Objective: To determine the functional and cognitive outcomes of patients with prolonged refractory status epilepticus (PRSE) lasting 7 or more days despite the use of anesthetic agents for seizure suppression.

Design: Retrospective analysis.

Setting: St Mary’s Hospital, Mayo Clinic, Rochester, Minnesota.

Participants: Fourteen patients with PRSE.

Intervention: Hospital follow-up interview.

Main Outcome Measures: Survival rate of PRSE and functional and cognitive outcome of surviving patients based on the modified Rankin Scale (mRS) and Telephone Interview for Cognitive Status (TICS).

Results: Forty-three percent of patients (6 of 14) died during hospitalization for PRSE, and 57% (8 of 14) had died by the last follow-up. Of the 6 surviving patients, 4 showed improvement and 2 showed no change in mRS score (median mRS change, −1; range, 0 to −3). Owing to pre-existing cognitive deficits, 1 patient could not complete the TICS. The 5 remaining patients scored a median of 34 on the TICS (range, 30-37; reference TICS score, ≥31; maximum TICS score, 41). Age, sex, PRSE duration, and etiology were not associated with chance of survival.

Conclusions: Despite the high mortality rate, survival with meaningful functional and cognitive recovery is possible after PRSE. Prolonged duration of status epilepticus alone should not be considered a reason to discontinue treatment.

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RESULTS

Fourteen patients with PRSE were identified. Eight subjects (57%) were men, and the median age was 42 years (range, 18-69 years) (Table 1). Six patients had a history of epilepsy. In 1 patient with chronic posttraumatic epilepsy, the episode of PRSE was caused by acute encephalitis, the specific etiology of which was not determined. Three patients with a history of epilepsy had progressive symptomatic etiologies including 1 patient with a brain tumor, 1 with strokes due to a mitochondrial cytopathy, and 1 with an undefined familial progressive myoclonic form of epilepsy. One patient with epilepsy had a history of ischemic stroke and subarachnoid hemorrhage 9 years prior to her PRSE episode, and another patient with a history of epilepsy had symptomatic Lennox-Gastaut syndrome of unknown cause. The cause of PRSE in the patient with Lennox-Gastaut syndrome was uncertain but may have been medication noncompliance. The etiology of PRSE in the patients without a history of epilepsy included acute ischemic stroke (2 patients), subdural hematoma, thrombotic thrombocytopenic purpura, encephalitis (2 patients), neuropsychiatric systemic lupus erythematosus, and indeterminate cause (1 patient). Prolonged refractory status epilepticus etiologies classified according to the International League Against Epilepsy recommendations are displayed in Table 1. One patient developed only nonconvulsive seizures, while all other patients had both convulsive and nonconvulsive seizures during their course of PRSE.

All patients without contraindication received a benzodiazepine and loprophentoin prior to initiation of anesthetic drugs. Three patients with phenytoin allergy received valproic acid and/or phenobarbital prior to anesthetic initiation. Patients received a median of 2 anesthetic drugs during treatment of PRSE (range, 1-5 drugs). Anesthetic drugs given included propofol, midazolam, pentobarbital, lidocaine, ketamine, and isoflurane, either as a single drug or in combination. In addition to anesthetic drugs, a median of 5 maintenance antiepileptic drugs (range, 4-6 drugs) were initiated per patient either singly or in combination in an effort to abort or maintain control of PRSE. These antiepileptic drugs included clonazepam, diazepam, felbamate, levetiracetam, lorazepam, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide. A temporal lobectomy was performed in 1 patient with unilateral frontal and temporal encephalomalacia and focal PRSE. This operation was unsuccessful in aborting PRSE, and the patient ultimately died. All but 1 patient required vasopressor use during anesthetic administration (Table 2, patient 9).

Forty-three percent of patients (6 of 14) died during hospitalization for PRSE and 57% (8 of 14 patients) had died by the last follow-up. Of the 6 patients who died during PRSE, 5 died after elective withdrawal of supportive care. Supportive care was withdrawn when prognosis was deemed poor in the presence of continued PRSE or lack of improvement in consciousness despite successful PRSE treatment. The sixth patient died of a cardiac arrhythmia. Two patients survived PRSE, but died after hospital discharge. One of these patients continued to have frequent seizures and died of pneumonia 3 months following hospital discharge. The other died of an unspecified cause 13 months after discharge.

The median duration of PRSE in the entire group was 18 days (range, 7-67 days), and 6 patients had PRSE for more than 2 weeks. The median durations of PRSE in survivors (19.5 days; range, 9-67 days) and nonsurvivors (18 days; range, 7-33 days) was not significantly different (P = .70). Of the 6 patients who survived to the time of interview, the median duration of PRSE was 33.5 days (range, 10-67 days). Survival of PRSE was not affected by age (odds ratio, 1.04; P = .22), sex (P > .99), or acute stroke or encephalitis as the PRSE etiology (P = .54 for acute stroke and P > .99 for encephalitis).
The median length of intensive care unit stay was 21.5 days (range, 7-97 days), and the median length of hospitalization was 31 days (range, 7-125 days). The difference in length of hospitalization for survivors (61 days) and nonsurvivors (19.5 days) was statistically significant (P = .01), as patients who died had shorter lengths of hospital stay.

All patients had medical complications during their hospitalization. These complications included pneumonia (9 patients), deep vein thrombosis (3 patients), pseudomembranous colitis (1 patient), critical illness myopathy (2 patients), critical illness neuropathy (1 patient), urinary tract infection (6 patients), sepsis (2 patients), rhabdomyolysis (1 patient), acute renal failure (1 patient), pseudomonas sinusitis (1 patient), ileus (3 patients), elevated liver enzymes (>3 times the reference value; 2 patients), line infection (1 patient), and Stevens-Johnson syndrome (1 patient) (Table 1).

Six of 8 patients who survived PRSE had worsening of their mRS score at hospital discharge compared with their premorbid score (median mRS change, 4; range, 0-4) (Table 2). The 2 patients without a decline were mentally retarded prior to onset of PRSE and had premorbid baseline mRS scores of 4 and 5. The median time from hospital discharge to telephone interview was 313 days (range, 131-2902 days). Hospital follow-up mRS scores were not available for the 2 patients who died prior to initiation of this study. Of the 6 patients who were interviewed following hospital discharge, 4 showed functional improvement on the mRS compared with their hospital dismissal scores and 2 showed no change (median mRS change, −1; range, 0 to −3). One of the 2 patients with no change in mRS score at last follow-up had a premorbid mRS score of 5 (severe disability) owing to preexisting mental retardation related to Lennox-Gastaut syndrome. This patient could not be evaluated with the TICS owing to preexisting cognitive deficits and inability to speak. The 5 remaining patients scored a median of 34 on the TICS (range, 30-37) (reference TICS score, ≥31; maximum TICS score, 41).

**COMMENT**

This study confirms that PRSE has high morbidity and mortality rates. All surviving patients in this study had poor functional outcome at hospital discharge based on dismissal mRS scores. However, improvement was seen...
in most survivors over time, and our results show that meaningful cognitive recovery is possible after successful treatment of PRSE. The study results suggest that functional improvement is possible after resolution of PRSE, and several months may be necessary to realize the full recovery potential of these patients. The range of time from hospital discharge to follow-up was large (131-2902 days) and may have affected the functional and cognitive outcome scores. Although only 2 of our 14 patients were independent at the time of last follow-up, it is possible that if the time to follow-up had been longer for some patients their scores may have improved more than our results show.

Owing to the retrospective study design, we do not have TICS scores at baseline or at hospital discharge to compare with the postdismissal TICS scores. A study by Adachi et al26 compared neuropsychological test scores in patients with epilepsy who had an episode of SE with a control population and did not find any significant change following SE. However, the patients in their study did not suffer from symptomatic etiologies of SE, unlike the patients in our study. In vivo and in vitro studies have demonstrated neuronal death associated with SE, precluding that patients with SE would be at risk of incurring long-term neurological deficits.17-20 Several other clinical studies have looked at functional outcome in SE and have shown that about 10% of patients who survived SE have disabling neurologic deficits afterward.21-24 It remains unclear if medical treatment of SE affects outcome or if outcome is determined solely by the etiology underlying SE.10,25,26

The hospital mortality rate of patients in our study was high (43%) when compared with studies on RSE, which show mortality rates ranging from 16% to 23%.2,3,25 The high mortality rate was likely owing to the prolonged nature of SE in our series in contrast to the typical duration in most RSE studies. All patients in this study were mechanically ventilated, which has also been associated with higher mortality rates.27 Duration of SE has been identified by other investigators to be a mortality risk factor.4,28 Although shorter duration of SE was associated with decreased chance of survival in our study, the shorter SE duration in fatal cases was likely owing to the decision to withdraw supportive care in these 5 patients.

Benzodiazepines and fosphenytoin were initially given to all patients who had no contraindication. Following administration of these 2 drugs, multiple other anesthetic agents and antiepileptic drugs were used. Owing to the retrospective nature of this study, we could not ascertain the precise reason for selection of the particular drugs used in each individual case. This finding is consistent with a survey of physicians regarding the treatment of RSE in which there was a lack of agreement on the choice of third- and fourth-line agents.29 At this time, no prospective randomized trials have been performed to compare the efficacy of the different treatment options available for RSE. One retrospective systematic review compared the reported outcomes of 3 anesthetic agents used in RSE but did not find a significant difference in mortality between them.30 Another retrospective study suggested that mortality may be higher with the use of propofol versus midazolam.31 A study of patients with RSE at our institution found complications due to propofol to be unacceptably high, prompting removal of propofol from our RSE treatment protocol.32 Other studies suggest that drug choice does not affect patient out-

### Table 2. Hospital Course, Functional Outcome, Anesthetics, and Reason for Death

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>PRSE Duration, d</th>
<th>ICU Stay, d</th>
<th>Premorbid mRS Score</th>
<th>Discharge mRS Score</th>
<th>Interview mRS Score</th>
<th>TICS Score</th>
<th>Discharge to Interview, d</th>
<th>Anesthetic Drugs</th>
<th>Reason for Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>16</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>30</td>
<td>358</td>
<td>Propofol</td>
<td>Pneumonia, 95 d after PRSE</td>
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<tr>
<td>2</td>
<td>9</td>
<td>36</td>
<td>1</td>
<td>5</td>
<td>NA</td>
<td>4</td>
<td>1580</td>
<td>Midazolam, propofol</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>21</td>
<td>1</td>
<td>6</td>
<td>NA</td>
<td>34</td>
<td>268</td>
<td>Midazolam, propofol, pentobarbital</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>14</td>
<td>1</td>
<td>6</td>
<td>NA</td>
<td>34</td>
<td>268</td>
<td>Propofol</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>67</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>34</td>
<td>268</td>
<td>Midazolam, propofol, pentobarbital</td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>22</td>
<td>3</td>
<td>6</td>
<td>NA</td>
<td>34</td>
<td>268</td>
<td>Midazolam, propofol, pentobarbital</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>NA</td>
<td>34</td>
<td>268</td>
<td>Midazolam, propofol, pentobarbital</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>97</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>34</td>
<td>268</td>
<td>Midazolam</td>
<td>Unknown cause, 399 d after PRSE</td>
</tr>
<tr>
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<td>9</td>
<td>15</td>
<td>4</td>
<td>4</td>
<td>NA</td>
<td>34</td>
<td>268</td>
<td>Midazolam, propofol</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>134</td>
<td>2902</td>
<td>Midazolam</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>18</td>
<td>3</td>
<td>6</td>
<td>NA</td>
<td>34</td>
<td>268</td>
<td>Propofol, pentobarbital</td>
<td>Supportive care withdrawn</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>31</td>
<td>3</td>
<td>6</td>
<td>NA</td>
<td>34</td>
<td>268</td>
<td>Midazolam, propofol, pentobarbital</td>
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</tr>
<tr>
<td>13</td>
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<td>4</td>
<td>3</td>
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<td>Supportive care withdrawn</td>
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<tr>
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<td>51</td>
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<td>4</td>
<td>1</td>
<td>37</td>
<td>131</td>
<td>Midazolam, propofol, pentobarbital</td>
<td>Supportive care withdrawn</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; mRS, modified Rankin scale; NA, not available; PRSE, prolonged refractory status epilepticus; TICS, Telephone Interview of Cognitive Status.

a Patient survived PRSE but died prior to telephone follow-up.
b Patient died during PRSE.
c Patient unable to participate in TICS owing to severe preexisting cognitive deficits.
d Temporal lobectomy performed on this patient.
come.7,25 Algorithms for the treatment of RSE have been proposed.6 A randomized controlled study may be necessary to determine if a superior treatment of RSE exists.

Our results indicate that, although the risks of death and severe neurologic sequelae are high in cases of PRSE, survival with meaningful functional recovery is possible. Thus, prolonged duration (≥1 week) of SE is not a sufficient reason to discontinue therapy. Others have suggested that aggressive care should be continued in prolonged RSE when serial neuroimaging appears normal.33 Further studies on risk factors of poor outcome in PRSE may help clinicians and families decide when it is appropriate to continue aggressive care.

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