatment for SE, we excluded 2 episodes in which a benzodiazepine was not given, leaving 83 episodes of SE in 74 patients for inclusion in the analysis.

SE DEFINITIONS

The primary cause of SE was classified as epilepsy related, structural (ie, stroke or brain tumor), or nonstructural (ie, metabolic or hypoxic-ischemic encephalopathy). Episodes of SE were classified as GCSE, nonconvulsive (NCSE), and simple partial motor on the basis of clinical descriptions and electroencephalographic (EEG) recordings. Generalized convulsive SE was considered present if any of the following were described: generalized tonic-clonic seizures, grand mal seizures, convulsions, bilateral rhythmic jerking, or similar descriptions. If none of these were present, if the patient was stuporous or comatose, and if the EEG showed ictal discharges, the seizures were considered nonconvulsive, whether or not subtle movements (eg, facial twitching, tonic eye deviation, and nystagmus) were observed. Periodic lateralized epileptiform discharges (PLEDs) were not considered ictal discharges. In all cases, we noted whether focal motor seizures (ie, lateralized tonic-clonic movements, head turning, and eye deviation) were present at the onset of SE. If the precise onset of seizures could not be determined, the onset of SE was judged to have occurred when it was diagnosed. Refractory SE was defined as continuous or intermittent seizures of at least 60 minutes' duration despite treatment with a benzodiazepine (lorazepam or diazepam, any dose) and intravenous phenytoin, fosphenytoin, or phenobarbital (≥10 mg/kg). We used ACD dosage criteria that are lower than those recommended for treating SE (15-20 mg/kg) because a higher cutoff value would have excluded many patients without RSE who responded to less than full loading doses. Cessation of SE was defined as the last clinical or electrographic seizure that occurred before becoming seizure free for at least 72 hours; at least 1 EEG was performed to exclude ongoing nonconvulsive seizures in patients with impaired unconsciousness after tonic-clonic activity was controlled. Treatment failure was judged to have occurred if any clinical or electrographic seizures occurred more than 1 hour after initiating first-, second-, or third-line therapy.[15]

CLINICAL VARIABLES

Medical records were reviewed independently by 2 reviewers using a structured data collection instrument. For each patient we recorded demographic information (sex, age, race or ethnicity, and weight) and medical history (epilepsy, hypertension, diabetes mellitus, coronary artery disease, and stroke). For each episode of SE we recorded the clinical characteristics of SE (primary cause,

used as third-line therapy, only a small percentage of patients will respond at this point. In the aforementioned VA study,[14] only 5% of patients with GCSE who did not respond to lorazepam and phenytoin therapy responded to phenobarbital administration. Accordingly, newer agents such as midazolam,[3,5,6,10,15] propofol,[4,6] and intravenous valproic acid[16] have been recommended as reasonable alternatives to phenobarbital for patients who do not respond to first- and second-line therapy, but experience with their use is relatively limited. Randomized controlled trials comparing treatment strategies for RSE have not been performed to date, to our knowledge. To assess the feasibility of such a study, we performed this retrospective analysis to (1) clarify how often RSE is encountered in routine clinical practice, (2) identify risk factors for RSE, and (3) evaluate clinical outcomes associated with RSE.

RESULTS

STUDY POPULATION

Mean age of the 74 patients with SE we studied was 63 years (range, 21-97 years); 44 (59%) were women. Thirty-one patients (42%) were black, 24 (32%) were white, and 19 (26%) were Hispanic. The most common comorbid conditions were hypertension (n=29, 39%), epilepsy (n=28, 38%), stroke (n=21, 28%), diabetes mellitus (n=21, 28%), and coronary artery disease (n=16, 22%).

CLINICAL FEATURES OF SE

In 74 episodes (89%), the patient was admitted through the emergency department, and in 9 (11%), the patient

seizure classification, interval from onset to arrival at the emergency department, and total duration); clinical variables on hospital admission (admission source, previous ACD use, APACHE [Acute Physiology and Chronic Health Evaluation] II score, worst Glasgow Coma Scale score, and maximum temperature within the first 24 hours); laboratory test results (peak creatine kinase and serum glucose levels, initial cerebrospinal fluid examination, and initial EEG); the dosage and highest blood levels of all ACDs given during the first 24 hours of hospitalization; hospital complications (fever [temperature >38.3°C], hypotension [systolic blood pressure <100 mm Hg], respiratory failure treated with mechanical ventilation, tachycardia [heart rate >120/min], pneumonia [fever or leukocytosis, purulent sputum, and infiltrate on chest radiography], urinary tract infection [positive culture findings], bacteremia [positive culture findings], hyperglycemia [glucose level >240 mg/dL (>13.3 mmol/L)], and anemia treated with blood transfusion); and outcome variables (Glasgow Outcome Scale score to assess functional status before hospital admission and at discharge, hospital and NICU length of stay [LOS], and cause of death).

STATISTICAL ANALYSIS

Statistics were analyzed using commercially available software (Statview 5.0; SAS Institute Inc, Cary, NC). Continuous values were compared using the 2-tailed *t* test or the Mann-Whitney test for nonnormally distributed data. Categorical variables were compared using the Pearson χ^2 test or the Fisher exact test as appropriate. To identify independent risk factors for RSE, clinical variables associated with RSE ($P<.05$) in a univariate analysis were entered into a backward stepwise logistic regression model, with RSE as the dependent variable. Complications, EEG findings, and outcome variables were analyzed separately as sequelae of RSE. Because complications are more likely to occur as LOS increases, we examined the relationship between RSE and specific complications while controlling for LOS using multiple logistic regression, with each complication as the dependent variable and RSE and hospital LOS as independent variables. Significance was established at $P<.05$.

was transferred from another hospital. The mean duration of seizures before emergency department admission was 1.3 hours (range, 0-4.25 hours). The most common causes of SE were low ACD levels or a recent change in medication in patients with epilepsy (n=26, 31%), toxic metabolic encephalopathy (n=16, 22%), stroke (n=16, 22%), hypoxic-ischemic encephalopathy (n=7, 8%), refractory epilepsy (n=5, 6%), brain tumor (n=4, 5%), and meningitis or encephalitis (n=3, 4%).

TREATMENT RESPONSE OF SE

Seizures continued after treatment with a benzodiazepine in 57 (69%) of the 83 SE episodes (**Figure 1**). Fifty episodes (60%) were treated with diazepam; 15 (18%), diazepam and lorazepam; 13 (16%), lorazepam alone; and 5 (6%), midazolam alone or in combination with other benzodiazepines. In 70 episodes (84%), phenytoin was given as the second-line ACD; in 9 episodes (11%), phenobarbital was given; and in 4 episodes that responded to benzodiazepines, no second agent was given. In 26 episodes (31%), seizures persisted after administration of a second-line ACD; in all of these cases, the total duration of SE exceeded 60 minutes, fulfilling our definition of RSE. In only 1 of 26 RSE episodes did the patient receive less than 15 mg/kg of phenytoin.

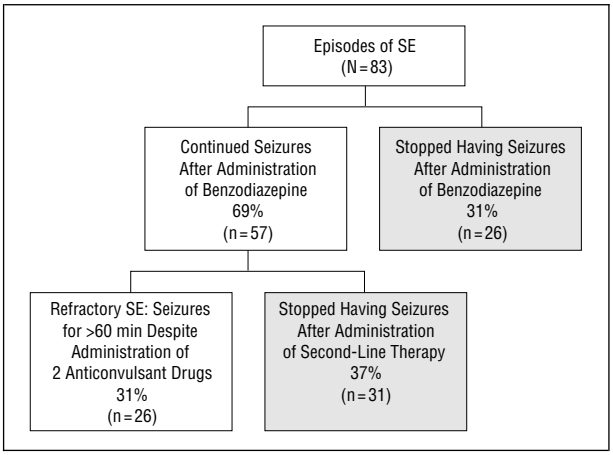

Figure 1. Flow chart showing the treatment response of 83 episodes of status epilepticus (SE).

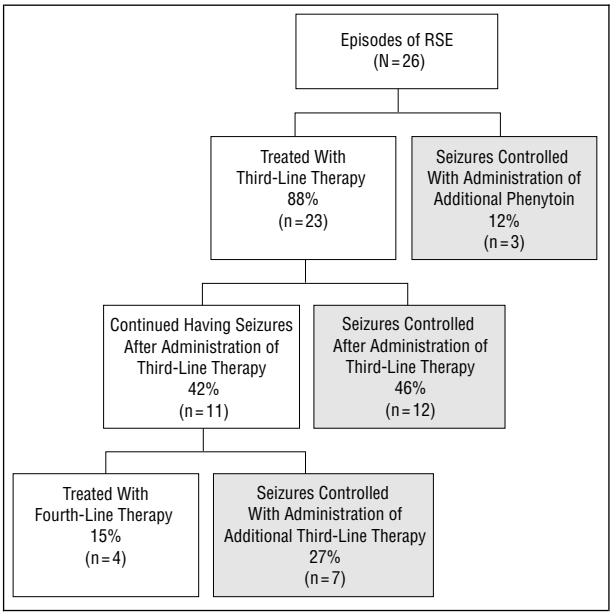

Figure 2. Flow chart showing the treatment response of 26 episodes of refractory status epilepticus (RSE).

TREATMENT RESPONSE OF RSE

Twenty-three of 26 episodes of RSE were treated with a third-line ACD (**Figure 2**); 21 patients received phenobarbital (mean dose, 10.3 mg/kg), and 1 each received valproic acid and midazolam. Eleven patients (42%) had seizures for longer than 1 hour after third-line therapy was initiated, and in 4 of these a fourth-line ACD was given (midazolam, pentobarbital, valproic acid, and phenobarbital were

Table 1. Univariate Analysis of Clinical Factors Related to RSE*

Variable	RSE (n = 26)	Non-RSE (n = 57)	*P* Value†
Primary cause of SE, No. (%)			
Nonstructural	10 (38)	17 (28)	.44
Epilepsy related	7 (27)	24 (42)	.18
Structural	9 (35)	16 (30)	.55
SE classification, No. (%)			
Generalized convulsive	19 (73)	55 (96)	**.004**
Nonconvulsive	7 (27)	1 (2)	**.001**
Focal motor	0 (0)	1 (2)	.99
Clinical features of SE			
Previous seizures, No. (%)	11 (42)	34 (60)	.14
Focal motor seizures at onset, No. (%)	19 (73)	21 (37)	**.002**
Interval from onset to arrival at ED, mean ± SD, h	1.3 ± 0.9	1.3 ± 0.8	.88
Continuous seizures at onset, No. (%)	1 (4)	9 (16)	.12
Hospital course			
Previous ACD therapy, No. (%)	11 (42)	24 (42)	.99
Admission GCS score, median	6.0	7.0	**.02**
Admission APACHE II score, mean ± SD	27 ± 8	25 ± 8	.37
Maximum temperature at onset, mean ± SD, °C	38.3 ± 1.3	38.1 ± 1.3	.51
Laboratory testing			
Peak creatine kinase level, median, U/L	500	469	.99
Peak serum glucose level, mean ± SD, mg/dL‡	457 ± 381	335 ± 372	**.04**
Lumbar puncture performed, No. (%)	16 (62)	23 (40)	.07
CSF white blood cell count, median/mm^2	1.0	1.0	.56
Treatment of SE			
First line: diazepam given, No. (%)	18 (69)	50 (88)	NA
Diazepam dose, median, mg/kg	0.20	0.19	.83
First line: lorazepam given, No. (%)	15 (58)	17 (30)	NA
Lorazepam dose, median, mg/kg	0.04	0.05	.85
Second line: phenytoin given, No. (%)	24 (92)	46 (81)	NA
Phenytoin dose, mean ± SD, mg/kg	21 ± 6	15 ± 8	**.001**
Peak phenytoin level, mean ± SD, μg/mL§	18 ± 9	18 ± 8	.76

*RSE indicates refractory status epilepticus; SE, status epilepticus; ED, emergency department; ACD, anticonvulsant drug; GCS, Glasgow Coma Scale; APACHE, Acute Physiology and Chronic Health Evaluation; CSF, cerebrospinal fluid; and NA, not applicable.

†*P* values refer to the χ^2 test for categorical data, the *t* test for normally distributed data, and the Mann-Whitney test for nonnormally distributed data. Bolded *P* values are significant ($P<.05$).

‡To convert glucose from milligrams per deciliter to the Système International Unit of millimoles per liter, multiply milligrams per deciliter by 0.05551.

§To convert phenytoin from micrograms per milliliter to the Système International Unit of micromoles per liter, multiply micrograms per liter by 3.96.

given to 1 patient each). All 4 of these patients experienced further seizures during the following 72 hours.

RISK FACTORS FOR RSE

Univariate analysis showed that patients with RSE were significantly less likely to have GCSE and more likely to have NCSE or focal motor seizures at onset (**Table 1**). Patients with RSE also had lower Glasgow Coma Scale scores and higher peak serum glucose levels and received more phenytoin within the first 24 hours than patients without RSE, although peak phenytoin levels were not different. In multivariate analysis, NCSE (odds ratio [OR], 11.6; 95% confidence interval [CI], 1.3-111.1; $P=.03$) and focal motor seizures at onset (OR, 3.1; 95% CI, 1.1-9.1; $P=.04$) were identified as independent risk factors for RSE.

Table 2. Initial EEG Findings During Hospitalization*

Variable	RSE (n = 26)	Non-RSE (n = 57)	*P* Value
EEG performed	26 (100)	31 (54)	
Diffuse slowing	13 (50)	23 (74)	.06
Focal slowing	6 (23)	7 (23)	.96
Interictal spikes or sharp waves	10 (38)	6 (19)	.11
PLEDs†	11 (42)	3 (10)	.004‡
Electrographic seizures	11 (42)	6 (19)	.06

*Data are given as number (percentage). EEG indicates electroencephalogram; RSE, refractory status epilepticus; and PLEDs, periodic lateralized epileptiform discharges.

†Generalized and bilateral periodic epileptiform discharges were also present in 1 patient each in the RSE group.

‡Significant ($P<.05$).

INITIAL EEG FINDINGS AND HOSPITAL COMPLICATIONS

Electroencephalography was performed in all patients with RSE and in slightly more than half of those without RSE (**Table 2**). In all cases, the initial EEG was performed within 72 hours of hospital admission. Although interictal epileptiform activity and electrographic seizures occurred more frequently after RSE, only PLEDs were significantly associated with RSE.

Respiratory failure treated with mechanical ventilation, fever, pneumonia, hypotension, bacteremia, and anemia treated with blood transfusion each occurred more often in patients with vs without RSE (**Table 3**). When controlling for LOS using multiple logistic regression, all of these complications continued to show significant associations with RSE except respiratory failure.

CLINICAL OUTCOME

Mortality was higher in patients with vs without RSE (23% vs 14%), but this difference was not significant (**Table 4**). Functional deterioration, reflected by a decreased Glasgow Outcome Scale score from hospital admission to discharge, occurred significantly more frequently in patients with RSE. Refractory SE was also associated with substantially increased hospital and NICU LOS. Overall, most deaths resulted from overwhelming medical complications. Of the 6 patients with RSE who did not survive, only 2 had uncontrolled seizures at the time of death.

COMMENT

In this study of patients in the NICU treated for SE, 31% of the episodes were refractory to first- and second-line ACD therapy. Nonconvulsive SE and focal motor seizures at onset were independent risk factors for RSE, and PLEDs occurred more frequently on initial EEG. Although the mortality rate was not increased, RSE was associated with more frequent medical complications, longer NICU and hospi-

Table 3. Complications During Hospitalization*

	RSE (n = 26)	Non-RSE (n = 57)	*P* Value	Association With†	
				LOS	RSE
Respiratory failure	23 (88)	36 (63)	**.02**	**.003**	.71
Fever (temperature >38.3°C)	21 (81)	27 (47)	**.004**	.42	**.02**
Tachycardia (heart rate >120/min)	11 (42)	49 (86)	.56	NA	NA
Pneumonia	17 (65)	18 (32)	**.004**	.64	**.01**
Hypotension (blood pressure <100 mm Hg)	17 (65)	14 (25)	**<.001**	**.02**	**.01**
Urinary tract infection	12 (46)	18 (32)	.20	NA	NA
Hyperglycemia (glucose level >240 mg/dL)	8 (31)	12 (21)	.41	NA	NA
Bacteremia	12 (46)	8 (14)	**.003**	.67	**.007**
Blood transfusion	13 (50)	7 (12)	**<.001**	**.007**	**.01**

*Data are given as number (percentage). Complications are listed in decreasing order of frequency. RSE indicates refractory status epilepticus; LOS, length of stay; and NA, not applicable.

†*P* values refer to strength of association between LOS and RSE (independent variables) and each complication (dependent variable) in a multiple logistic regression analysis. Bolded *P* values are significant ($P<.05$).

tal LOS, and increased functional disability at discharge. More than 40% of patients with RSE had seizures after a third-line ACD was given, and the median duration of refractory status was 20 hours. Randomized controlled trials are needed to identify more effective treatments for RSE and to improve outcomes for these patients.

Our study population differs from other hospital-based series of SE[12,19,20] in that alcohol withdrawal was an uncommon cause of SE and because women outnumbered men. Ninety percent of our patients were admitted to the hospital via the emergency department, with a mean duration of seizures before admission of 1.3 hours. Only 31% stopped having seizures after first-line benzodiazepine treatment (diazepam alone or in combination with another agent in 78% of episodes; mean dose, 0.2 mg/kg), reflecting the prevailing practice at that time.[12] The period we studied predated the VA Cooperative Study,[13] which has since established that lorazepam, 0.1 mg/kg, is at least as effective as other first-line treatments for SE. The clinical response rate to lorazepam therapy in the VA study was 51%, but comparison of their results with ours is hampered since we used lower doses of ACDs in general, treated a smaller proportion of patients with NCSE, and used a more stringent criterion to define the cessation of SE (no recurrent seizures for 72 hours vs 40 minutes).

The frequency of RSE (>60 minutes of seizure activity despite treatment with 2 intravenous ACDs) was 31%. This percentage is somewhat lower than the 40% reported for patients with GCSE at San Francisco General Hospital in the 1980s.[12] In our study, the frequency of RSE was substantially higher in patients with NCSE (88% [7/8]) than in those with GCSE (26% [19/74]). This finding is consistent with the VA Cooperative Study,[13] in which RSE occurred in 82% of patients with subtle SE (coma and ictal discharges on EEG, with or without subtle convulsive movements) compared with 38% of patients with overt SE (≥2 generalized convulsions). Except for primary generalized NCSE (absence status, petit mal status, or "spike wave stupor"), which occurs exclusively in patients with idiopathic epilepsy and generally responds well to treatment,[21] these findings confirm that NCSE is much more likely to be refractory than is GCSE. Although the association of complex partial and subtle secondary generalized NCSE with a high risk of mortality is well established,[22,23] it remains to be seen whether aggressive treatment with continuous-infusion ACDs improves clinical outcomes, particularly in the elderly.[23,24]

Table 4. Clinical Outcome*

	RSE (n = 26)	Non-RSE (n = 57)	*P* Value†
Seizure duration, median, h	20.1	2.5	**<.001**
Mortality, No. (%)	6 (23)	8 (14)	.31
Reduced GOS score at discharge‡	14 (54)	16 (28)	**.02**
Hospital LOS, median, d	32.5	11.0	**<.001**
NICU LOS, median, d	7.5	1.0	**<.001**

*RSE indicates refractory status epilepticus; GOS, Glasgow Outcome Scale; LOS, length of stay; and NICU, neurological intensive care unit.

†*P* values refer to the χ^2 test for categorical data and the Mann-Whitney test for nonnormally distributed data. Bolded *P* values are significant.

‡Compared with the admission GOS score.

Fifty-eight percent (15/26) of our patients with RSE had no further seizures after receiving additional phenytoin or a third-line agent, which in most cases was phenobarbital. By contrast, only 5.3% of patients with GCSE in the VA Cooperative Study[14] responded to phenobarbital administration after failing to respond to lorazepam and phenytoin therapy. This discrepancy probably reflects the fact that patients in the VA study were more refractory in that they had a longer median duration of SE before treatment, had already received higher doses of first- and second-line ACDs, and had a higher frequency of hypoxic-ischemic encephalopathy than our study population.

In multivariate analysis, we identified NCSE and focal motor seizures at onset (which occurred in patients with NCSE and patients with GCSE) as independent risk factors for RSE. One possible interpretation of this finding is that in contrast to seizures that rapidly generalize and spontaneously abate, repetitive or continuous seizures that do not readily generalize may be associated with more severe underlying brain pathology and hence may be more refractory to therapy. Another possible explanation is that a substantial proportion of our patients with GCSE may have had generalized-onset seizures, which tend to be more

responsive to treatment than secondary generalized seizures.[25] Although we did not determine how many of our patients with GCSE had generalized-onset seizures because of incomplete EEG data, they have constituted 20% to 40% of GCSE in other series.[1,20] Factors not associated with RSE included the cause of seizures, the duration of seizures before treatment, APACHE II scores, and body temperature. Although patients with RSE received significantly more phenytoin than patients without RSE, there was no difference in peak 24-hour blood levels, which might be explained by larger volumes of distribution or increased hepatic metabolism in patients with RSE.

Periodic lateralized epileptiform discharges are EEG discharges characterized by a spike or sharp wave followed by a slow wave that occurs every 1 to 2 seconds. They may occur in patients with acute focal brain injury in the absence of seizures, but they also appear frequently in the aftermath of prolonged, untreated seizures[26] and have been associated with poor outcome in SE.[27,28] Accordingly, the association of PLEDs with RSE in our study most likely reflects the longer duration of SE in these patients (Table 4). The clinical significance of PLEDs after SE is controversial; opinions differ on whether they represent a benign postictal phenomenon or harmful "agonal" ictal discharges that require treatment.[26] Persistent electrographic seizures have been reported in 15% of treated patients after the cessation of clinical SE[23] and are associated with poor prognosis.[27] Although nearly 30% (17/57) of our subjects had ictal discharges on initial EEG (Table 2), we were retrospectively unable to determine how many of these subjects had stopped having seizures clinically at this point.

Even after controlling for hospital LOS, RSE was associated with several serious medical complications, including fever, pneumonia, hypotension, bacteremia, and anemia treated with blood transfusions. Refractory SE was also associated with increased hospital and NICU LOS and more frequent functional deterioration at discharge, defined as a decrease in the Glasgow Outcome Scale score from admission to discharge. Morbidity after SE may result from neurological deficits caused by acute brain disease or seizures or from physical deconditioning related to secondary medical complications and prolonged hospitalization. In a separate analysis of this study cohort, we found that morbidity was predicted by acute symptomatic causes of SE and by prolonged LOS.[29]

Given the poor treatment response and morbidity rate associated with RSE, better treatment strategies are needed. The most reasonable options for third-line therapy after failure of lorazepam and phenytoin include intravenous phenobarbital or valproic acid or continuous-infusion therapy with midazolam or propofol. Treatment practices for RSE vary widely, and only small, nonrandomized cohort studies have directly compared therapies for RSE.[4,6] Prospective randomized controlled trials are needed to define the optimal treatment of refractory GCSE and NCSE.

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