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# Is favorable outcome possible after prolonged refractory status epilepticus?

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**Abstract:**

When status epilepticus (SE) remains refractory to appropriate therapy, it is associated with high mortality, and with substantial morbidity in survivors. Many outcome predictors such as age, seizure type, level of consciousness before treatment, and mostly, etiology are well-established. A longer duration of SE is often associated with worse outcome, but duration may lose its prognostic value after several hours. Several terms and definitions have been used to describe prolonged, refractory SE, including “malignant SE,” “prolonged” SE, and more recently, “super-refractory” SE, defined as “SE that has continued or recurred despite 24h of general anesthesia (or coma-inducing anticonvulsants).” There are few data available regarding the outcome of prolonged refractory SE, and even fewer for SE remaining refractory to anesthetic drugs. This article reviews reports of outcome after prolonged, refractory and “super-refractory” SE. Most information detailing the clinical outcome of patients surviving these severe illnesses, in which seizures can persist for days or weeks (and especially those concerning “super-refractory” SE) come from case reports and retrospective cohort studies. In many series, prolonged, refractory SE has a mortality of 30 – 50%, and several indicate that most survivors have a substantial decline in functional status. Still, several reports demonstrate that good functional outcome is possible even after several days of SE and coma induction. Treatment of refractory SE should not be withdrawn from younger patients without structural brain damage at presentation solely because of the duration of SE.

## 1. Introduction:

Status epilepticus (SE) is a neurologic emergency. There are many established outcome predictors, such as age, seizure type, level of consciousness before treatment, and mostly, etiology (Logroscino et al., 1997), (Rossetti et al., 2006). A longer duration of SE has been associated with worse outcome in several studies (Towne et al., 1994), (Logroscino et al., 2002), (Sagduyu et al., 1998), but duration may be a much less valuable predictor after several hours (Drislane et al., 2009), and good outcome has been reported after very prolonged SE (Hocker et al., 2014). Evidence about refractory status epilepticus (RSE), defined as ongoing seizures despite treatment with adequate doses of a benzodiazepine and a second line anticonvulsant (Brophy et al., 2012), is sparse, including just one prospective study (Novy et al., 2010), and most information on the outcome of RSE comes from case reports and retrospective cohort studies. Definitions of severe, prolonged SE vary. They include “malignant SE” (Holtkamp et al., 2005), “prolonged SE” (Cooper et al., 2009), “very prolonged SE” (Drislane et al., 2011), and “super refractory SE” (Shorvon, 2011), the last pertaining to SE resistant to anesthetic (i.e. coma-inducing) therapy. Although the outcome of all these forms of severe SE is often dismal, some RSE has a good outcome, and some patients even return to their normal, premorbid states.

This article reviews the different definitions of prolonged, refractory SE and their reported outcomes in adult patients. Papers were sought in “PubMed” using the search term “refractory status epilepticus” associated with “malignant”, “prolonged”, “super-refractory”, “severe”, “outcome”, and “anesthetic drug”. Reference lists of relevant papers and references were included. All articles including case series or case reports detailing the outcome of prolonged, refractory SE were included. Articles describing solely in-hospital mortality were not included, except in brief mention.

## **2. Definitions.**

To date, many definitions have been used to describe SE episodes that are particularly longer-lasting and refractory to anticonvulsant and anesthetic drug treatment. Most have included a duration criterion and failure to control seizure activity after two appropriately dosed anticonvulsant medications, or even after ‘anesthetic’ drugs (usually entailing use of pentobarbital, thiopental, midazolam, or propofol) and their discontinuation.

In a retrospective study performed in Germany assessing risk factors, frequency, and outcome of highly refractory SE (Holtkamp et al., 2005), “*malignant SE*” was defined as “persistent clinical and/or electrophysiologic epileptic activity immediately recurring within 5 days after tapering of the maximal dose of intravenous anesthetic anticonvulsants required to achieve an electroencephalographic (EEG) burst suppression pattern previously.” Two studies assessing clinical characteristics and outcome of SE defined “*prolonged SE*” as that requiring at least seven days of anesthetic drugs being necessary to control the SE (Cooper et al., 2009), (Kilbride et al., 2013). In another study comparing survivors and non-survivors of “*very prolonged SE*”, episodes lasted at least 4 days (Drislane et al., 2011).

The term “*super-refractory SE*” (SRSE) was introduced in 2011 and defined as “SE that has continued or recurred despite 24 hours of general anesthesia,” and including SE that relapsed after the anesthesia was stopped (Shorvon, 2011). This term has been used several times recently (Shorvon and Ferlisi, 2011), (Shorvon and Ferlisi, 2012), (Thakur et al., 2014), (Hocker et al., 2014) and is the term used in an ongoing international registry (<https://www.status-epilepticus.net>) (Ferlisi and Hocker, 2013). It may also be the most pertinent term for most of the cases described in this review.

## **3. Review of outcome in published data.**

A single prospective study (Novy et al., 2010) demonstrated that SE became RSE (as defined above) in 22.6% of SE episodes. Severity of consciousness impairment and absence of earlier seizures were independently associated with refractoriness. Because the

study did not state whether patients had undergone 24 hours of ‘anesthetic’ anticonvulsant treatment, it was not possible to assess the prevalence of ‘super refractory’ SE. All other studies detailed here were retrospective, including case reports and cohorts of patients with SRSE. They are reviewed according to the type and focus of the studies.

### **3.1.1 Outcome in cohorts of unselected cases of SRSE.**

We found four cohort studies of unselected cases of SRSE, summarized in **Table 1** (Holtkamp et al., 2005), (Cooper et al., 2009), (Drislane et al., 2011), (Kilbride et al., 2013) and one cohort focusing on RSE, 90% of which was SRSE (Hocker et al., 2013)

Holtkamp and colleagues retrospectively identified seven patients with “malignant” SE (i.e. recurring at least 5 days after maximal anti-seizure treatment, including ‘anesthetics,’ thus also meeting criteria for SRSE) among 35 patients with SE in a neuro-intensive care unit (Holtkamp et al., 2005). One patient (14%) with MRSE died -- a rate similar to that of patients with less prolonged RSE. Among the six survivors, five had a reduction of at least 2 points in the Glasgow Outcome Scale, indicating marked functional dependency.

A retrospective study from the (US) Mayo Clinic detailed the functional and cognitive outcome of 14 patients with “prolonged refractory SE,” also treated with ‘anesthetic’ drugs and meeting criteria for SRSE (Cooper et al., 2009). Eight died, six in hospital. Among the six survivors, the best modified Rankin Score (mRS) was 4 (= unable to walk without assistance and unable to attend to own bodily needs without assistance) upon hospital discharge. Despite this dismal early outcome, two survivors were functionally independent at the time of last follow-up, at least five months later.

Another study from the US attempted to identify factors associated with survival after “very prolonged refractory status epilepticus,” comparing the 10 survivors and the 11 non-survivors with the longest SE duration from a cohort of 119 patients with SE (Drislane et al., 2011). Due to this study design, the overall mortality rate of SRSE was not available. Older age,

multiple medical problems, and coma upon presentation were strongly associated with mortality. SE duration, however, did not appear to influence outcome.

The largest cohort of “prolonged refractory SE” (PRSE) included 63 patients (Kilbride et al., 2013), collected in four US academic centers. Nearly half of cases were due to central nervous system inflammation, including viral and auto-immune encephalitis. Other etiologies included chronic epilepsy, following neurosurgical procedures, traumatic brain injury, brain tumor, vascular causes, and metabolic derangement. By the time of discharge, 33% had died. Fourteen patients (22% of the total; 33% of survivors) had a good functional recovery (mRS 0-3), including six without disability. Patients with good recovery tended to be younger, but some older patients (up to 69 years) had good outcomes. Normal structural brain imaging (a probable surrogate for etiology) was associated with greater likelihood of a good outcome.

A recent retrospective cohort study, also from the Mayo Clinic, focused on RSE (Hocker et al., 2013), but nearly 90% of the cohort fulfilled the definition of SRSE. Three quarters of the 54 patients had a poor outcome at discharge (mRS  $\geq$  4), including 20 deaths. Despite the dismal outcome in most patients, a minority (8 patients; 17% of the total) regained their premorbid functional status, including two after more than a month in iatrogenic coma.

From the three studies above that could assess overall mortality (excluding the earlier and smaller Mayo Clinic study), 42 of 124 patients (34%) died – very similar to the figure in many reports of RSE not reviewed here. From the same studies, 14% - 22% of patients had good functional outcome despite the prolonged SE and usual iatrogenic coma. Younger age was usually associated with a better outcome. Absence of a structural brain lesion was associated with survival in the largest cohort. Interestingly, duration of SE was found to influence the outcome in only one of the five studies.

### **3.2 Outcome in cohorts of SRSE with particular groups of etiologies or treatment.**

#### **3.2.1 Outcome in prolonged RSE due to autoimmune encephalitis.**

Autoimmune encephalitis as a cause of RSE has attracted much attention in the last decade. In a recent prospective study of 15 patients presenting with seizures and other neurologic symptoms with positive autoantibodies (Pandit et al., 2013), seven had anti-N-methyl-D-aspartate (anti-NMDA) receptor antibodies, five had antibodies against potassium channel complex (anti-VGKC), two had anti-glutamate decarboxylase (anti-GAD) antibodies, and one had anti-ANA antibodies. Of those 15 patients, four (29%) presented with SE (3 with anti-NMDA, 1 with anti-VGKC). One died (anti-NMDA), one had a moderate outcome (mRS = 3) after 10 weeks of symptoms, and two had good outcomes (mRS = 1) after 8 and 24 weeks of symptoms.

In a large series of anti-NMDA encephalitis (Dalmau et al., 2008) or limbic encephalitis (Vincent et al., 2004), (Lai et al., 2010), there were not enough details regarding the refractoriness or duration of SE to assess an outcome of prolonged RSE. Nevertheless, favorable outcome has been described in patients with this illness and epileptic seizures (Davies et al., 2010), even after 3 months of SRSE (Finné Lenoir et al., 2013).

Encephalitis associated with anti-GABA<sub>A</sub> receptor antibodies has been described recently (Petit-Pedrol et al., 2014) and is associated with severe epileptic seizures. Among 18 patients, five had RSE requiring multiple anti-seizure drugs (ASDs) and iatrogenic barbiturate coma. Acute disease lasted four, eight, 10 and 12 weeks (unspecified in one patient), suggesting frequent SRSE. Two patients died during hospitalization, and one had only a partial cognitive improvement and refractory epilepsy at 2.5 years of follow-up. One patient, however, returned to school 15 months later, and another was back to work 18 months later.

### **3.2.2 Cryptogenic RSE, or New Onset Refractory Status Epilepticus (NORSE)**

There have been several recent reports describing (usually young) previously healthy men or women who develop cryptogenic SRSE – i.e. without a clear etiology determined despite a comprehensive assessment (Van Lierde et al., 2003). This has prompted the eponym NORSE, for New Onset Refractory Status Epilepticus (Wilder-Smith et al., 2005). We found



four published series of NORSE in adults (Van Lierde et al., 2003), (Wilder-Smith et al., 2005), (Costello et al., 2009), (Gall et al., 2013) (see **Table 2**). Altogether, they included 24 young, previously healthy patients with RSE lasting from six to 191 days. Of the 23 patients for whom data were available, 10 died, two survivors were in vegetative states, and five survivors were severely disabled or had refractory epilepsy, but six had good outcomes, or at least independence in daily life.

### **3.2.3 Outcome in cohorts evaluating specific treatment for super refractory SE.**

Several treatment options for SRSE have been reviewed in detail recently (Shorvon and Ferlisi, 2011), (Shorvon and Ferlisi, 2012) and are beyond the scope of this review. Still, some of these articles can supply perspective on possible outcome after SRSE.

In an early study of pentobarbital treatment for RSE, 11 of 17 patients fulfilled criteria for SRSE (Yaffe and Lowenstein, 1993). Nine of 17 patients (53%) died, and two of the eight survivors had severe neurologic deficits. Similarly, in the largest study of pentobarbital treatment for RSE (most with SRSE), 55% of the 40 patients died, but no data were available on longer-term outcome for survivors (Krishnamurthy and Drislane, 1996). In another study of patients with SRSE (Prasad et al., 2001), 57% of patients treated with propofol and 17% of those treated with midazolam died, but again, data on longer follow up was not given. In a larger meta-analysis of many studies (including the three just above) of coma-induction for RSE, and mostly SRSE (Claassen et al., 2002), mortality was 46% with midazolam, 48% with pentobarbital, and 52% with propofol. In almost all reports, the high case fatality rate was attributed to the severe underlying etiology of the SE. As the data came from many studies, without standardized reporting, information on longer-term follow-up was variable, but the authors reported that when data were available, it appeared that only 29% of all patients returned to normal baseline function. Another study from the same group (Mayer et al., 2002) showed that of 83 episodes of SE, 26 (31%) became RSE, and 42% of these, SRSE. Patients with RSE had a mortality of 23%, not statistically different from those with

non-refractory SE. Of 20 RSE survivors, 14 had reduced Glasgow Outcome Scores at discharge, but longer follow up was not reported.

Gaspard and colleagues evaluated the role of ketamine in the treatment of 60 cases of RSE (Gaspard et al., 2013). The median duration of SE was 26.5 days (range: 1 day – 10 months). Slightly more than half of the patients were alive at discharge, but most survivors had a poor outcome. Only 2 of the 46 adults with available follow up data from this study had a mRS  $\leq$  2 (slight or no disability).

In a series of ten patients treated with ketogenic diet for SRSE, the mean induced coma duration was 29 days (range: 8 – 76 days) (Thakur et al., 2014). All patients survived the SRSE episode (although two died later), but only three had favorable outcomes, with mRS  $\leq$  2.

Currently, there are only two registered prospective therapeutic trials for SRSE enrolling patients. One assesses safety, tolerability, side effects, and effectiveness of the ketogenic diet in SRSE (ClinicalTrials.gov: NCT01796574). The other studies the safety and pharmacokinetics of a neurosteroid, allopregnanolone, as adjunctive therapy in SRSE (ClinicalTrials.gov: NCT02052739).

### **3.3 Case reports of prolonged SRSE in adults with detailed description.**

We found 14 adult cases of SRSE with detailed clinical descriptions (Mirski et al., 1995), (Krishnamurthy and Drislane, 1997), (Robakis and Hirsch, 2006), (Kanter et al., 2008), (Kondziella et al., 2008), (Prüss and Holtkamp, 2008), (Fugate et al., 2010), (Johnson et al., 2010), (Bausell et al., 2011), (Standley et al., 2012), (Thordstein and Constantinescu, 2012), (Finné Lenoir et al., 2013), (Hocker et al., 2014), (Moseley and Degiorgio, 2014) (see **Table 3**). Almost all of these patients were young (27 years-old; range: 17-68). Median coma or SE duration was 90 days (range 26 - 257). None of these patients died, but eight of 14 had poor outcomes, including two in persistent vegetative states. Five patients were

described as independent at last follow-up, and two were reported as free of any physical or cognitive impairment.

#### **4. Conclusion.**

Status epilepticus may be severe and prolonged. It may persist despite appropriate treatment with two ASDs (refractory SE, RSE), or even become “super-refractory SE.” Such SRSE is often associated with a high mortality rate – over 30% in the studies reviewed above, and with over 50% dying or in vegetative states among the patients with NORSE reviewed here. Further, these studies show major morbidity and dependence among survivors – with good functional status being reached in fewer than 30% of SRSE survivors and under 50% of NORSE survivors. Considering both mortality and morbidity among all reports reviewed here, under 1/3 of all SRSE and NORSE patients had a good outcome. The individual case reports cited above noted survival in all cases, but there was clearly an important publication bias in these cases toward successful outcome -- often illustrating the advantages of a particular treatment. Also, while all of these patients survived, most had significant residual impairment.

With regard to etiology, the patients with autoimmune encephalitis had somewhat better survival rates but often extremely long hospitalizations and severe residua. Several reports have indicated that infectious encephalitis leads to significant mortality and appears particularly likely to lead to severe residua among survivors, but none of these reports focused solely on that illness. Also, most papers excluded patients with RSE or SRSE caused by anoxia, already known to be associated with a terrible prognosis (Rossetti et al., 2007).

It is difficult to assess outcome from studies of specific treatments. For example, most patients treated with longer courses of midazolam, propofol, or pentobarbital had particularly severe illnesses and poor outcomes – almost always attributed to the underlying illnesses. Further, under 10% of patients treated with ketamine had good outcomes, but ketamine was

very likely the final of many treatments for severe, prolonged, SE and thus less likely to rescue the patient.

Nevertheless, as is evident in several published series, excellent outcome is possible after RSE and SRSE. Some patients return to their premorbid conditions, even after more than 90 days in coma (Finné Lenoir et al., 2013). Because of the lack of prospective data, however, it is difficult to discern the precise factors associated with good outcome. Younger age, absence of structural brain damage at presentation, and the absence of multiple concomitant medical problems have been associated with favorable outcome (Drislane et al., 2011), (Kilbride et al., 2013). After the initial period, duration of SE has not been a reliable predictor in most of these series. Thus, a decision to withdraw medical care should not be made based on SE duration alone. Rather, such clinical decisions should focus more on the underlying etiology, comorbidities, etc. Better outcome data on RSE and SRSE are unfortunately not available to guide clinicians' choices; prospective data are needed to produce a better understanding of these often-devastating and understudied neurologic illnesses.

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