Therapeutic coma for status epilepticus

Differing practices in a prospective multicenter study

Vincent Alvarez, MD
Jong Woo Lee, MD, PhD
M. Brandon Westover, MD, PhD
Frank W. Drislane, MD
Jan Novy, MD, PhD
Mohamed Faouzi, PhD
Nicola A. Marchi, MD
Barbara A. Dworetzky, MD
Andrea O. Rossetti, MD

Correspondence to Dr. Alvarez: vincent.alvarez@hopitalvs.ch

ABSTRACT

Objective: Our aim was to analyze and compare the use of therapeutic coma (TC) for refractory status epilepticus (SE) across different centers and its effect on outcome.

Methods: Clinical data for all consecutive adults (>16 years) with SE of all etiologies (except postanoxic) admitted to 4 tertiary care centers belonging to Harvard Affiliated Hospitals (HAH) and the Centre Hospitalier Universitaire Vaudois (CHUV) were prospectively collected and analyzed for TC details, mortality, and duration of hospitalization.

Results: Two hundred thirty-six SE episodes in the CHUV and 126 in the HAH were identified. Both groups were homogeneous in demographics, comorbidities, SE characteristics, and Status Epilepticus Severity Score (STESS); TC was used in 25.4% of cases in HAH vs 9.75% in CHUV. After adjustment, TC use was associated with younger age, lower Charlson Comorbidity Index, increasing SE severity, refractory SE, and center (odds ratio 11.3 for HAH vs CHUV, 95% confidence interval 2.47–51.7). Mortality was associated with increasing Charlson Comorbidity Index and STESS, etiology, and refractory SE. Length of stay correlated with STESS, etiology, refractory SE, and use of TC (incidence rate ratio 1.6, 95% confidence interval 1.22–2.11).

Conclusions: Use of TC for SE treatment seems markedly different between centers from the United States and Europe, and did not affect mortality considering the whole cohort. However, TC may increase length of hospital stay and related costs.

Classification of evidence: This study provides Class III evidence that for patients with SE, TC does not significantly affect mortality. The study lacked the precision to exclude an important effect of TC on mortality. ***Neurology*® 2016;87:1650–1659**

GLOSSARY

ASD = antiseizure drug; **BZD** = benzodiazepine; **CCI** = Charlson Comorbidity Index; **CHUV** = Centre Hospitalier Universitaire Vaudois; **CIVAD** = continuous IV anesthetic drug; **HAH** = Harvard Affiliated Hospitals; **ICU** = intensive care unit; **LOS** = length of stay; **NCSEC** = nonconvulsive status epilepticus in coma; **ROC** = receiver operating characteristic; **SE** = status epilepticus; **STESS** = Status Epilepticus Severity Score; **TC** = therapeutic coma.

Status epilepticus (SE) is a frequent life-threatening neurologic emergency[1]; rapid and effective treatment is advocated. Treatment guidelines[2,3] recommend a stepwise approach. Randomized controlled trials[4,5] have demonstrated the role of benzodiazepines (BZDs) as initial treatment. If this fails, guidelines recommend the use of a nonsedative antiseizure drug (ASD), and when SE is refractory, continuous IV anesthetic drugs (CIVADs) should be considered to induce therapeutic coma (TC), especially in convulsive SE. The available evidence to guide clinical decision-making is nevertheless of low level.[1] The rationale of using TC is to stop seizure activity to hypothetically prevent seizure-induced brain damage and to reduce cerebral metabolism[6]; however, supporting data are missing.[7]

TC is resource-consuming: it requires an intensive care unit (ICU) and continuous EEG.[8] Moreover, CIVADs are related to rare but potentially serious side effects, such as hemodynamic instability, propofol infusion syndrome, propylene glycol toxicity (a vehicle for many anesthetic

Editorial, page 1636

Supplemental data at Neurology.org

From the Department of Neurology (V.A.), Hôpital du Valais, Sion; Department of Clinical Neurosciences (V.A., J.N., N.A.M., A.O.R.) and Institute of Social and Preventive Medicine (M.F.), CHUV and University of Lausanne, Switzerland; Department of Neurology, Brigham and Women's Hospital (V.A., J.W.L., B.A.D.), Department of Neurology, Massachusetts General Hospital (M.B.W.), and Department of Neurology, Beth Israel Deaconess Medical Center (F.W.D.), Harvard Medical School, Boston, MA; and Department of Clinical Neurosciences (N.A.M.), Geneva University Hospitals, Switzerland.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

drugs), and bowel ischemia.[9] In the context of limited evidence supporting the practice of TC and the unfavorable side-effect profile, recent retrospective observational studies[10–12] suggested that TC may be independently associated with increased mortality. While these studies are not yet sufficient to change clinical practices, they have raised important questions.

Given the current uncertainty, our aim was to compare different policies of TC use for SE management, in the sense of a natural experiment, and its potential effect on mortality and hospital length of stay (LOS), using a prospective multicenter SE registry.

METHODS

Primary research question. The primary aim was to compare different TC policies across different hospitals of 2 countries and their potential effect on mortality and on LOS, with Class III level of evidence.

Cohort and SE definition. Data on all consecutive adult patients (>16 years) with SE of all etiologies (except postanoxic SE) admitted to 4 university tertiary care centers were prospectively collected from February 1, 2011, at the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland); from June 1, 2013, at the Brigham and Women's Hospital and the Massachusetts General Hospital (Boston, MA); and from November 1, 2013, at the Beth Israel Deaconess Medical Center (Boston, MA), all through March 31, 2014. The 3 Boston hospitals are affiliated with Harvard Medical School and represent here the HAH (Harvard Affiliated Hospitals) group. Patients from the Centre Hospitalier Universitaire Vaudois (CHUV) represent the second group.

Since all patients with suspected SE have an EEG within 24 hours in all centers, patients were screened daily through EEG requests. Inclusion criteria were checked (V.A. for HAH; A.O.R., J.N. for CHUV) on a daily basis. The authors have already collaborated on several projects related to SE,[13,14] ensuring a uniform process for data collection.

SE was defined as an ongoing seizure lasting more than 5 minutes, or by repeated seizures without complete recovery in-between.[2] In case of nonconvulsive SE, EEG criteria were used.[15]

Treatment protocol. The 4 hospitals have local treatment protocols based on current US and European guidelines.[2,3] Details can be found in a previous publication.[14] Briefly, a BZD is advocated as first line, with HAH favoring lorazepam or midazolam and CHUV using preferentially clonazepam. Second, an urgent seizure-control medication is recommended with a nonsedative ASD (phenytoin or fosphenytoin, valproic acid, levetiracetam, or lacosamide). In case of refractory SE, TC using propofol and/or midazolam, or barbiturates, is recommended, especially for convulsive SE. In case of a nonconvulsive SE, an additional line of nonsedative ASD is recommended before considering TC.

Definition of variables. We collected demographics and worst seizure type (categorized in increasing order of severity as absence seizures, myoclonic seizures in genetic generalized epilepsy, focal seizure without or with consciousness impairment, and generalized convulsive seizures, or nonconvulsive SE in coma [NCSEC]; generalized convulsive SE and NCSEC were grouped into one category for analysis, as they represent the 2 most severe types of seizures). SE severity was assessed using the STESS (Status Epilepticus Severity Score) for every patient[16] ranging from 0 to 6 (see figure e-1 at Neurology.org for more details). Also, for each patient, the Charlson Comorbidity Index (CCI) was retrieved based on comorbidities known on admission,[17] excluding SE etiology. CCI is a validated measure based on 17 common medical conditions with scores ranging from 0 to 33 (see figure e-2 for more details).

The beginning time for SE was determined using prehospital charts and emergency department summaries. For SE episodes without clear onsets (unwitnessed, subtle nonconvulsive SE), the time last seen well was considered as the beginning of SE. Each treatment line, including out-of-hospital medication, was prospectively recorded using premedical, emergency, and in-hospital patient records, including the drug used, total loading (repeated doses given before introduction of the next line of treatment was considered as a total loading dose), maintenance dose (highest prescribed dose), and timing of administration. Initial ASD treatment was considered adequate if local recommendations were followed in terms of sequence (meaning a BZD first and then a nonsedative ASD) and in terms of dosage (within a range of ±25% of the recommended dose, as previously described).[14] Patients were counted as having received TC only if CIVADs were used to treat seizures: use of TC was not considered if CIVADs were administered to maintain sedation in a patient intubated for airway protection, as previously described.[12]

SE was considered as refractory if persisting despite the first 2 treatment lines.[2] It was considered as controlled after the last clinical or electrical seizure without recurrence for 48 hours, following weaning of sedative medication. Clinical outcome at hospital discharge was assessed using hospital discharge summaries. All data except for the CCI were prospectively collected.

Primary and secondary outcomes. The rate of TC use was the primary outcome. Mortality and LOS of survivors in acute facilities were considered as secondary outcomes.

Standard protocol approvals, registrations, and patient consents. The institutional review boards of each center approved this study. Because this observational study involved no risk for patients and focused on acutely ill patients, consent was waived.

Statistical analysis. The data were separately summarized for both groups (CHUV and HAH). Continuous variables were described by mean and SD, or median and interquartile range, depending on distribution of variables. Categorical variables were described by frequencies. The 2 hospital groups were compared using χ^2, Wilcoxon rank sum, or Student t tests, as required.

Associations of different clinically relevant variables with the use of TC and with mortality were assessed using univariate logistic regression. Variables with p value <0.2 (with age, sex, cohort, or use of TC being forced into models because of primary interest) were entered into a stepwise, backward procedure to fit a multivariable logistic regression model. A similar analysis was performed for the duration of hospitalization of survivors, using a negative binomial regression model. Linearity of continuous covariates was checked using fractional polynomials.

Model diagnostics were performed as a post estimation step (influence statistics, deviance residuals, leverages, Pearson or Hosmer-Lemeshow goodness-of-fit tests, as required). Because the LOS is greater than zero and attributable to overdispersion, the negative binomial regression model was compared to the Poisson regression model using the countfit Stata command that allows informal assessment of the fit of count models by plotting observed–predicted vs counts. In addition, likelihood ratio test

of overdispersion and Vuong test were performed to compare the 2 models. Discrimination was tested using the area under the receiver operating characteristic (ROC) curve. Results with a p value <0.05 were considered statistically significant. Calculations were performed using Stata version 12 (StataCorp, College Station, TX).

RESULTS During the study period, 236 SE episodes in the CHUV and 126 in the HAH were identified. Both groups were homogeneous in demographics, comorbidities, SE characteristics, and etiologies (table 1). Initial treatments were more often in line with local guidelines at the CHUV than in HAH (42.8% vs 11.9%), and patients treated in HAH received significantly more ASDs (3 vs 2) and TC (25.4% vs 9.75%). However, when TC was used, it occurred within a similar delay from SE start and after a similar number of ASDs. Outcomes were similar in terms of mortality (14% vs 15%) and LOS (10 vs 9 days). Approximately half of the patients (52%) in the CHUV and more than a third (32.6%) in HAH were back to their clinical premorbid baseline at hospital discharge.

Table 2 displays associations between the use of TC and all clinically relevant variables. The multivariable logistic regression model shows that TC was independently associated with younger age, lower CCI, increasing STESS, SE refractoriness, and hospital group. This model had an excellent goodness-of-fit (Hosmer-Lemeshow: $p = 0.859$, $\chi^2 = 316.8$). The area under the ROC curve was 0.85 (95% confidence interval 0.80–0.90). Figure 1 displays adjusted margin probabilities for the use TC by hospital groups, SE refractoriness, STESS, and CCI (Hosmer-Lemeshow goodness-of-fit test: 0.86): the likelihood of TC was higher in HAH overall, for refractory SE, for all STESS between 1 and 5, and for all CCI ≤ 4.

Several clinically relevant variables including demographics and SE characteristics (severity, type of seizure, etiology, and duration) were significantly associated with mortality in univariate logistic regression analysis (table 3). In the multivariate logistic regression model, increasing CCI and STESS, a potentially fatal etiology, and refractory SE remained associated with mortality. Of note, the use

Table 1 Cohort description

	CHUV (n = 236)	HAH (n = 126)	*p* Value
Demographic and SE characteristics			
Age, median (IQR)	65 (18–89)	60 (25–84)	0.13[a]
STESS, mean (SD)	2.65 (1.5)	2.62 (1.7)	0.88[b]
CCI, median (IQR)	1 (0–8)	2 (0–7)	0.35[a]
Potentially fatal etiology, n (%)	123 (52.1)	66 (52.8)	0.9[c]
Seizure type, n (%)			
Absence	4 (1.7)	1 (0.79)	
Focal without consciousness impairment	48 (20.4)	15 (11.9)	
Focal with consciousness impairment	71 (30.1)	40 (31.8)	
Generalized convulsive	96 (40.7)	52 (41.3)	
NCSEC	17 (7.2)	18 (14.3)	0.085[c]
Treatments			
Adequate 1st and 2nd line, n (%)	101 (42.8)	15 (11.9)	<0.001[c]
Total no. ASDs, median (IQR)	2 (0–5)	3 (1–6)	<0.001[a]
TC, n (%)	23 (9.8)	32 (25.4)	<0.001[c]
Delay SE to TC, h, median (IQR)	1.75 (0–24)	1.45 (0–14.6)	0.23[a]
ASDs before TC, median (IQR)	2 (1–3)	2 (1–3)	0.35[a]
Outcomes			
Mortality, n (%)	33 (14)	19 (15.1)	0.75[c]
Length of stay of survivors, d, median (IQR)	10 (1–67)	9 (2–58)	0.85[a]

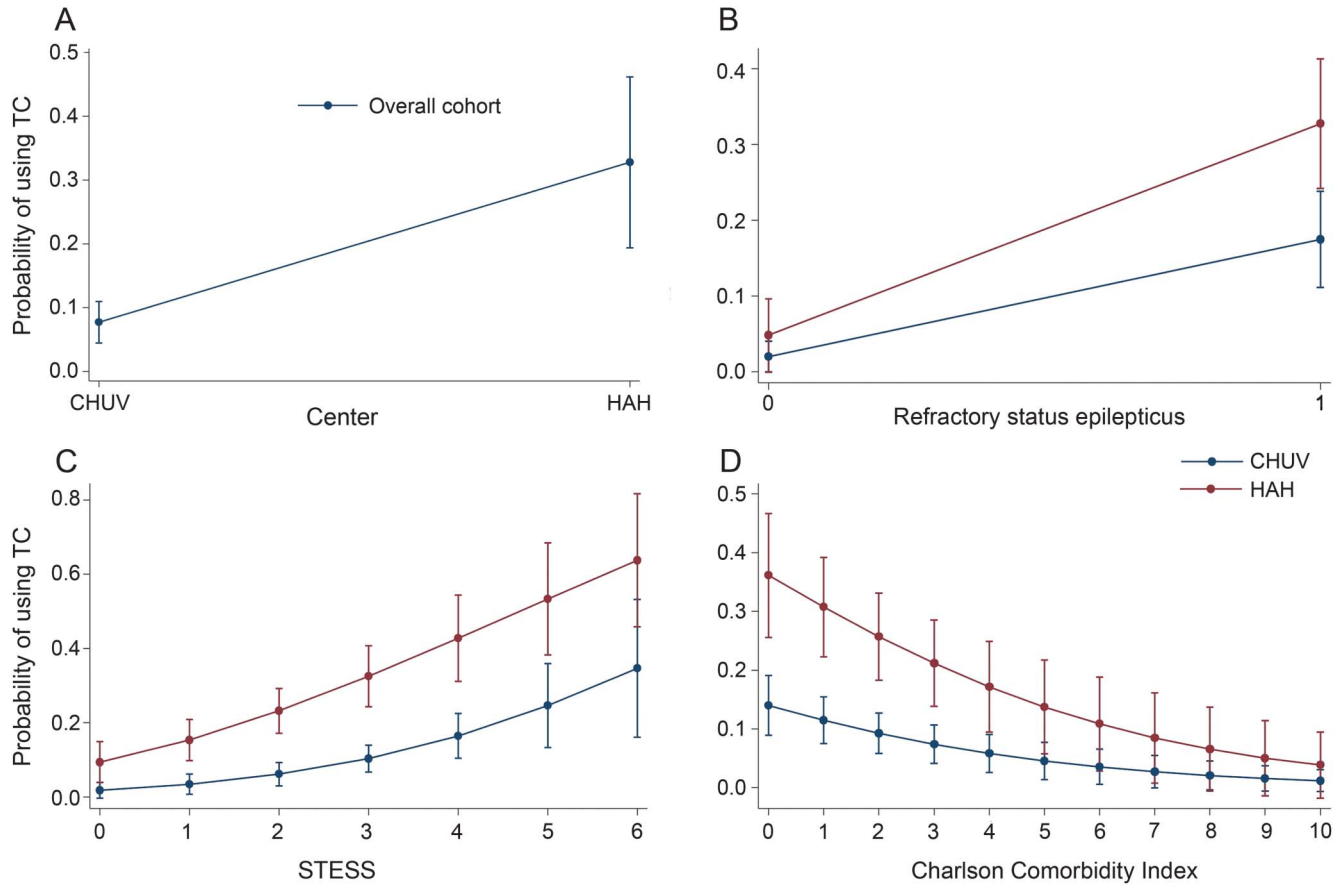
Abbreviations: ASD = antiseizure drug; CCI = Charlson Comorbidity Index; CHUV = Centre Hospitalier Universitaire Vaudois; HAH = Harvard Affiliated Hospitals; IQR = interquartile range; NCSEC = nonconvulsive status epilepticus in coma; SE = status epilepticus; STESS = Status Epilepticus Severity Score; TC = therapeutic coma.
[a] Wilcoxon rank sum test.
[b] Student *t* test.
[c] Chi-square test.

Table 2 Clinically relevant variables and their association with the use of TC after univariate and multivariate analyses using logistic regression

	Univariate analysis						Multivariate analysis		
	Use of TC	No use of TC	OR	95% CI	*p*		OR	95% CI	*p*
Total = 362, n (%)	55 (15.2)	307 (84.8)							
Demographics									
Age, median (IQR)	57 (30–82)	65 (18–79)	0.98	0.96–0.99	0.029	→	0.96	0.94–0.98	0.002
Sex, n (%)									
Female	32/170 (18.8)	138/170 (81.2)	Ref.						
Male	23/192 (12)	169/192 (88)	0.58	0.32–1.04	0.072	→	0.6	0.31–1.17	0.14
CCI, median (IQR)	1 (0–4)	2 (0–8)	0.8	0.69–0.93	0.006	→	0.75	0.62–0.89	0.002
SE characteristics									
STESS, mean (SD)	2.96 (1.55)	2.59 (1.61)	1.15	0.96–1.38	0.1	→	2	1.35–3	0.001
Worse type of seizure, n (%)									
SP, CP, absence of myoclonic	14/179 (7.8)	165/179 (92.2)	Ref.						
GC or NCSEC	41/183 (22.4)	142/183 (77.6)	3.4	1.78–6.5	<0.001				
Duration, n (%)									
>30 min	301/356 (84.5)	55/356 (15.5)							
<30 min	0/6 (0)	6/6 (100)	1						
Etiology, n (%)									
Premorbid seizures									
No	30/188 (16)	158/188 (84)	Ref.						
Yes	25/174 (14.4)	149/174 (86.6)	0.88	0.49–1.57	0.674				
Acute etiology									
No	24/154 (15.6)	130/154 (84.4)	Ref.						
Yes	31/208 (14.9)	177/208 (85.1)	0.94	0.53–1.7	0.85				
Potentially fatal etiology									
No	30/172 (17.4)	142/172 (82.6)	Ref.						
Yes	25/189 (13.2)	164/189 (86.8)	0.72	0.4–1.2	0.27				
Treatment, n (%)									
Center									
CHUV	23/236 (9.8)	213/236 (90.2)	Ref.						
HAH	32/126 (25.4)	94/126 (74.6)	3.15	1.75–5.67	<0.001	→	11.3	2.47–51.7	0.002
1st and 2nd ASD in line with guidelines									
No	42/246 (17)	204/246 (83)	Ref.						
Yes	13/116 (11)	103/116 (88)	0.6	0.32–1.2	0.15				
Time to treatment									
<1 h	26/130 (20)	104/130 (80)	Ref.						
≥1 h	29/231 (12.5)	202/231 (87.5)	0.5	0.3–1.02	0.06				
Refractory SE									
No	4/160 (2.5)	156/160 (97.5)	Ref.						
Yes	51/202 (25.3)	151/202 (74.7)	13.2	4.64–37.34	<0.001	→	12.3	4.13–36.4	<0.001
Interaction variable									
STESS × center						→	0.58	0.38–0.9	0.016

Abbreviations: ASD = antiseizure drug; CCI = Charlson Comorbidity Index; CHUV = Centre Hospitalier Universitaire Vaudois; CI = confidence interval; CP = complex partial; GC = generalized convulsive; HAH = Harvard Affiliated Hospitals; IQR = interquartile range; NCSEC = nonconvulsive status epilepticus in coma; OR = odds ratio; Ref. = reference group; SE = status epilepticus; STESS = Status Epilepticus Severity Score; SP = simple partial; TC = therapeutic coma.

Figure 1 Adjusted margin probability for using TC comparing the 2 groups: HAH in red and CHUV in blue



(A) Overall probability by groups. (B) Probability by refractory status epilepticus. (C) Probability at equally spaced STESS values. (D) Probability at equally spaced Charlson Comorbidity Index values. Vertical axes represent probability of reaching outcome (using TC) based on the multivariate logistic regression model from table 2. CHUV = Centre Hospitalier Universitaire Vaudois; HAH = Harvard Affiliated Hospitals; STESS = Status Epilepticus Severity Score; TC = therapeutic coma.

of TC and the involved center had no influence on mortality (model goodness-of-fit: $p = 0.43$, $\chi^2 = 348.8$). The area under the ROC curve was 0.76 (95% confidence interval 0.69–0.83).

Details regarding the relationship between selected variables and the LOS are shown in table 4. After adjustment for relevant variables using a negative binomial regression model, increasing STESS, a potentially fatal etiology, refractory SE, and the use of TC were significantly associated with longer hospitalizations. The associated χ^2 value [chibar2 (01) = 2178.29, Prob ≥ chibar2 = 0.000] of the fitted multivariate model strongly suggests that α is nonzero and the negative binomial model is more appropriate than the Poisson model. The offset was not used. Informal goodness-of-fit was checked by plotting observed–predicted vs counts.

DISCUSSION This cohort study performed as a natural experiment shows that there are major differences in the TC use between the 2 groups. Our study provides Class III evidence that after controlling for SE severity and patient comorbidities, TC was much more frequent in the Boston hospitals as compared to the Swiss center (adjusted odds ratio: 11.3). While there was no increase of mortality with TC, it was associated with increased duration of acute hospitalization.

The difference in TC preference between sites may be explained by several factors. First, in the context of relatively weak evidence supporting it, there may be cultural differences and different practice habits across different centers. Observational SE studies have reported different rates of CIVAD prescription: 5% in Germany,[18] 8% in Italy,[19] 10.7%[12] in Switzerland, 22% in France,[20] and up to 31%[21] or 36% in the United States.[22] The same is true when describing treatment of refractory SE: CIVADs were used in 30%[23] and 43%[24] of patients in Switzerland, as opposed to 87.3% in the United States.[25] Three recent studies performed in the United States and Switzerland[10–12] have questioned the risk/benefit ratio of TC, with observational data showing an independent association with worse outcome after correction for major confounders. Nevertheless, more aggressive treatment, including TC, is recommended by some experts.[26,27] Another explanation may be that the

Table 3 Clinically relevant variables and their association with mortality after univariate and multivariate analyses using logistic regression

	Univariate analysis						Multivariate analysis		
	Survivors	Nonsurvivors	OR	95% CI	*p*		OR	95% CI	*p*
Total = 362, n (%)	310 (85.6)	52 (14.4)							
Demographics									
Age, median (IQR)	62 (18–89)	68.5 (26–86)	1.01	0.99–1.03	0.1	→	0.98	0.96–1.01	0.275
Sex, n (%)									
Female	147/170 (86.5)	23/170 (13.5)	Ref.						
Male	163/192 (84.9)	29/192 (15.1)	1.13	0.62–2.05	0.67	→	1.12	0.58–2.14	0.726
CCI, median (IQR)	1 (0–8)	2 (0–7)	1.2	1.07–1.34	0.002	→	1.18	1.04–1.34	0.011
SE characteristics									
STESS, mean (SD)	2.49 (1.58)	3.54 (1.46)	1.53	1.25–1.86	<0.001	→	1.54	1.19–1.99	0.001
Worse type of seizure, n (%)									
SP, CP, absence of myoclonic	156/179 (87.1)	23/179 (12.9)	Ref.						
GC or NCSEC	154/183 (84.1)	29/183 (15.9)	1.27	0.7–2.3	0.81				
Duration, n (%)									
>30 min	305/356 (85.7)	51/356 (14.3)	Ref.						
<30 min	5/6 (83.3)	1/6 (16.7)	1.19	0.13–10.44	0.87				
Etiology, n (%)									
Premorbid seizures									
No	152/188 (80.9)	38/188 (19.2)	Ref.						
Yes	158/175 (90.8)	16/174 (9.2)	0.42	0.22–0.8	0.008				
Acute etiology									
No	134/154 (87)	20/154 (13)	Ref.						
Yes	176/208 (84.6)	32/208 (15.4)	1.21	0.66–2.22	0.521				
Potentially fatal etiology									
No	160/172 (93)	12/172 (7)	Ref.						
Yes	149/189 (78.9)	40/189 (21.2)	3.57	1.8–7.08	<0.001	→	2.6	1.25–5.4	0.01
Treatment, n (%)									
Center									
CHUV	203/236 (86)	33/236 (14)	Ref.						
HAH	107/126 (84.9)	19/126 (15.1)	1.09	0.6–2	0.78	→	0.79	0.4–1.58	0.518
1st and 2nd ASD in line with guidelines									
No	210/246 (85.4)	36/246 (14.6)	Ref.						
Yes	100/116 (86.2)	16/116 (13.8)	0.9	0.49–1.76	0.83				
Time to treatment									
<1 h	115/130 (88.4)	15/130 (11.6)	Ref.						
≥1 h	194/231 (83.9)	37/231 (16.1)	1.46	0.76–2.78	0.25				
Refractory SE									
No	147/160 (91.9)	13/160 (8.1)	Ref.						
Yes	163/202 (80.7)	39/202 (19.3)	2.7	1.38–5.26	0.003	→	2.13	1.01–4.5	0.047
Use of TC									
No	266/307 (86.6)	41/307 (13.4)	Ref.						
Yes	44/55 (80)	11/55 (20)	1.62	0.77–3.39	0.19	→	1.4	0.58–3.39	0.447

Abbreviations: ASD = antiseizure drug; CCI = Charlson Comorbidity Index; CHUV = Centre Hospitalier Universitaire Vaudois; CI = confidence interval; CP = complex partial; GC = generalized convulsive; HAH = Harvard Affiliated Hospitals; IQR = interquartile range; NCSEC = nonconvulsive status epilepticus in coma; OR = odds ratio; Ref. = reference group; SE = status epilepticus; STESS = Status Epilepticus Severity Score; SP = simple partial; TC = therapeutic coma.

Table 4 Clinically relevant variables and their association with the length of stay after univariate and multivariate analyses using negative binomial regression (survivors only)

	Univariate analysis					Multivariate analysis		
	Length of stay, d	IRR	95% CI	*p*		IRR	95% CI	*p*
Total = 310 survivors, median (IQR)	10 (1–77)							
Demographics								
Age	NA	1	0.99–1	0.7	→	0.99	0.99–1	0.7
Sex, median (IQR)								
Female	10 (2–74)	Ref.						
Male	9 (1–58)	0.86	0.71–1	0.14	→	0.86	0.72–1.03	0.1
CCI	NA	1	0.97–1.05	0.5				
SE characteristics, median (IQR)								
STESS	NA	1.1	1.05–1.19	<0.001	→	1.1	1.02–1.18	0.007
Worse type of seizure								
SP, CP, absence of myoclonic	9 (1–58)							
GC or NCSEC	10 (2–66)	1.17	0.97–1.42	0.09				
Duration								
>30 min	10 (1–77)	Ref.						
<30 min	6 (4–10)	0.63	0.29–1.37	0.25				
Etiology, median (IQR)								
Premorbid seizures								
No	13 (3–67)	Ref.						
Yes	7 (1–62)	0.62	0.52–0.75	<0.001				
Acute etiology								
No	7.5 (1–32)	Ref.						
Yes	12 (2–77)	1.7	1.41–2.05	<0.001				
Potentially fatal etiology								
No	8 (1–45)	Ref.						
Yes	12 (2–77)	1.56	1.3–1.88	<0.001	→	1.6	1.34–1.91	<0.001
Treatment, median (IQR)								
Center								
CHUV	10 (1–67)	Ref.						
HAH	9 (2–58)	1.03	0.86–1.25	0.71	→	0.85	0.74–1.04	0.12
1st and 2nd ASD in line with guidelines								
No	10 (1–74)	Ref.						
Yes	9 (2–60)	0.93	0.76–1.15	0.52				
Time to treatment								
<1 h	9 (2–66)	Ref.						
≥1 h	10 (1–62)	1.03	0.85–1.25	0.73				
Refractory SE								
No	9 (1–45)	Ref.						
Yes	11 (2–74)	1.38	1.15–1.67	0.001	→	1.28	1.06–1.55	0.01
Use of TC								
No	9 (1–67)	Ref.						
Yes	16.5 (4–60)	1.68	1.3–2.2	<0.001	→	1.6	1.22–2.11	0.001

Abbreviations: ASD = antiseizure drug; CCI = Charlson Comorbidity Index; CHUV = Centre Hospitalier Universitaire Vaudois; CI = confidence interval; CP = complex partial; GC = generalized convulsive; HAH = Harvard Affiliated Hospitals; IQR = interquartile range; IRR = incident rate ratio; NA = not applicable; NCSEC = nonconvulsive status epilepticus in coma; Ref. = reference group; SE = status epilepticus; SP = simple partial; STESS = Status Epilepticus Severity Score; TC = therapeutic coma.

more frequent inadequacy of initial treatment in HAH as compared to current guidelines, mostly attributable to lorazepam underdosing,[14] might lead to an increased need for CIVADs following SE refractoriness. Adequate initial treatment is indeed associated with more rapid seizure cessation.[20] However, association between use of TC and inadequate initial ASD was not found, possibly reflecting the confounding action of further treatment. Furthermore, our group previously showed that treatment inadequacy has no significant influence on mortality.[28] Finally, the systematic use of continuous EEG in HAH, which is more common than in Europe, may influence treatment choices: electrographic seizures could have been missed in some patients at CHUV, preventing treatment escalation. Breakdown of seizure types was remarkably similar between the 2 groups, except that NCSEC was more frequent in HAH, supporting this hypothesis. However, because temporal relationships between the start of EEG recordings and treatment were not recorded, this hypothesis remains unproven.

TC was not associated with mortality after controlling for demographics, SE severity, refractoriness, and comorbidities but correlated to a 60% increase in the LOS in acute facilities. Ten years ago, the median direct cost of an inpatient hospital stay for SE has been estimated at up to $1,458 US dollars per day[29]; any increase in duration of hospital stay may thus exert an important effect on health care costs.

Mortality was mainly related to SE severity, etiology, comorbidities, and refractoriness, in line with several previous studies,[30,31] but not TC. Besides the aforementioned possible relationship of TC to increased mortality,[10–12] which has been questioned in view of methodologic limitations,[32] one recent review demonstrated a high rate of infectious complications after CIVADs (>50%).[33] Two other studies did not show a TC influence on mortality in particular subtypes of SE—new-onset refractory SE[34] and NCSE.[35] Finally, one study modeling decision-making on the aggressiveness of treatment of nonconvulsive SE in the ICU showed that, even in cases in which NCSE was thought to cause brain damage, aggressive treatment may yet confer a greater overall risk.[36] Of interest, a randomized study from India assessed treatment protocols avoiding CIVADs in the context of ICU nonavailability[37]: 92% of patients with generalized convulsive SE could avoid CIVADs (used in their protocol as a fifth-line rescue therapy after failure of BZD and 3 different nonsedative ASDs); 29% of SE episodes were considered refractory; and mortality was 13.6% overall and 25.6% for refractory SE, in line with studies from Western countries.[23,30] As such, there is still a major controversy as to whether TC increases mortality or improves outcome. TC seems, however, independently related to an increased LOS, according to our data, and infections.[12] Because of these considerations, we believe that our findings reinforce the call for a well-conducted evaluation of the role of TC in the treatment of SE, going beyond short-term survival after SE.[32]

A subset of patients from CHUV included in this analysis was also part of a previous study showing an independent increase of mortality associated with the use of TC.[12] When combined with the HAH group, TC seemed to lose this negative effect. There are several possible explanations. First, the significant influence on mortality was strongest for SE types other than generalized convulsive SE or NCSEC at the time of treatment in the Swiss study, meaning that patients with initial generalized convulsive SE evolving into focal SE were included in the more benign SE forms for analysis, as opposed to the present study, which categorized patients according to the worst seizure type. Second, the negative effect of TC may have been lost because more benign forms of SE with favorable outcome were treated with CIVADs in HAH as opposed to at CHUV, where TC is usually reserved for more severe SE. Also, the increase of mortality associated with TC in the aforementioned study[12] may be attributable to an unrecognized and as-yet unmeasurable factor influencing mortality and the clinician's decision to put a patient in a TC. Finally, the vast majority of patients in Boston were treated in a neuro-ICU, as opposed to patients in Switzerland, treated in a multidisciplinary ICU with a consultant neurologist. Neurointensivists may be more aware of systemic complications of CIVADs, although this probably has a minor role, as a neuro-ICU vs multidisciplinary ICU setting did not appear to affect mortality or LOS in SE in a previous study.[38]

The strengths of this study include the large number of patients and the first direct comparison of TC use between 2 geographical settings assessed through a systematic and comprehensive, prospective data collection. Moreover, statistical models were constructed in order to strictly include all known relevant outcome predictors. We acknowledge, however, some limitations. First, because of the observational design, we cannot be certain that some unidentified confounder influencing the probability of using TC or mortality was missed. Also, the reasons for death of patients were not systematically assessed. We also cannot exclude the possibility that there was a higher rate of care withdrawal in one group, and we were not able to evaluate whether death occurred because of CIVAD side effects. In a dedicated study, while 106 of 120 deaths after SE were primarily related to the underlying etiology, complications of therapy were considered to contribute to death in one-third

of cases.[39] Another important limitation of all studies to date, including this one, is that no one has controlled for the quality or depth of TC. This limitation is important in light of evidence that management of pharmacologically induced coma is highly variable and often fails to achieve therapeutic targets (i.e., EEG burst suppression, seizure suppression, or suppression pattern) (unpublished results of M.B.W.). The potential benefit of TC may be offset in practice by adverse effects associated with over- and underdosing of anesthetics. Finally, because functional outcomes were not assessed based on controlled and validated scores, the data were not sufficient to determine whether there was an independent association with TC.

We show that different policies regarding TC induction for SE management exist, despite relatively uniform treatment guidelines. The more "aggressive" and resource-consuming treatment seems to increase length of hospital stay (and thus costs) without improvement of survival. This appears highly relevant in the context of high daily costs related to management of acutely ill patients and the increased burden of SE.[40] Based on these findings, we recommend that TC should be reserved for severe refractory convulsive SE forms and tailored to the underlying biological background. Also, every effort should be made to improve awareness and translation into practice of SE guidelines, in order to minimize underdosage of the first treatment line. Until an urgently needed randomized trial is performed, SE management should always consider Galen's principle: *primum non nocere*.

AUTHOR CONTRIBUTIONS

Dr. Alvarez: drafting/revising the manuscript for content, study concept and design, analysis and interpretation of data, acquisition of data, statistical analysis. Dr. Jong Woo Lee: drafting/revising the manuscript for content, acquisition of data, analysis and interpretation of data. Dr. M. Brandon Westover: drafting/revising the manuscript for content, acquisition of data, analysis and interpretation of data. Dr. Frank W. Drislane: drafting/revising the manuscript for content, acquisition of data, analysis and interpretation of data. Dr. Mohamed Faouzi: drafting/revising the manuscript for content, analysis and interpretation of data, statistical analysis. Dr. Nicola Marchi: drafting/revising the manuscript for content, acquisition of data. Dr. Jan Novy: drafting/revising the manuscript for content, acquisition of data. Dr. Barbara A. Dworetzky: drafting/revising the manuscript for content, acquisition of data. Dr. Andrea O. Rossetti: drafting/revising the manuscript for content, study concept and design, analysis and interpretation of data, acquisition of data, study supervision.

ACKNOWLEDGMENT

The investigators thank Christine Staehli, RN (CHUV), Christine Scott, R Tech (MGH), and the EEG fellows at times of data acquisition from the EEG laboratories at the BWH (Swapna Putta and Hong Yu), BIDMC (Andrew Schomer and Stephen VanHaerents), CHUV (Muriel Tschirren, Spyridoula Tsetsou, Myriam Guidon, Anita Barbey), and MGH (Kheder Amar, Yuan Fan, Arash Hadipour Niktarash, Lidia Moura, Marcus Ng, Deirdre O'Rourke, and Sandipan Pati) for their help in patient identification and data collection.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

V. Alvarez was funded by the Swiss National Science Foundation, grant P2GEP3_148510, and the Gottfried und Julia Bangerter-Rhyner Foundation during data collection. J. Lee was supported by NINDS (research funding), Advance Medical and SleepMed/DigiTrace (consultant/contract work), UCB (research funding). M. Westover was supported by NIH-NINDS 1K23NS090900, the Rappaport Foundation, the Andrew David Heitman Neuroendovascular Research Fund. F. Drislane received honoraria from UpToDate, LWW, and American Academy of Neurology. J. Novy received travel and speaker honoraries from UCB and Pfizer. M. Faouzi and N. Marchi report no disclosures relevant to the manuscript. B. Dworetzky was funded by the Federal Drug Administration, the American Epilepsy Society, and the Epilepsy Foundation. In addition, she is a consultant for SleepMed and for Best Doctors. A. Rossetti received research support from Sage, UCB, Eisai, and the Swiss National Science Foundation, grant CR32I3_143780. Go to Neurology.org for full disclosures.

Received December 7, 2015. Accepted in final form May 20, 2016.

REFERENCES

1. Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. Lancet Neurol 2011;10:922–930.
2. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3–23.
3. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 2010;17:348–355.
4. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339:792–798.
5. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366:591–600.
6. Young GB, Jordan KG. Do nonconvulsive seizures damage the brain?—yes. Arch Neurol 1998;55:117–119.
7. Aminoff MJ. Do nonconvulsive seizures damage the brain?—no. Arch Neurol 1998;55:119–120.
8. Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med 2013;39:1337–1351.
9. Wijdicks EF. The multifaceted care of status epilepticus. Epilepsia 2013;54(suppl 6):61–63.
10. Kowalski RG, Ziai WC, Rees RN, et al. Third-line antiepileptic therapy and outcome in status epilepticus: the impact of vasopressor use and prolonged mechanical ventilation. Crit Care Med 2012;40:2677–2684.
11. 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;82:656–664.
12. Marchi NA, Novy J, Faouzi M, Stähli C, Burnand B, Rossetti AO. Status epilepticus: impact of therapeutic coma on outcome. Crit Care Med 2015;43:1003–1009.
13. Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia 2011;52:1292–1296.
14. Alvarez V, Lee JW, Drislane FW, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia 2015;56:1275–1285.

15. Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013;54(suppl 6):28–29.
16. 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;255:1561–1566.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
18. Kellinghaus C, Stögbauer F. Treatment of status epilepticus in a large community hospital. Epilepsy Behav 2012; 23:235–240.
19. Vignatelli L, Rinaldi R, Galeotti M, de Carolis P, D'Alessandro R. Epidemiology of status epilepticus in a rural area of northern Italy: a 2-year population-based study. Eur J Neurol 2005;12:897–902.
20. Aranda A, Foucart G, Ducassé JL, Grolleau S, McGonigal A, Valton L. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. Epilepsia 2010;51:2159–2167.
21. Claassen J, Lokin JK, Fitzsimmons BF, Mendelsohn FA, Mayer SA. Predictors of functional disability and mortality after status epilepticus. Neurology 2002;58:139–142.
22. Cook AM, Castle A, Green A, et al. Practice variations in the management of status epilepticus. Neurocrit Care 2012;17:24–30.
23. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia 2010; 51:251–256.
24. Sutter R, Marsch S, Fuhr P, Rüegg S. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. Epilepsia 2013;54:502–511.
25. Hocker SE, Britton JW, Mandrekar JN, Wijdicks EF, Rabinstein AA. Predictors of outcome in refractory status epilepticus. JAMA Neurol 2013;70:72–77.
26. Fernandez A, Lantigua H, Lesch C, et al. High-dose midazolam infusion for refractory status epilepticus. Neurology 2014;82:359–365.
27. Riviello JJ, Claassen J, LaRoche SM, et al. Treatment of status epilepticus: an international survey of experts. Neurocrit Care 2013;18:193–200.
28. Rossetti AO, Alvarez V, Burnand B, Januel JM. Treatment deviating from guidelines does not influence status epilepticus prognosis. J Neurol 2013;260:421–428.
29. Penberthy LT, Towne A, Garnett LK, Perlin JB, DeLorenzo RJ. Estimating the economic burden of status epilepticus to the health care system. Seizure 2005;14: 46–51.
30. Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Short-term mortality after a first episode of status epilepticus. Epilepsia 1997;38:1344–1349.
31. Drislane FW, Blum AS, Lopez MR, Gautam S, Schomer DL. Duration of refractory status epilepticus and outcome: loss of prognostic utility after several hours. Epilepsia 2009;50:1566–1571.
32. Hirsch LJ. Finding the lesser of two evils: treating refractory status epilepticus. Epilepsy Curr 2015;15:313–316.
33. Prabhakar H, Bindra A, Singh GP, Kalaivani M. Propofol versus thiopental sodium for the treatment of refractory status epilepticus. Cochrane Database Syst Rev 2012;8: CD009202.
34. Gaspard N, Foreman BP, Alvarez V, et al. New-onset refractory status epilepticus: etiology, clinical features, and outcome. Neurology 2015;85:1604–1613.
35. Uysal U, Quigg M, Bittel B, Hammond N, Shireman TI. Intravenous anesthesia in treatment of nonconvulsive status epilepticus: characteristics and outcomes. Epilepsy Res 2015;116:86–92.
36. Ferguson M, Bianchi MT, Sutter R, et al. Calculating the risk benefit equation for aggressive treatment of nonconvulsive status epilepticus. Neurocrit Care 2013;18: 216–227.
37. Mundlamuri RC, Sinha S, Subbakrishna DK, et al. Management of generalised convulsive status epilepticus (SE): a prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam: pilot study. Epilepsy Res 2015;114:52–58.
38. Varelas PN, Corry J, Rehman M, et al. Management of status epilepticus in neurological versus medical intensive care unit: does it matter? Neurocrit Care 2013;19:4–9.
39. Sokic DV, Jankovic SM, Vojvodic NM, Ristic AJ. Etiology of a short-term mortality in the group of 750 patients with 920 episodes of status epilepticus within a period of 10 years (1988–1997). Seizure 2009;18: 215–219.
40. Betjemann JP, Josephson SA, Lowenstein DH, Burke JF. Trends in status epilepticus-related hospitalizations and mortality: redefined in US practice over time. JAMA Neurol 2015;72:650–655.