Epilepsy & Behavior 101 (2019) 106567

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Why do patients die after status epilepticus?

Sara Hocker, MD

Division of Neurocritical Care and Hospital Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States of America

ARTICLE INFO

Article history:
Received 28 June 2019
Revised 12 September 2019
Accepted 13 September 2019
Available online 8 November 2019

Keywords:
Status epilepticus
Anesthetic
Causes of death
Withdrawal of life sustaining treatment

ABSTRACT

The epidemiology of status epilepticus (SE) and predictors of outcome in particular have been well described with consistent findings around the world. Understanding of the actual causes of death in patients hospitalized with SE is limited. The following is a summary of published information about causes of death in patients hospitalized with SE and a reconciling of conflicting studies examining the influence of continuous intravenous anesthetic drugs on the mortality of SE. A recently published paper was presented at the Colloquium and is summarized here, along with new data addressing an audience question about withdrawal of care in SE. In the spirit of the conference, we end with a call to arms and invitation for collaborators.

Proceedings of the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures.

A 53-year-old woman without prior history of seizures developed super-refractory convulsive status epilepticus (SE) that had developed after weeks of progressive depression, anxiety, and general decline in function. Having initially been refractory to lorazepam, levetiracetam, valproic acid, and propofol, initial seizure control was achieved with a combination of ketamine and midazolam. Following 24 h of control, seizures recurred upon weaning midazolam. Valproate and levetiracetam levels were at the high end of the therapeutic range. She developed ventilator-associated pneumonia and acute kidney injury necessitating transition of midazolam to pentobarbital as ketamine monotherapy proved insufficient to maintain control of seizures. Exhaustive evaluation including neuroimaging, comprehensive infectious studies from serum and cerebrospinal fluid (CSF), autoimmune encephalopathy panels, head and body computed tomography positron emission tomography scanning, and genetic testing were unrevealing as to a cause of her new-onset refractory SE. Ultimately, after 90 days in the intensive care unit with the inability to liberate the patient from pentobarbital without return of definite electrographic SE, the decision was made to withdraw life sustaining treatments and allow a natural death while providing palliative care. What killed the patient? Was it the medical complications? Was it the continuous intravenous anesthetic drugs (CIVADs)? Or was it the seizures?

The epidemiology of SE, and specifically the outcomes and influencers of outcome, have been a subject of extensive study and debate over the last 20 years. Nonrefractory SE has a mortality of up to 10%, while refractory and super-refractory SE have mortalities approaching 30 and 50%, respectively [1–26]. Risk factors for death, most of which are nonmodifiable, have been well described (Fig. 1) [27]. The most predictive of these comprise the STatus Epilepticus Severity Score (STESS) [12] in which a score of 0–2 confers a 97% likelihood of survival and a score of 3–6 a 61% chance at survival (Fig. 2). Yet, despite having reasonable clarity on the epidemiology, outcome, and predictors of outcome in SE, most studies do not report the actual causes of death. It is even less common for information about withdrawal of life sustaining treatment (WOLST) to be included in published studies, and when it is, the reasons for withdrawal are rarely described (Table 1). Published randomized controlled trials [6,7,14,15,22] did not systematically report causes of death or WOLST, although the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) [15] and Hypothermia for Brain Enhancement Recovery by Neuroprotective and Anticonvulsant Action after Convulsive Status Epilepticus (HYBERNATUS) [22] studies listed 'do not resuscitate' orders as exclusion criteria. Among the retrospective studies examining the impact of CIVADs on outcome, two reported causes of death and frequency of WOLST [16,18], while the other three did not [10,20,21]. Mortality seems to be pretty consistent across the world; however, there may be an impact of geography on the proportion of deaths due to WOLST as low frequencies were reported from Germany [9], the global audit of the treatment of refractory SE [19], and a large series from China [23], while higher frequencies were reported by centers in the United States and Switzerland [16–18].

In a recently published study, we sought to determine the actual causes of death in patients hospitalized with SE over a 5-year period [27]. In addition, we aimed to understand the relative contributions of seizure etiology, refractoriness, CIVAD use, and medical complications to in-hospital mortality. We included patients aged 18 years and older and excluded those with an anoxic–ischemic etiology. Among the 244 consecutive patients hospitalized at our institution with SE during the study period, median STESS was 3 and 24 (9.8%) patients required CIVADs for seizure control (CIVADs were used for ventilator synchrony or sedation alone in another 30.3%). Mortality was 9.2% (24 patients) at

E-mail address: hocker.sara@mayo.edu.

https://doi.org/10.1016/j.yebeh.2019.106567
1525-5050/

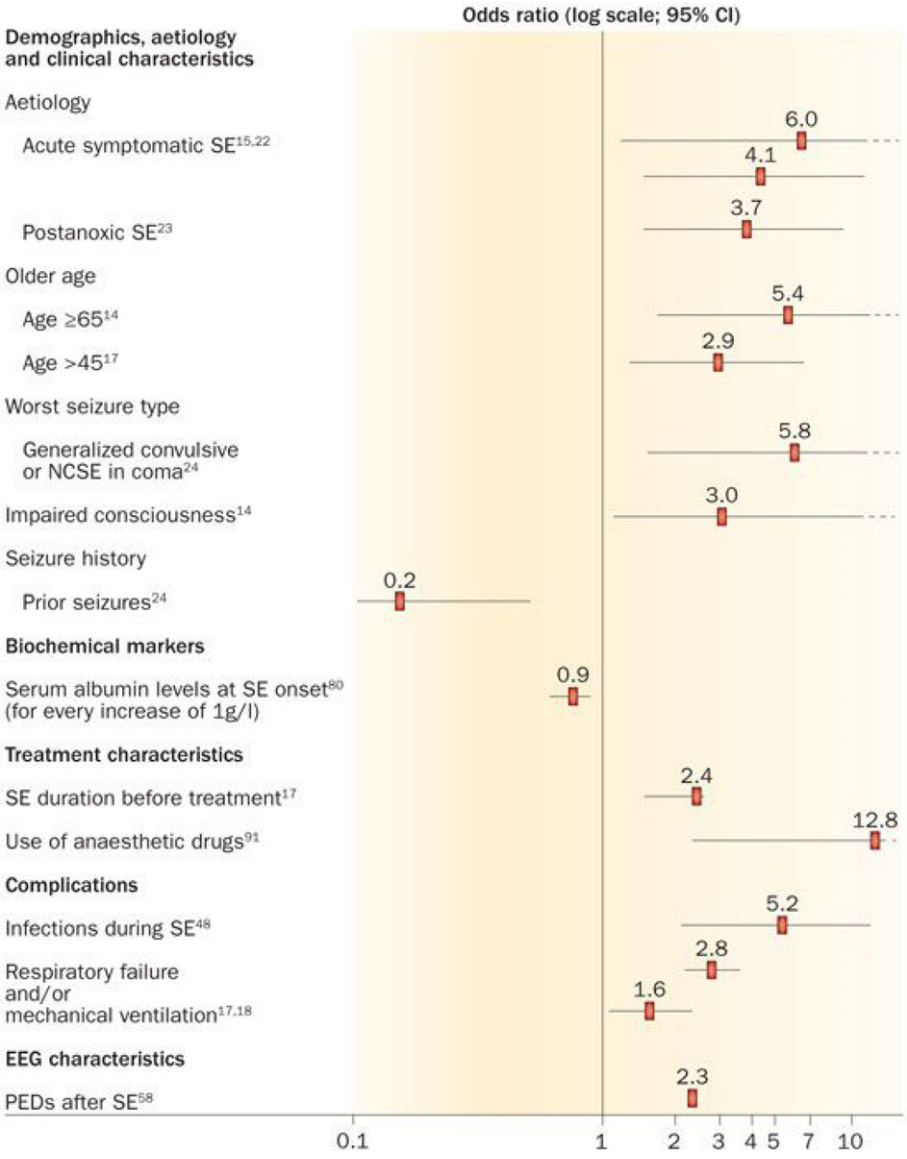

Fig. 1. Odds ratios of the most studied risk factors for death in SE. *Abbreviations: NCSE, nonconvulsive SE; PED, periodic epileptiform discharge; SE, status epilepticus. Permission obtained to reuse from Sutter R. et al. Nat Rev Neurol. 2013;9(9):525–34.

hospital discharge, 86.3% of which occurred after WOLST (19 patients). Only STESS was independently associated with in-hospital mortality, whereas the use of CIVADs, etiology, medical complications, and seizure refractoriness were not [25].

In the discussion following presentation of this study at the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures, a question was asked about the potential for self-fulfilling prophecy with respect to prognostication and decisions regarding WOLST in SE. To address this concern, additional data were collected and are reported here. All 19 patients in whom WOLST occurred had acute symptomatic or progressive etiologies of SE as defined by the 2015 International League Against Epilepsy (ILAE) classification of SE, and WOLST occurred at mean 25.3 (range: 3–115) days. For the purposes of analysis, we divided all patients into age ≥ or < 65 years as that is the age cutoff used in STESS (Fig. 2). Among patients ≥65 years, mean STESS was 4.6 in the 14 patients in whom treatment was withdrawn compared with 3.7 in patients in whom life sustaining treatment was not withdrawn. In the 14 patients who had treatment withdrawn, 2 had super-refractory, 6 had refractory, and 6 had nonrefractory SE. Withdrawal of life sustaining treatment occurred at a mean 14.4 days compared with a mean SE diagnosis to hospital discharge of 10.0 days in patients in whom treatment was not withdrawn. Among patients <65 years, mean STESS was 3.0 in the 5 patients who underwent WOLST compared with 1.9 in those patients in which treatment was not withdrawn. Four of the 5 had super refractory status epilepticus (SRSE), and the fifth had refractory SE. Withdrawal of life sustaining treatment occurred at a mean 56.0 days compared with a mean SE diagnosis to hospital discharge of 9.8 days in patients in whom treatment was not withdrawn.

In-hospital SE deaths are primarily caused by WOLST secondary to progressive or severe etiology. Continuous intravenous anesthetic drugs are not likely to be independent contributors to death if they are used for patients with impaired consciousness and truly after failure of a second antiepileptic drug (AED). The results of our study may be less generalizable given that it took place in a dedicated neuroscience intensive care unit (ICU) where all patients were managed by four neurointensivists with neurology backgrounds and a generally low frequency of CIVAD use.

The case presented at the beginning of this manuscript is one included in our recently published study [25]. As supported by the results of the study, it was not the medical complications or anesthetic drugs that caused this patient's death in SE, nor was it a self-fulfilling prophecy by premature withdrawal of care. Rather, the patient died because of a

A. Status Epilepticus Severity Score (STESS). A favorable score is 0–2.

	Features	STESS
Consciousness	Alert or somnolent/confused Stuporous or comatose	0 1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic* Generalized convulsive Nonconvulsive status epilepticus in coma	0 1 2
Age	<65 years ≥65 years	0 2
History of previous seizures	Yes No or unknown	0 1
Total		0-6

* complicating idiopathic generalized epilepsy

B. Logistic regression model for variables associated with mortality

	OR	95 % CI	P
Age (mean ± SD)	1.03	1.00-1.06	0.045
Potentially fatal etiology	4.14	1.37-12.49	0.012
History of previous seizures	0.23	0.08-0.65	0.0006
Seizure type GC or NCSEC	5.8	2.11-15.90	0.001

C. STESS characteristics related to mortality in the 154 patients.

	Alive	Dead	Total
Score 0-2 (favorable)	72 (97%)	2 (3%)	74
Score 3-6 (unfavorable)	49 (61%)	31 (39%)	80
Total	121 (79%)	33 (21%)	154

Sensitivity: 0.94 (95 % CI: 0.804–0.983)
Specificity: 0.60 (95 % CI: 0.506–0.678)
Positive predictive value: 0.39 (95 % CI: 0.288–0.497)
Negative predictive value: 0.97 (95 % CI: 0.907–0.993)
Unweighted accuracy: 0.767

Fig. 2. Status epilepticus severity score.
Adapted with permission from Rossetti AO. et al. J Neurol. 2008;255(10):1561–6.

devastating neurologic syndrome, for which there is not yet adequate understanding or treatment. In the absence of a progressive seizure etiology such as glioblastoma multiform or carcinomatous meningitis, patients can be kept alive for many months or even years with careful critical care management, making prognostic certainty with respect to a patient's ability to awaken and regain function a critical need in SE research. Published literature highlights this need as mortalities are stable across the world while causes of death differ. Indeed, it seems that only the timing and final cause of death changes depending on regional cultural differences and physician practices surrounding goals of care.

Declaration of Competing Interest

Dr. Hocker is a member of the NORSE Institute but receives no financial remuneration for this activity.

Table 1
Causes of death in a representative sample of status epilepticus studies 1998–2019 (variable seizure classifications and degrees of refractoriness).

Year	First author	Mortality N (%)	Time mortality measured	WOLST N (% of deaths)	Causes of death in patients without WOLST
1998	Treiman [6]	190 (36.7)	30 days	NR	NR
2001	Alldredge [7]	24 (11.7)	Hsp. discharge	NR	"Severe underlying illnesses were the probable causes of death in most patients."
2002	Mayer [8]	14 (16.9)	Hsp. discharge	NR	"most deaths resulted from overwhelming medical complications"
2005	Holtkamp [9]	10 (12.0)	Hsp. discharge	0	4 — "persisting seizures" 6 — "medical complications"
2005	Rossetti [10]	16 (12.6)	Hsp. discharge	NR	NR
2007	Koubeissi [11]	405 (3.5)	Hsp. discharge	NR	NR
2008	Rossetti [12]	33 (21.4)	Hsp. discharge	NR	NR
2010	Novy [13]	21 (17.8)	Hsp. discharge	NR	NR
2011	Rossetti [14]	9 (37.5)	Hsp. discharge	NR	Reported in 1/9 deaths — "Ileus with diffuse intestinal ischemia"
2012	Silbergleit [15]	NR	NA	NR	NR
2012	Kowalski [16]	10 (6.9)	Hsp. discharge	9 (90)	"Cardiac arrest," not otherwise described
2013	Hocker [17]	20 (31.8)	Hsp. discharge	16 (80.0)	1 — brain death 2 — PRIS 1 — "severe pneumonia"
2014	Sutter [18]	67 (39.2)	Hsp. discharge	37 (55.2)	8 — died during SE (cause NR) 14 — "likely from infections" 2 — multiorgan failure 1 — "could not be determined" 5 — "progression of the underlying pathologic condition"
2015	Ferlisi/Hocker [19]	109 (26.4)	Hsp. discharge	16 (14.7)	NR
2015	Marchi [20]	67 (14.3)	Hsp. discharge	NR	NR
2016	Alvarez [21]	52 (14.4)	Hsp. discharge	NR	NR
2016	Legriel [22]	37 (13.8)	Hsp. discharge	NR	NR
2017	Sun [23]	15 (6.7)	Hsp. discharge	0	11 — "multiple organ dysfunction syndrome" 1 — "sudden cardiac arrest" 1 — "respiratory failure" 2 — "etiology of SE"
2018	Vilella [24]	28 (31.1)	Hsp. discharge	NR	NR
2019	Hawkes [25]	22 (9.2)	Hsp. discharge	19 (86.3)	3 — cardiac arrest after resolution of SE and transfer from ICU with DNR orders in place
2019	Leitenger [26]	36 (16.3)	Within 5-year study period	NR	NR

DNR = do not resuscitate; Hsp = hospital; NA = not applicable; NR = not reported; PRIS = propofol infusion syndrome; WOLST = withdrawal of life sustaining treatment.

References

[1] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46(4):1029–35.

[2] Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Short-term mortality after a first episode of status epilepticus. Epilepsia 1997;38:1344–9.

[3] Logroscino G, Hesdorffer DC, Cascino G, Hauser WA, Coeytaux A, Galobardes B, et al. Mortality after a first episode of status epilepticus in the United States and Europe. Epilepsia 2005;46(Suppl. 11):46–8.

[4] Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135(Pt 8):2314–28.

[5] Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care 2014;20(3):476–83.

[6] Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339(12):792–8.

[7] Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345(9):631–7.

[8] Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol 2002;59(2):205–10.

[9] Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J Neurol Neurosurg Psychiatry 2005;76(4):534–9.

[10] Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Arch Neurol 2005;62(11):1698–702.

[11] Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. Neurology 2007;69(9):886–93.

[12] Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol 2008;255(10):1561–6.

[13] Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia 2010;51(2):251–6.

[14] Rossetti AO, Milligan TA, Vulliémoz S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. Neurocrit Care 2011;14(1):4–10.

[15] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al, NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366(7):591–600.

[16] Kowalski RG, Ziai WC, Rees RN, Werner Jr JK, Kim G, Goodwin H, et al. Third-line antiepileptic therapy and outcome in status epilepticus: the impact of vasopressor use and prolonged mechanical ventilation. Crit Care Med 2012;40(9):2677–84.

[17] Hocker SE, Britton JW, Mandrekar JN, Wijdicks EF, Rabinstein AA. Predictors of outcome in refractory status epilepticus. JAMA Neurol 2013;70(1):72–7.

[18] Sutter R, Marsch S, Fuhr P, Kaplan PW, Rüegg S. Anesthetic drugs in status epilepticus: risk or rescue? A 6-year cohort study. Neurology 2014;82(8):656–64.

[19] Ferlisi M, Hocker S, Grade M, Trinka E, Shorvon S, International Steering Committee of the StEp Audit. Preliminary results of the global audit of treatment of refractory status epilepticus. Epilepsy Behav 2015;49:318–24.

[20] Marchi NA, Novy J, Faouzi M, Stähli C, Burnand B, Rossetti AO. Status epilepticus: impact of therapeutic coma on outcome. Crit Care Med 2015;43(5):1003–9.

[21] Alvarez V, Lee JW, Westover MB, Drislane FW, Novy J, Faouzi M, et al. Therapeutic coma for status epilepticus: differing practices in a prospective multicenter study. Neurology 2016;87(16):1650–9.

[22] Legriel S, Lemiale V, Schenck M, Chelly J, Laurent V, Daviaud F, et al, HYBERNATUS Study Group. Hypothermia for neuroprotection in convulsive status epilepticus. N Engl J Med 2016;375(25):2457–67.

[23] Sun L, Han C, Lin W. The clinical characteristics and prognostic analysis of status epilepticus in Northeast China. Eur Neurol 2017;78(5–6):234–9.

[24] Vilella L, González Cuevas M, Quintana Luque M, Toledo M, Sueiras Gil M, Guzmán L, et al. Prognosis of status epilepticus in elderly patients. Acta Neurol Scand 2018;137(3):321–8.

[25] Hawkes MA, English SW, Mandrekar JN, Rabinstein AA, Hocker S. Causes of death in status epilepticus. Crit Care Med 2019;47(9):1226–31.

[26] (a) Leitinger M, Trinka E, Giovannini G, Zimmermann G, Florea C, Rohracher A, Kalss G, Neuray C, Kreidenhuber R, Höfler J, Kuchukhidze G, Granbichler C, Dobesberger J, Novak HF, Pilz G, Meletti S, Siebert U. Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. Epilepsia. 2019;60(1):53–62. doi: https://doi.org/10.1111/epi.14607. Epub 2018 Nov 26. (b) Sutter R, Kaplan PW, Rüegg S. Outcome predictors for status epilepticus—what really counts. Nat Rev Neurol 2013;9(9):525–34.

[27] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus—report of the ILAE task force on classification of status epilepticus. Epilepsia 2015;56(10):1515–23.