

# REFRACTORY STATUS EPILEPTICUS: IS EEG BURST SUPPRESSION AN APPROPRIATE TREATMENT TARGET DURING DRUG-INDUCED COMA? WHAT IS THE HOLY GRAIL?

## Refractory Status Epilepticus: Effect of Treatment Aggressiveness on Prognosis

Rossetti AO, Logroscino G, Bromfield EB

*Arch Neurol* 2005;62(11):1698–1702

**BACKGROUND:** Administration of antiepileptic drugs for coma induction in refractory status epilepticus (RSE) has not been widely studied. Moreover, the effect on outcome of electroencephalographic (EEG) burst suppression remains unclear.

**OBJECTIVE:** To investigate whether various coma-inducing options are associated with different prognoses after RSE.

**DESIGN:** Retrospectively assessed case series.

**SETTING:** Two tertiary referral hospitals in Boston, Massachusetts.

**PATIENTS:** Among 127 consecutive episodes (107 patients) of status epilepticus, we identified episodes that were refractory to first-line and second-line antiepileptic drugs, needing induced coma with barbiturates, propofol, or midazolam for clinical management.

**MAIN OUTCOME MEASURES:** Short-term mortality and prevalence of return to functional baseline after the acute episode of status epilepticus were analyzed in relation to demographic and clinical variables and to

treatment option (antiepileptic agents and EEG burst suppression).

**RESULTS:** Forty-nine episodes of RSE (47 patients) were found, occurring more frequently in incident than in recurrent episodes of status epilepticus ( $p = .06$ ). Mortality was 23% for patients with RSE and 8% for those without RSE ( $p = .05$ ). Return to baseline occurred more often in the non-RSE group ( $p = .04$ ). In 20 (61%) of 33 monitored episodes, EEG burst suppression was achieved. Demographic data, clinical variables, and outcome did not differ significantly with the various coma-inducing agents or between episodes with and without EEG burst suppression.

**CONCLUSIONS:** Refractory status epilepticus is more prevalent in incident than in recurrent status epilepticus and is associated with higher mortality; clinical status is less likely to return to baseline than with non-RSE. Outcome was independent of the specific coma-inducing agents used and the extent of EEG burst suppression, suggesting that the underlying cause represents its main determinant.

## COMMENTARY

Holy Grail

“A very desired object or outcome that borders on a sacred quest”

(1).

Over the last decade, a major effort has been made to stress the importance of prompt and aggressive treatment of status epilepticus (SE). This campaign has been motivated by the realization that untreated or undertreated SE, even if nonconvulsive (e.g., complex partial seizures), can lead to irreversible neuronal damage, independent of metabolic and systemic consequences. Refractory status epilepticus (RSE) is defined as SE which is not controlled with initial parenteral therapy, such as benzodiazepines, phenytoin/fosphenytoin, or barbiturates. In instances of RSE, general anesthesia should be

rapidly employed, since there is evidence (these studies are difficult to do in a controlled fashion) that SE can become more refractory with time. One of the general principles in administering coma-inducing agents is not only to suppress seizure activity, but also to try to achieve an EEG burst-suppression pattern, typically for 12–24 hours. In spite of the most appropriate and aggressive therapy in intensive care units, mortality from SE is still 15%–20%.

The article by Rossetti and colleagues is a retrospective study of 127 episodes of SE at two university hospitals between 1997 and 2004. Patients with anoxic injury were excluded, and less than 5% of patients had nonconvulsive SE, although the number with complex partial and simple partial SE (which were separate categories) was not specifically quantified. Of the patients with SE, 38% of the episodes (or 44% of incident cases) had RSE. While the rate may seem high, the authors mention that their findings are similar to values of 31% and 43%

published in other studies. Interestingly, of 49 episodes of RSE reported here, almost half ( $n = 24$ ) occurred in patients with no previous history of epilepsy. The incidence of acute, potentially serious, or fatal etiologies was not different between nonrefractory and refractory SE. Mortality, however, was 23% for the refractory group compared with 8% for the nonrefractory group. In addition to assessing mortality, this study looked at the percentage of patients who returned to baseline—an important consideration often ignored in other studies. Only 31% of the patients in the RSE group returned to baseline compared to 50% of those with nonrefractory SE ( $P = .04$ ). This finding also calls attention to the morbidity associated with nonrefractory SE, an issue that deserves more study.

In the Rossetti et al. study, treatment with coma-inducing agents involved six different regimens, and better than half of the patients received more than one agent. The exact sequence of administration is not mentioned. Barbiturates or propofol were the most common agents used either singly or in combination; no significant differences in outcome were seen with any single drug or combination of agents. While the study may not have been sufficiently powered to reveal these differences with so many treatment groups, no clear trends were evident. Other studies have shown barbiturates, midazolam, and propofol all to be effective for RSE; yet, no good randomized trials of treatment exist (2).

The subtitle of the Rossetti et al. article is: “Effect of Treatment Aggressiveness on Prognosis.” Here the term “aggressiveness” is not defined as the mean time to institution of general anesthesia, but rather as the degree of EEG suppression achieved. Surprisingly, only about two-thirds of the patients had continuous EEG monitoring (the others had daily EEGs). There was no apparent benefit in achieving burst suppression; 6 of 20 patients with RSE who attained burst suppression died, and 2 of 11 patients with RSE who did not achieve burst suppression died ( $P = \text{n.s.}$ ). In this retrospective study, the conclusion that the achievement of burst suppression does not influence prognosis is compromised by the fact that one-third of the patients were not monitored continuously and that no patient achieved “complete, sustained EEG burst suppression.” Indeed, the duration of burst suppression achieved is not documented.

Are there data to support the hypothesis that burst suppression should be the targeted outcome of drug-induced coma for RSE? One literature review of RSE treatment suggests that patients with “EEG background suppression” may have done better than the patients titrated to seizure suppression, but the

agents were different in the groups being evaluated. In one prominent review of SE, the discussion of the protocol for RSE, suggests that the “primary endpoint for therapy is suppression of electroencephalographic spikes [and] if blood pressure is adequate, secondary endpoint is burst-suppression pattern with short intervals between bursts” (3). A recent, excellent review states: “stopping seizures is the holy grail, but most people accept a burst suppression pattern.” (4). It is known that moderate-to-deep general anesthesia produces a burst-suppression pattern in normal patients, and it is presumed that total EEG suppression (possibly desirable for severe brain injury) may not be necessary for treating SE and does produce more hemodynamic instability. However, the fact is that there are no studies that have established EEG burst suppression as the optimal degree of suppression for the most favorable patient outcome from coma-inducing drugs in treating RSE.

This large study on RSE, perhaps the largest to date, raises the question of whether using EEG burst suppression as the target for therapy should be reexamined. The authors appropriately call for prospective studies. It would be ethical to prospectively study patients with RSE who require coma-inducing agents to assess whether suppression of epileptiform activity alone is equally (or more) effective than achieving EEG burst suppression. If suppression of epileptiform activity is equally as effective as burst suppression for treating RSE (a possibility suggested by this report), the finding could have benefits for patients by advancing a treatment that produces less respiratory depression, has less hemodynamic instability, and results in shorter hospital stays than are associated with EEG burst suppression. Unfortunately, if the underlying cause of RSE remains the major determinant of outcome, mortality likely may remain unchanged. The quest for the holy grail of RSE treatment must continue.

by Gregory K. Bergey, MD

## References

1. Computer Desktop Encyclopedia. Available at: [http://lookup.computerlanguage.com/host\\_app/search](http://lookup.computerlanguage.com/host_app/search). Accessed on April 8, 2006.
2. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002;43:146–153.
3. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998;388:970–976.
4. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol* 2006;5:246–256.