Mortality Associated with Status Epilepticus

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Status epilepticus (SE) is a neurologic and medical emergency associated with a high mortality rate. This strong assertion, although widely accepted, must be defined specifically to compare epidemiologic studies. Proposed definitions of SE by episode durations of 60, 20, 10, and even 5 minutes have been advocated, with briefer episode durations operationally used to prompt early treatment (1). The majority of research studies, however, have used the guidelines agreed on by the International Classification of Epileptic Seizures and by the Epilepsy Foundation of America's Working Group on Status Epilepticus, which define SE as 30 or more minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures (2). According to a large prospective database compiled through the Greater Richmond Metropolitan Area Status Epilepticus Project (GRMASE), by using the 30-minute definition, 30-day mortality rates for subjects with seizures lasting 10 to 29 minutes was only 2.6% compared with a 19% rate in patients diagnosed with SE but who otherwise had comparable clinical features ($P < .001$) (3). It would appear, then, that the traditional definition of SE is a quite defensible one, as mortality statistics support the notion that after about 30 minutes of seizures, mortality takes a robust leap. Rather than adding to confusion in the literature by modifying a widely used and certainly not inappropriate definition of SE, I have advocated using the term "impending SE" to emphasize the urgency of initiating effective treatment within 30 minutes and preventing a progression of the episode from a mortality of one in 40 to a mortality of one in five (3).

The relevance of other variables found in the literature regarding SE mortality rates, such as differences in length of follow-up, population demographics, and the definition of timing of death after ictus (i.e., death within 30 days), remains confusing. As it is uncommon for patients to die during SE, studies generally define SE-related mortality in terms of days lived after resolution of SE. Typically, death rates peak within 30 days after SE. The most long-term follow-up data on SE have been acquired through the Rochester Epidemiology Project and document a cumulative subsequent mortality of 43% in patients surviving the initial 30 days, with the worst risk for death being associated with SE lasting more than 24 hours, myoclonic SE, and acute symptomatic etiologies (4). Long-term mortality appears to be little different from that of the overall intractable epilepsy population.

Assuming optimal treatment, three other primary determinants of mortality exist with SE: age, duration, and etiology. Age at time of SE predicts a bimodal mortality, with peak rates for the very young and the very old (5). Although neonates have extremely high mortality rates, infants and children to age 16 years had an overall mortality of only 3% in the GRMASE study (6). Shinnar et al. (7) found similar low mortality in febrile and nonfebrile SE in children aged between 4 and 60 months. Pediatric patients also have a higher recurrence rate than do most adults, indicating a tendency to survive and have repeated bouts of SE rather than succumb after one episode. A small proportion of adults appear to be habitual SE patients, with a tendency toward multiple recurrences and a very low risk of death—similar to the pattern seen in most children. Unfortunately, despite their large numbers, population-based studies have yet to identify any unique clinical or diagnostic characteristics of an adult SE "survivor profile." Usual mortality rates in adult studies range from 16% to 25%, although risk steadily increases with advancing age. In the GRMASE study, overall adult mortality was 26%, but 38% for patients older than 60 years. This same study demonstrated SE-related mortality at greater than 50% in patients older than 80 years (8).

Duration of SE is the only potentially modifiable determinant of mortality. With earlier diagnosis as well as prompt initiation and completion of treatment, duration can be directly modified. Unfortunately, issues that are highly individual to a given patient, such as transportation, intravenous (IV) access, electroencephalogram (EEG) availability, hemodynamic instability, and airway management can add critical minutes, even hours to the timing of initiation and effectiveness of treatment. Most published treatment protocols for SE are based on a time schedule designed to treat aggressively within the first hour of seizures to determine whether continuous IV infusion management must be initiated as the second hour begins. Justification for this time schedule is easily found, given the rapid increase in 30-day mortality rates from 3.7% to 34.8% for all patient

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ages at 1 hour from onset of ictus (11). Once the 3-hour mark has passed, mortality again increases drastically, but the rate of increase reaches an asymptote over subsequent hours and even days. No data indicate optimal duration of pharmacologic EEG suppression for survival.

Etiology is probably the most obvious but complex determinant of SE mortality. Anoxia accounts for the highest mortality in older patients with SE, not unexpectedly after cardiac arrest. Overall, adult mortality from anoxia is 71% but reaches 92% in those patients older than 65. These numbers are higher, but not significantly higher than mortality rates over 30 days after in-hospital cardiac arrest in the absence of SE (9). Thus anoxia has a phenomenally high mortality rate, whether associated with SE or not. Mortality from this condition does not, therefore, appear to be increased synergistically with SE, simply because of its devastating effects to all other concomitant diagnoses. Typical etiologies associated with lower mortality include subtherapeutic antiepileptic drug (AED) levels and alcohol withdrawal. Etiologies linked to an intermediate risk of mortality include stroke, metabolic derangements, drug overdose, tumors, and trauma (8). In contrast to anoxia, mortality from SE with ischemic brain injury, the most common etiology in adults in the GRMASE study, appears synergistic (10). Not surprisingly, acute symptomatic etiologies (e.g., rapidly expanding mass lesions, acute infection) tend to be associated with additive higher mortality than do remote symptomatic etiologies (e.g., old strokes, prior trauma). The combined effects of SE and another acute illness, as well as the complications of acute SE and medical treatments, generate a complex, acute situation for the patient. The severity and number of comorbidities also determines prognosis. Delanty et al. (11) reviewed cases of SE arising in the hospital setting in patients with multiple acute medical problems and found a mortality of 61%, with a third of the patients dying during the ictus. Obviously, the sicker the patient, the higher the mortality rate.

Careful review of EEG patterns in SE patients indicates that some EEG characteristics are more highly correlated with mortality than are others. The overall mortality rates of partial and generalized convulsive SE (GCSE) EEG patterns have not been found to be significantly different (8). Although focality of EEG discharge does not appear to change mortality, the disassociation of EEG from clinical seizures appears to have a striking effect on mortality. In the Veterans Affairs cooperative study of the treatment of GCSE, patients who have generalized convulsive movements coincident with EEG discharges (overt GCSE) were found to have a 30-day mortality of 26.8%, whereas those who had no obvious convulsive movements coincident with their ongoing EEG discharges (subtle GCSE) had a mortality of 64.9% (12). It has been proposed that inadequately treated GCSE EEG patterns deteriorate through a series of predictable changes in which the EEG shows that discrete seizures are followed by a period of merging seizures, eventually becoming a continuous monomorphic pattern. The monomorphic pattern subsequently is interrupted by suppressed periods that become more prevalent, with the terminal pattern of GCSE appearing as periodic epileptiform discharges (PEDs) (13). However, such stereotypic sequences have not reliably been found in prospective EEG studies, although recording of the hypothesized "later" pattern of PEDs at any time during or after SE correlates with worse outcome, independent of etiology (14). A prospective study of intermittent and continuous SE patterns on EEG monitoring found a significantly higher mortality in those patients who had a continuous, monomorphic pattern (15). Although PEDs correlate with mortality when occurring in patients known to have SE, the pattern, even when not necessarily associated with known seizures, also is associated with mortality rates of 40% to 50% in children for whom there is no clinical evidence of SE (16,17). Ictal electroclinical dissociation also may occur with conversion from an overt-convulsive to a subtle-nonconvulsive state. In the GRMASE study, 14% of comatose patients were found to have persistent nonconvulsive SE after initial convulsive movements stopped (18). Patients may be seen in coma or a stuporous state for days before the diagnosis of SE is entertained, thus prolonging the duration of SE and thereby increasing the risk of mortality.

With the advances made in parenteral pharmacotherapy, intensive care unit (ICU) management, and the availability of high-quality EEG monitoring, one would expect that death rates from SE would have declined substantially in recent years. Although some clinical series have suggested such a decrease, the Rochester Epidemiologic Study (4), which calculated incidence and case-fatality rates over 30 years (1955 to 1984), on the whole, found that the 30-day case-fatality rate remained stable. However, incidence rates increased as a result of greater numbers of patients who were elderly and survivors of cardiac arrest with anoxic etiology for SE. Thus despite the better treatment options and trends toward recommending more aggressive ICU management for SE, it appears that these improvements in patient care are merely matching the increased proportion of high-mortality SE cases.

For epileptologists to reduce overall SE mortality in the future, it will be necessary to do more than merely treat the emergency at hand. Prevention of the potential cascade of neurally-mediated dysfunction of vital organs in the weeks after SE may be as important as stopping ictal patterns on EEG. Although it is obvious that convulsive activity will initially result in massive autonomic activation, with resultant tachycardia, hyperthermia, increased plasma glucose, lactic acidosis, and hypertension, these changes are physiologically appropriate to prolonged seizures. After these responses subside and possibly decrease below baseline levels, with ongoing convulsions or even nonconvulsive SE, the danger of terminal damage to the

nervous system, and ultimately the rest of the body, becomes a serious threat. Increased intracranial pressure and relative hypotension occurring with convulsive SE will result in impaired cerebral perfusion pressure and exacerbation of neurologic and systemic dysfunction. Neuropathologic changes have been reported, even in chemically paralyzed animal models of prolonged SE with control of metabolic variables, indicating that the ictal discharge itself contributes significantly to neuronal damage (19). *N*-Methyl-D-aspartate (NMDA)-receptor activation has been shown to mediate the loss of γ-aminobutyric acid (GABA) inhibition observed in experimental SE (20). Whereas this and other experimental models indicate the potential role for neuroprotection in SE, further improvement in mortality of SE likely depends on identifying effective human protocols. Until that time, it perhaps provides some strange sense of satisfaction that if we were not so successful resuscitating patients from cardiac arrest, and if people were not living so long, at least the statistical mortality of SE would likely be declining.

References

1. Lowenstein DH, Bleck T, MacDonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999;40:120–122.
2. Gastaut H. Classification of status epilepticus. In: Delgado-Escueta A, Wasterlain C, Treiman D, Porter R, eds. Status epilepticus: Mechanisms of brain damage and treatment. New York: Raven Press, 1983:15–35.
3. DeLorenzo RJ, Garnett LK, Towne AR, Waterhouse EJ, Boggs JG, Morton L, Choudrhry MA, Barnes T, Ko D. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia 1999;40:164–169.
4. Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. Neurology 2002;58:537–541.
5. Hauser WA. Status epilepticus: Epidemiologic considerations. Neurology 1990;40(5 suppl 2):9–13.
6. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, Barnett L, Fortner CA, Ko D. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029–1035.
7. Shinnar S, Pellock JM, Berg AT. An inception cohort of children with febrile status epilepticus. Epilepsia 1995;36(suppl 4):31.
8. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994;35:27–34.
9. Dumot JA, Burval DJ, Sprung J, Waters JH, Mraovic B, Karafa MT, Mascha EJ, Bourke DL. Outcome of adult cardiopulmonary resuscitations at a tertiary referral center including results of "limited" resuscitations. Arch Intern Med 2001;161:1751–1758.
10. Waterhouse EJ, Vaughan JK, Barnes TY, Boggs JG, Towne AR, Kopec-Garnett L, DeLorenzo RJ. Synergistic effect of status epilepticus and ischemic brain injury on mortality. Epilepsy Res 1998;29:175–183.
11. Delanty N, French JA, Labar DR, Pedley TA, Rowan AJ. Status epilepticus arising de novo in hospitalized patients: an analysis of 41 patients. Seizure 2001;10:116–119.
12. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. DVA Status Epilepticus Cooperative Study Group: A comparison of four treatments for generalized convulsive status epilepticus. N Engl J Med 1998;339:792–798.
13. Treiman DM. Generalized convulsive status epilepticus in the adult. Epilepsia 1993;34(suppl 1):S2–S11).
14. Nei M, Lee JM, Shanker VL, Sperling MR. The EEG and prognosis in status epilepticus. Epilepsia 1999;40:157–163.
15. Waterhouse EJ, Garnett LK, Towne AR, Morton LD, Barnes T, Ko D, DeLorenzo RJ. Prospective population-based study of intermittent and continuous status epilepticus in Richmond, Virginia. Epilepsia 1999;40:752–758.
16. Walsh JM, Brenner RP. Periodic lateralized epileptiform discharges: Long-term outcome in adults. Epilepsia 1987;28:533–536.
17. Garg BP, Patel H, Markand ON. Clinical correlation of periodic lateralized epileptiform discharges in children. Pediatr Neurol 1995;12:225–229.
18. DeLorenzo RJ, Waterhouse EJ, Towne AR, Boggs JG, Ko D, DeLorenzo GA, Brown A, Garnett L. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia 1998;39:833–840.
19. Nevander G, Ingvar M, Auer R, Sjesjo BK. Status epilepticus in well-oxygenated rats causes neuronal necrosis. Ann Neurol 1985;18:281–290.
20. Kapur J, Lothman EW. NMDA receptor activation mediates the loss of GABAergic inhibition induced by recurrent seizures. Epilepsy Res 1990;5:103–111.