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Status epilepticus: impact of therapeutic coma on outcome

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Status epilepticus: impact of therapeutic coma on outcome

THESE

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Rapport de synthèse

L'état de mal épileptique (EME) est la plus fréquente urgence neurologique après les accidents vasculaires cérébraux, avec des hauts taux de morbidité et mortalité (Coeytaux et al., 2000). Son traitement est basé sur une approche en trois étapes (Meiekord et al., 2010). Dans ce contexte, un EME ne répondant pas aux benzodiazépines (1er ligne de traitement) suivi par des médicaments antiépileptiques (2ème ligne de traitement) est appelé EME réfractaire. Pour cette condition, représentant entre le 23% et le 43% des EME (Novy et al., 2010; Holtkamp et al., 2005), les actuelles recommandations préconisent un traitement par coma pharmacologique (3ème ligne de traitement), malgré un faible niveau d'évidence (Rossetti et al., 2011). En effet, l'impact du coma pharmacologique sur l'issue clinique n'a pas encore été clairement établi. Récemment, deux études américaines (Kowalski et al., 2012; Hocker et al., 2013) et une étude suisse (Sutter et al., 2014), ont montré un effet potentiellement délétère de ce type de traitement. Cependant, ces études étaient limitées à des patients hospitalisés aux soins intensifs et les analyses n'étaient pas ajustées pour tous les facteurs pronostiques connus.

Le but de notre travail, publié dans *Critical Care Medicine* (Marchi et al., 2015), était d'évaluer l'impact spécifique du coma pharmacologique sur le pronostic des patients avec EME, sans limitations aux soins intensifs et avec un ajustement plus attentif concernant les autres facteurs pronostiques. En utilisant notre registre prospectif des patients avec EME traités aux Centre Hospitalier Universitaire Vaudois, nous avons comparé l'issue clinique à la sortie de l'hôpital des patients traités avec ou sans coma pharmacologique (467 épisodes au total). Ensuite, nous avons utilisé une régression logistique multinomiale pour ajuster les résultats par les autres facteur pronostiques connus (âge, absence de crises épileptiques précédentes, étiologie potentiellement fatale, gravité clinique de l'EME, comorbidités). Nous avons pu mettre ainsi en évidence que le traitement avec coma pharmacologique est associé avec une mauvaise issue clinique après un EME. De plus, nous avons pu pour la première fois montrer que cet effet est d'autant plus important chez les patients avec un EME de type partiel complexe au moment du traitement. Nos résultats suggèrent que l'utilisation du coma pharmacologique ne doit pas être indiscriminée dans l'EME réfractaire et qu'une évaluation de la situation clinique de base permet une optimisation son emploi.

Bibliographie:

Coeytaux A, Jallon P, Galobardes B, et al: Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 2000; 55:693–697

Hocker SE, Britton JW, Mandrekar JN, et al: Predictors of outcome in refractory status epilepticus. JAMA Neurol 2013; 70:72–77

Holtkamp M, Othman J, Buchheim K, et al: Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J Neurol Neurosurg Psychiatry 2005; 76:534–539

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

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

Meierkord H, Boon P, Engelsen B, et al; European Federation of Neurological Societies: EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 2010; 17:348–355

Novy J, Logroscino G, Rossetti AO: Refractory status epilepticus: A prospective observational study. Epilepsia 2010; 51:251–256

Rossetti AO, Lowenstein DH: Management of refractory status epilepticus in adults: Still more questions than answers. Lancet Neurol 2011; 10:922–930

Sutter R, Marsch S, Fuhr P, et al: Anesthetic drugs in status epilepticus: Risk or rescue? A 6-year cohort study. Neurology 2014; 82:656–664

Status Epilepticus: Impact of Therapeutic Coma on Outcome*

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Objectives: Therapeutic coma is advocated in guidelines for management of refractory status epilepticus; this is, however, based on weak evidence. We here address the specific impact of therapeutic coma on status epilepticus outcome.

Design: Retrospective assessment of a prospectively collected cohort.

Setting: Academic hospital.

Patients: Consecutive adults with incident status epilepticus lasting greater than or equal to 30 minutes, admitted between 2006 and 2013.

Measurements and Main Results: We recorded prospectively demographics, clinical status epilepticus features, treatment, and outcome at discharge and retrospectively medical comorbidities, hospital stay, and infectious complications. Associations between potential predictors and clinical outcome were analyzed using multinomial logistic regressions. Of 467 patients with incident status epilepticus, 238 returned to baseline (51.1%), 162 had new disability (34.6%), and 67 died (14.3%); 50 subjects (10.7%) were managed with therapeutic coma. Therapeutic coma was associated with poorer outcome in the whole cohort (relative risk ratio for new disability, 6.86; 95% CI, 2.84–16.56; for mortality, 9.10; 95% CI, 3.17–26.16); the effect was more important in patients with complex partial compared with generalized convulsive or nonconvulsive status epilepticus in coma. Prevalence of infections was higher (odds ratio, 3.81; 95% CI, 1.66–8.75), and median hospital stay in patients discharged alive was longer (16 d [range, 2–240 d] vs 9 d [range, 1–57 d]; $p < 0.001$) in subjects managed with therapeutic coma.

Conclusions: This study provides class III evidence that therapeutic coma is associated with poorer outcome after status epilepticus; furthermore, it portends higher infection rates and longer hospitalizations. These data suggest caution in the straightforward use of this approach, especially in patients with complex partial status epilepticus. (*Crit Care Med* 2015; 43:1003–1009)

Key Words: hospital stay; infections; mortality; prognosis; semiology; treatment

*See also p. 1144.

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Status epilepticus (SE) is the second most frequent neurologic emergency after stroke, with an important risk of morbidity and mortality (1–3). Treatment recommendations for SE are based on a three-step approach (4, 5); in this context, SE not responding to benzodiazepines (first-line therapy) followed by an antiepileptic drug (second-line therapy) is commonly labeled as refractory SE (RSE). This condition occurs in 23–43% of patients with SE (6, 7), and management with therapeutic coma (TC) is advocated in current guidelines (third-line therapy) (4, 5, 8, 9), although there is no high-level evidence.

The effective impact of third-line therapy on outcome, however, has not been clearly established. Recently, a cohort study of 126 patients with SE suggested that this approach may be associated with poorer outcome and death (10), but this analysis was not adjusted for all known principal outcome

predictors. Another study including 54 subjects with RSE showed that longer duration of TC is associated with unfavorable prognosis (11); however, this cohort was restricted to a neurologic ICU environment, and the authors did not adjust for SE outcome predictors. Conversely, in a cohort of 111 patients, the use of general anesthetics did not have any impact on mortality; here again the patients were evaluated only in ICU settings, and interaction with SE refractoriness was not assessed (12). Finally, a study by the same group recently showed that the use of anesthetic agents is related to worse outcome; again, this analysis was limited to an ICU setting (13). These divergent observations and the related methodological limitations (including a retrospective approach in most studies) prevent a conclusive judgment upon the impact of coma induction on SE outcome, independently from the underlying cause and the severity of the episode.

The objective of this study was to assess the specific impact of TC on prognosis of patients with SE, without restriction to ICU, after adjustment for the most important prognostic factors.

MATERIALS AND METHODS

Cohort Definition

We included consecutive adult patients (more than 16 yr old) with SE, admitted to our center between April 1, 2006, and July 30, 2013 (88 mo), who were prospectively enrolled in our registry that received full approval from our Ethic commission. Cases with postanoxic etiologies were not enrolled in our registry. SE was defined as the occurrence of continuous seizures or repetitive seizures between which there is incomplete recovery of baseline clinical conditions for greater than or equal to 30 minutes (until 2008) and for greater than or equal to 5 minutes (since 2008) (14). SE episodes were clinically diagnosed by neurology consultants and confirmed with electroencephalogram (EEG) studies, which was mandatory for nonconvulsive forms. Further details on this registry have been published previously (6). This study considered only incident cases of SE which lasted greater than or equal to 30 minutes, in order to avoid overrepresentation of certain individuals and include only episodes with consistent prognostic implications.

Variables

Age, gender, and history of previous seizures were prospectively recorded on admission. Etiology leading to death if not specifically treated was categorized as "potentially fatal" as previously detailed (15). Level of consciousness before treatment was categorized as alert, confused or somnolent (arousable toward a clear clinical contact), stuporous (arousable, but without contact), and comatose; the latter two were classified as "severe impairment of consciousness." Type of SE was defined by the worst clinical seizure in the given episode and classified, in increasing order of severity, as simple partial (focal without consciousness impairment), absence, myoclonic (related to genetic generalized epilepsy), complex partial (focal with consciousness impairment), generalized convulsive SE (GCSE), or nonconvulsive SE in coma (NCSEC). GCSE episodes were further dichotomized into "proper" GCSE (those which presented prolonged generalized convulsive seizures up to the SE diagnosis and treatment) and "GCSE then focal" (those with focal seizures without coma on diagnosis, but having presented an earlier generalized convulsion during the same episode), as we hypothesized that these two forms might have different prognostic implications. The SE severity score (STESS), a validated clinical scoring system considering age, worst seizures type, level of consciousness impairment, and history of previous seizures, was calculated for each patient at admission (16, 17).

We prospectively recorded use of TC for SE treatment, specific anesthetic agents administered in each episode, and treatment latency (representing the best estimated time from SE onset to administration of the first medication, and dichotomized at 1 hr following the beginning of the SE episode). TC was a clinically driven endpoint, monitored by EEG (with seizure suppression, or burst suppression, as target), and it was accomplished using anesthetic drugs as continuous IV drips. Our hospital is a third-level center including a multidisciplinary ICU; patients with SE are mostly treated in the neurology ward (intermediate care unit) and admitted to the ICU if they need mechanical ventilation. The main clinical outcome, prospectively assessed at hospital discharge, was categorized into three groups: return to baseline, new disability (defined as new neurological impairment, as compared to the situation before the incident SE episode), or death.

By screening the computerized hospital database, medical comorbidities were retrospectively retrieved after discharge using the 17-item version of the Charlson Comorbity Index (CCI), using the *International Statistical Classification of Disease and Related Health Problems*, 10th Revision, coding algorithms (18, 19); medical conditions considered as SE etiology for the specific episode were excluded from CCI, in order to avoid redundancy. Duration of acute hospital stay (defined as ICU and acute neurology ward stay) was also retrospectively retrieved in selected patients (see below), as was the occurrence of infectious complications requiring antibiotics (classified into respiratory tract, urinary tract, bloodstream, or others) arising during SE treatment; infections occurring prior to SE or after SE treatment were not considered.

Statistical Analysis

The association between potential predictors and clinical outcome was analyzed using univariable multinomial logistic regressions. Multinomial (polytomous) logistic regression fits maximum likelihood models with discrete dependent variables, when the dependent variable takes on more than two outcomes and the outcomes have no natural ordering, as in the present study (**supplemental data**, Supplemental Digital Content 1, http://links.lww.com/CCM/B200). Outcome prognosticators with a p value less than 0.05 were used in a backward procedure to fit a multivariable multinomial model. Results were described with relative risk ratios and 95% CIs. We conducted analyses in the complete cohort as well as in patients with GCSE "proper" or NCSEC versus other SE forms.

Prevalence of infectious complications was analyzed in a nested case-control assessment comparing all patients managed with TC and a control group of the same number of subjects treated without TC, matched for outcome, potentially fatal etiology, STESS, and CCI; results are given in odds ratio (OR) and 95% CI. The same approach was used to analyze the length of hospital stay using a Wilcoxon test; patients who died were excluded from this analysis in order to avoid bias of shorter hospitalization. We chose to adjust for the aforementioned variables in order to specifically address the role of TC (exposure) on infections, respectively duration of in-hospital stay (outcomes), as clinical outcome may confound these relationships. The use of specific anesthetic drugs for coma induction was investigated with a Fisher exact test comparing the three outcome groups. Analysis was performed using the Stata software version 12 (StataCorp, College Station, TX); significance was considered at p value less than 0.05.

RESULTS

During the 88-month study period, we identified 467 incident episodes of adult SE lasting greater than or equal to 30 minutes (representing 77.2% of 606 events in our registry; 52 episodes lasting < 30 min and 86 recurrent episodes were excluded). Mean age was 60.3 years (SD ± 18.6) and 228 were women (48.8%). An overview of the clinical characteristics of patients according to functional outcome is presented in **Table 1**. At hospital discharge, half of patients returned to baseline conditions (51.0%), one third had a new disability (34.7%), and mortality occurred in 14.3%. Fifty subjects (10.7%) were managed with TC. Of the 67 patients who died, 23 died during SE and seven had anesthetic treatments (four propofol, three thiopental). A potentially fatal etiology was identified in 237 episodes; the most frequent occurrences were 50 primary brain tumors (21.1%) (mostly glioblastoma multiforme), 44 intracranial hemorrhages (18.6%), 35 metastatic brain tumors (14.8%), and 22 encephalitis or meningoencephalitis (9.3%). On univariable analysis, worse outcome occurred more frequently in elderly subjects as well as in patients having no history of previous seizures, a potentially fatal etiology, a severe impairment of consciousness, a higher STESS, a higher CCI, and TC for SE treatment.

The most common forms of SE encountered in our cohort were complex partial SE and "proper" GCSE (representing each about one third of the cohort); clinical characteristics of patients according to TC are shown in **Table 2**. Of note, there was no significant difference among the three outcome groups

TABLE 1. Demographics and Clinical Characteristics of 467 Patients With Incident Status Epilepticus According to Clinical Outcome at Hospital Discharge

Variable	Return to Baseline ($n = 238$) (%)	New Disability ($n = 162$) (%)	Death ($n = 67$) (%)	New Disability Versus Return to Baseline; RRR, 95% CI, p	Death Versus Return to Baseline; RRR, 95% CI, p
Age (yr; mean ± SD)	54.9 ± 18.9	65.3 ± 16.4	67.5 ± 17.1	**1.03, 1.02–1.05, < 0.001**	**1.04, 1.02–1.06, < 0.001**
Female gender ($n = 228$)	112 (47.1)	84 (51.8)	32 (47.8)	0.83, 0.55–1.23, 0.347	0.97, 0.56–1.67, 0.919
Previous seizures ($n = 199$)	138 (58.0)	42 (25.9)	19 (28.4)	**0.25, 0.16–0.39, < 0.001**	**0.29, 0.16–0.52, < 0.001**
Potentially fatal etiology ($n = 237$)	83 (34.9)	100 (61.7)	54 (80.6)	**3.01, 1.99–4.56, < 0.001**	**7.76, 4.00–15.03, < 0.001**
Proper generalized convulsive status epilepticus or nonconvulsive status epilepticus in coma ($n = 180$)	92 (38.7)	59 (36.4)	29 (43.3)	0.91, 0.60–1.37, 0.651	1.21, 0.70–2.10, 0.494
Severe impairment of consciousness ($n = 257$)	119 (50.0)	89 (54.9)	49 (73.1)	1.22, 0.82–1.82, 0.332	**2.72, 1.50–4.95, 0.001**
Status epilepticus severity score (median [range])	2 [0–5]	3 [0–6]	3 [1–6]	**1.61, 1.38–1.89, < 0.001**	**2.09, 1.66–2.62, < 0.001**
Charlson Comorbidity Index (median [range])	0.5 [0–10]	1 [0–9]	3 [0–8]	1.10, 1.01–1.21, 0.028	**1.29, 1.16–1.44, < 0.001**
Treatment latency > 1 hr ($n = 312$)	150 (63.0)	113 (69.8)	48 (71.6)	1.35, 0.88–2.07, 0.165	1.48, 0.82–2.68, 0.193
Therapeutic coma ($n = 50$)	10 (4.2)	27 (16.7)	13 (19.4)	**4.56, 2.14–9.71, < 0.001**	**5.49, 2.29–13.18, < 0.001**

RRR = relative risk ratio.
Significant values are given in bold.

TABLE 2. Demographics and Clinical Characteristic of Patients With and Without Therapeutic Coma

Variable	All Patients ($n = 467$) (%)	Patients Without Therapeutic Coma ($n = 417$) (%)	Patients With Therapeutic Coma ($n = 50$) (%)
Age (yr; mean ± SD)	60.3 ± 18.6	60.7 ± 18.5	57.2 ± 19.2
Female gender	228 (48.2)	204 (48.9)	24 (48)
Potentially fatal etiology	237 (50.7)	210 (50.4)	27 (54)
Status epilepticus severity score (median, range)	3 (0–6)	3 (0–6)	3 (1–6)
Type of status epilepticus			
Simple partial	91 (19.5)	91 (21.8)	
Absence	7 (1.5)	7 (1.7)	
Myoclonic	1 (0.2)	1 (0.2)	
Complex partial	154 (33.0)	144 (34.5)	10 (20.0)
GCSE then partial	34 (7.3)	30 (7.2)	4 (8.0)
Proper GCSE	155 (33.2)	130 (31.2)	25 (50.0)
Nonconvulsive status epilepticus in coma	25 (5.4)	14 (3.4)	11 (22.0)

GCSE = generalized convulsive status epilepticus.

concerning the specific anesthetics agents used for coma induction (**Table 3**).

The multivariable model showed that the risk for new disability was independently higher in patients with increasing age, lack of previous seizures, a potentially fatal etiology, and TC. Furthermore, age, potentially fatal etiology, STESS, CCI, and TC were independently associated with mortality (**Table 4**). The relationship between these predictors and mortality was also explored in the subgroups of patients with "proper" GCSE and NCSEC versus other SE forms (**Fig. 1**). After adjustment for the other predictors, TC for SE treatment was significantly related to outcome in both groups, but the effect magnitude tended to be higher among patients with complex partial SE forms at the time of treatment initiation.

Regarding the nested case-control assessment, among the 50 patients treated with TC, the prevalence of infectious complications was higher than in the 50 matched controls (31 vs 15; OR = 3.81; 95% CI, 1.66–8.75). Most (38; 64.4%) were lower respiratory tract infections, followed by urinary tract (11; 18.6%), and sepsis (10; 17%; some were combined in the same patient). Furthermore, the median acute hospital stay was significantly longer in the 37 patients discharged alive and managed with this approach than in the control group composed of 37 matched surviving subjects (16 d [range, 2–240] vs 9 d [range, 1–57]; $p < 0.001$; Wilcoxon).

DISCUSSION

The principal finding of this study is that TC administered for SE treatment is associated with a worse clinical outcome, including mortality, after taking into account the etiology and severity of the underlying condition; this relationship (class III evidence) appears stronger in patients with forms of SE other than "proper" GCSE and NCSEC. In addition, subjects treated with this approach displayed higher infection rates and longer acute hospital stay when discharged alive.

TC is advocated in current guidelines for management of SE, although its impact on functional outcome has not been clearly established, and somewhat surprisingly has received relatively little attention to date. This approach has been reported to be related to worse prognosis (10, 13), especially if lasting for many days (11), but not invariably (12) (although in this study interaction with SE refractoriness was not assessed). All these analyses

TABLE 3. Clinical Outcome in 50 Patients Categorized by the Anesthetics Used for Therapeutic Coma

Anesthetic	Return to Baseline ($n = 10$) (%)	New Disability ($n = 27$) (%)	Death ($n = 13$) (%)	p^a
Propofol	8 (80.0)	26 (96.3)	11 (84.6)	0.186
Midazolam	2 (20.0)	9 (33.3)	4 (30.8)	0.844
Thiopental	1 (10.0)	3 (11.1)	3 (23.1)	0.552
Ketamine	0 (0.0)	2 (7.4)	0 (0.0)	0.713

[a]Fisher exact test.

TABLE 4. Identified Variables Associated With Clinical Outcome in 467 Adults With Incident Status Epilepticus From the Fitted Multivariable Model

Variable	New Disability	Mortality
Age	**1.03 (1.01–1.05)**	**1.03 (1.01–1.05)**
Lack of previous seizures	**2.48 (1.49–4.15)**	1.35 (0.66–2.78)
Potentially fatal etiology	**2.72 (1.70–4.35)**	**7.2 (3.45–15.04)**
Status epilepticus severity score	1.12 (0.92–1.38)	**1.56 (1.17–2.10)**
Charlson Comorbidity Index	1.02 (0.92–1.13)	**1.18 (1.05–1.33)**
Therapeutic coma	**6.86 (2.84–16.56)**	**9.10 (3.17–26.16)**

Results are given as relative risk ratio and 95% CI, as compared to return to baseline clinical conditions. Variables with $p < 0.05$ in the univariable analysis were retained for the multivariable assessment. Significant values are given in bold.

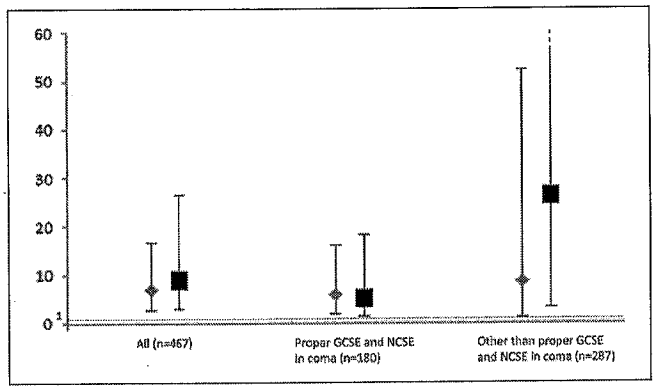

Figure 1. Adjusted relative risk ratios of therapeutic coma (*gray diamonds*: new disability; *black squares*: mortality). GCSE = generalized convulsive status epilepticus, NCSE = nonconvulsive status epilepticus.

had a retrospective design, and findings were not adjusted for all known outcome predictors, especially potentially fatal etiology; it is also at times unclear how recurrent cases were handled. Furthermore, in three of those studies (11–13), the analyzed cohort was exclusively composed of patients seen in ICUs, thus potentially limiting the generalizability; this is highlighted by the higher rate of administration of anesthetic agents (33–87%) and prevalence of GCSE and NCSEC (46–92%) as compared to the present cohort (11% and 46%, respectively).

In the present study, the prognostic impact of TC in 467 consecutive adult patients with incident SE was investigated after adjustment for all major prognostic factors, such as etiology (15, 20, 21), STESS (including age, seizures type, consciousness impairment, and history of previous seizures) (16, 17), and comorbid conditions assessed with the CCI (22, 23); of note, apart from the CCI, the aforementioned items were recorded prospectively. The combination of these variables has recently been shown to account for more than 90% of the mortality prediction (24); their predictive robustness is consistently found across studies (25) and seems further confirmed by our findings. We also adjusted for age and lack of previous seizures. TC was significantly related to outcome in the whole cohort, and this relationship turned out to be even more important in the subgroup of patients with forms of SE other than "proper" GCSE or NCSEC: the vast majority of patients in this group were diagnosed with complex partial SE, an SE form felt to be less dangerous in terms of prognostic implication (26–28).

There is an ongoing lively debate among experts about the need to proceed quickly to coma induction in patients with "nonconvulsive" SE (including complex partial) (29); some recent guidelines indeed recommend intensive care treatment with TC for RSE, without specifying whether specific forms need an adapted treatment (5). The present finding suggests in fact that this approach may prove especially harmful in such patients. To our knowledge, this is the first study investigating in detail the impact of TC on prognosis focusing on different forms of SE classified by semiology. Particularly, we differentiated "GCSE then focal" (those with focal seizures without coma on diagnosis, but having presented previously a generalized convulsion during the same episode) from "proper" GCSE (those presenting with prolonged generalized convulsions up to the SE diagnosis and treatment), as we hypothesized that the former might represent a form of SE with prognostic implications similar to complex partial SE. Our results, added to the aforementioned studies (10, 11, 13), seem thus to offer a rationale corroborating a relatively conservative therapeutic approach in patients without "proper" GCSE or NCSEC, in line with several expert opinions and recommendations suggesting to try additional nonsedating antiepileptic drugs before considering coma induction in these patients (4, 30–32).

A potential consequence of using TC relates to a higher risk of complications, such as infections, and longer hospitalizations. A recent study considering 160 subjects with SE in an ICU environment showed that infections were related to longer SE duration, longer ICU stay, higher risk of RSE, and higher mortality; the overall infection rate was 23% (33). This was confirmed in a recent analysis by the same group (13). Indeed, we also observed a significant higher infection rate in patients treated with TC. Hospitalization length has been suggested to increase in patients with SE needing airway intubation (34). Furthermore, among 54 patients with RSE, mean duration of coma was 11.0 days and mean hospital stay was 27.7 days (11); recently, a longer hospitalization in patients treated with coma induction was shown (13), but without accounting for bias resulting from mortality. In our nested case-control study, acute hospitalization was significantly longer among surviving

patients treated with TC compared with matched controls. This finding implies potential major practical consequences since prolonged hospitalization may expose patients to medical complications (33) and induce additional healthcare costs.

Our study has of course limitations. First, it is based on a single tertiary center cohort, and some data (such as CCI, acute hospital stay, and infection rates) were retrospectively retrieved. However, we used a prospective registry for all other data (representing the most important prognostic variables), with homogeneous assessment criteria over the entire recruitment period, and the retrospectively added data were recorded by the same author (N.A.M.), elements that in our view corroborate its internal validity. Furthermore, to the best of our knowledge, our study represents the largest cohort of SE adult patients, with the advantage of being representative of the SE population seen in a hospital, as it was not restricted to particular SE forms or an ICU environment: while of course patients with mechanical ventilation are found in the ICU, subjects with RSE managed outside the ICU were included in this study, as they represent a situation found in clinical practice (in fact, in our center patients not needing mechanical ventilation are mostly managed in intermediate care units). Second, as TC allocation was not randomized, we cannot formally exclude additional, not yet identified, confounding factors. Particularly, we acknowledge that patients treated with TC were probably felt more ill, in some way that might not always have been accounted for by the analyses. However, multivariate analyses were used to adjust for the most important known outcome predictors (which together account for over 90% of SE prognosis) (24), reducing this risk. Third, we investigated the effect of TC on functional outcome at hospital discharge, but we cannot exclude that long-term prognosis might have changed. Therefore, we also used mortality during the hospital stay, which represents a robust, nondebatable outcome. Additionally, our mortality rate of 14.3% corroborates the present findings, lying in the middle range as compared to several prospective, population-based studies (1, 2, 35). Fourth, treatment latency represents an estimate, as SE onset is sometimes subtle or unclear (especially in patients with out-of-hospital SE onset); nonetheless, there was no significant difference among the outcome groups, and it was not taken into account for the multinomial logistic regression (being nonsignificant in the univariable approach). Finally, we unfortunately do not have information regarding coma duration (but we retrieved hospitalization length in the nested case-control study), and specific EEG patterns, and we did not adjust for treatment options before TC; however, medication appropriateness seems to play a negligible role in the prognosis of SE (24, 36).

CONCLUSIONS

This study shows that TC is associated with mortality, poorer functional outcome, higher infection rates, and longer acute hospital stay after adjustment for the most important outcome predictors, and thus suggests caution in the straightforward use of this therapeutic approach, particularly in patients with complex partial SE at the moment of diagnosis. However, we acknowledge that factors such as severe impairment of consciousness with loss of airways protection or durable generalized convulsive seizure leading to neuronal injury may direct the risk-benefit scale in favor of TC. Accordingly, the use of this approach for patients with GCSE or NCSEC appears fully justified. Multicenter, prospective studies are needed to better identify which further category of patients with SE would take the best advantage from this approach, since the feasibility of a randomized trial in this setting unfortunately appears very unlikely (37).

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REFERENCES

1. DeLorenzo RJ, Hauser WA, Towne AR, et al: A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996; 46:1029–1035
2. Coeytaux A, Jallon P, Galobardes B, et al: Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 2000; 55:693–697
3. Lowenstein DH, Alldredge BK: Status epilepticus. *N Engl J Med* 1998; 338:970–976
4. Meierkord H, Boon P, Engelsen B, et al; European Federation of Neurological Societies: EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010; 17:348–355
5. Brophy GM, Bell R, Claassen J, et al; Neurocritical Care Society Status Epilepticus Guideline Writing Committee: Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012; 17:3–23
6. Novy J, Logroscino G, Rossetti AO: Refractory status epilepticus: A prospective observational study. *Epilepsia* 2010; 51:251–256
7. Holtkamp M, Othman J, Buchheim K, et al: Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 2005; 76:534–539
8. Ferlisi M, Shorvon S: The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain* 2012; 135(Part 8):2314–2328
9. Rossetti AO, Lowenstein DH: Management of refractory status epilepticus in adults: Still more questions than answers. *Lancet Neurol* 2011; 10:922–930
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. Hocker SE, Britton JW, Mandrekar JN, et al: Predictors of outcome in refractory status epilepticus. *JAMA Neurol* 2013; 70:72–77
12. Sutter R, Marsch S, Fuhr P, et al: Mortality and recovery from refractory status epilepticus in the intensive care unit: A 7-year observational study. *Epilepsia* 2013; 54:502–511
13. Sutter R, Marsch S, Fuhr P, et al: Anesthetic drugs in status epilepticus: Risk or rescue? A 6-year cohort study. *Neurology* 2014; 82:656–664
14. Lowenstein DH, Bleck T, Macdonald RL: It's time to revise the definition of status epilepticus. *Epilepsia* 1999; 40:120–122
15. Rossetti AO, Hurwitz S, Logroscino G, et al: Prognosis of status epilepticus: Role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry* 2006; 77:611–615
16. Rossetti AO, Logroscino G, Milligan TA, et al: Status Epilepticus Severity Score (STESS): A tool to orient early treatment strategy. *J Neurol* 2008; 255:1561–1566
17. Sutter R, Kaplan PW, Ruegg S: Independent external validation of the status epilepticus severity score. *Crit Care Med* 2013; 41:e475–e479

18. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987; 40:373–383
19. Quan H, Sundararajan V, Halfon P, et al: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43:1130–1139
20. Towne AR, Pellock JM, Ko D, et al: Determinants of mortality in status epilepticus. *Epilepsia* 1994; 35:27–34
21. Logroscino G, Hesdorffer DC, Cascino G, et al: Short-term mortality after a first episode of status epilepticus. *Epilepsia* 1997; 38:1344–1349
22. Koubeissi M, Alshekhlee A: In-hospital mortality of generalized convulsive status epilepticus: A large US sample. *Neurology* 2007; 69:886–893
23. Alvarez V, Januel JM, Burnand B, et al: Role of comorbidities in outcome prediction after status epilepticus. *Epilepsia* 2012; 53:e89–e92
24. Rossetti AO, Alvarez V, Januel JM, et al: Treatment deviating from guidelines does not influence status epilepticus prognosis. *J Neurol* 2013; 260:421–428
25. Sutter R, Kaplan PW, Rüegg S: Outcome predictors for status epilepticus–What really counts. *Nat Rev Neurol* 2013; 9:525–534
26. Drislane FW: Evidence against permanent neurologic damage from nonconvulsive status epilepticus. *J Clin Neurophysiol* 1999; 16:323–331; discussion 353
27. Kaplan PW: No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: "the cure may be worse than the disease"). *Neurophysiol Clin* 2000; 30:377–382
28. Meierkord H, Holtkamp M: Non-convulsive status epilepticus in adults: Clinical forms and treatment. *Lancet Neurol* 2007; 6:329–339
29. Jordan KG, Hirsch LJ: In nonconvulsive status epilepticus (NCSE), treat to burst-suppression: Pro and con. *Epilepsia* 2006; 47(Suppl 1):41–45
30. Holtkamp M, Masuhr F, Harms L, et al: The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: A survey among epileptologists and critical care neurologists. *J Neurol Neurosurg Psychiatry* 2003; 74:1095–1099
31. Ferguson M, Bianchi MT, Sutter R, et al: Calculating the risk benefit equation for aggressive treatment of non-convulsive status epilepticus. *Neurocrit Care* 2013; 18:216–227
32. Outin H, Blanc T, Vinatier I; le groupe d'experts: [Emergency and intensive care unit management of status epilepticus in adult patients and children (new-born excluded). Société de réanimation de langue française experts recommendations]. *Rev Neurol (Paris)* 2009; 165:297–305
33. Sutter R, Tschudin-Sutter S, Grize L, et al: Associations between infections and clinical outcome parameters in status epilepticus: A retrospective 5-year cohort study. *Epilepsia* 2012; 53:1489–1497
34. Spatola M, Alvarez V, Rossetti AO: Benzodiazepine overtreatment in status epilepticus is related to higher need of intubation and longer hospitalization. *Epilepsia* 2013; 54:e99–e102
35. Knake S, Rosenow F, Vescovi M, et al; Status Epilepticus Study Group Hessen (SESGH): Incidence of status epilepticus in adults in Germany: A prospective, population-based study. *Epilepsia* 2001; 42:714–718
36. Jaques L, Rossetti AO: Newer antiepileptic drugs in the treatment of status epilepticus: Impact on prognosis. *Epilepsy Behav* 2012; 24:70–73
37. Rossetti AO, Milligan TA, Vulliémoz S, et al: A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care* 2011; 14:4–10