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Etat de mal épileptique : traitements et facteurs pronostiques

THESE

préparée sous la direction du Docteur Andrea O. Rossetti

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par

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Rapport de Synthèse

L'état de mal épileptique est une condition médicale sévère fréquemment rencontrée dont la mortalité est importante. Son traitement représente donc une urgence médicale. Il a déjà été démontré par des études bien conduites (Treiman et al., 1998) que l'administration de benzodiazépines est efficace en première intention. Or, 35-45% des états de mal échappent à ce traitement et malheureusement, les données scientifiques concernant le traitement de deuxième ligne sont nettement moins consistantes. Par ailleurs, si le rôle pronostique des caractéristiques de l'état de mal (type de crise, étiologie, état de conscience, âge du patient) sont connues (Rossetti et al., 2006), (Neligan and Shorvon, 2011), le rôle des comorbidités n'a reçu que peu d'attention à ce jour.

Dans la première partie de ce travail publiée dans *Epilepsia* (Alvarez et al., 2011) nous nous sommes intéressé au traitement de deuxième ligne et principalement aux trois substances les plus prescrites : la phénytoine (PHT), le valproate (VPA) et plus récemment le lévétiracetam (LEV). A ce jour, aucune étude n'avait comparé l'efficacité de ces substances pourtant largement utilisées. Ainsi, afin de savoir lequel ces anti-épileptiques utilisés en 2ème ligne est le plus efficace, nous avons extrait de notre base de données regroupant tout les états de mal épileptiques traités au Centre Hospitalier Universitaire Vaudois, tous les épisodes durant lesquelles le traitement par benzodiazépines à échoué (187 épisodes). Nous avons ensuite comparé les différentes caractéristiques cliniques et les différents outcomes de trois groupes de patients (ceux qui ont reçu de la PHT, du VPA ou du LEV). Nous avons pu mettre ainsi en évidence certaines différences d'efficacité inconnues jusqu'alors entre le VPA et le LEV, impliquant une certaine prudence face à l'emploi grandissant de ce dernier.

La seconde partie de notre publiée dans *Epilepsia* (Alvarez et al., 2012) s'est portée sur les facteurs pronostiques de l'état de mal et plus précisément sur le rôle joué par les comorbidités. En utilisant la même base de données, nous avons pu démontrer que le pronostique d'un état de mal est très majoritairement influencé par l'étiologie et l'âge et que les comorbidités ne jouent qu'un rôle marginal. La présence de comorbidités n'impliquant pas forcément une mauvaise issue, la fragilité de certains patients ne doit pas dissuader les cliniciens à traiter adéquatement ces patients souffrant d'une condition aussi sévère qu'un état de mal épileptique.

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FULL-LENGTH ORIGINAL RESEARCH

Second-line status epilepticus treatment: Comparison of phenytoin, valproate, and levetiracetam

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Summary

Purpose: Phenytoin (PHT), valproic acid (VPA), or levetiracetam (LEV) are commonly used as second-line treatment of status epilepticus (SE), but comparative studies are not available.

Methods: Among 279 adult SE episodes identified prospectively in our tertiary care hospital over 4 years, we retrospectively identified 187 episodes in which PHT, VPA, or LEV were given after benzodiazepines. Patients with postanoxic SE were not included. Demographics, clinical SE features, failure of second-line treatment to control SE, new handicap, and mortality at hospital discharge were assessed. Uni- and multivariable statistical analyses were applied to compare the three agents.

Key Findings: Each compound was used in about one third of SE episodes. VPA failed to control SE in 25.4%, PHT in 41.4%, and LEV in 48.3% of episodes in which these were prescribed. A deadly etiology was more frequent in the VPA group, whereas SE episodes tended to be more severe in the PHT group. After adjustment for these known SE outcome predictors, LEV failed more often than VPA [odds ratio (OR) 2.69; 95% confidence interval (CI) 1.19–6.08]; 16.8% (95% CI: 6.0–31.4%) of second-line treatment failures could be attributed to LEV. PHT was not statistically different from the other two compounds. Second-line treatment did not seem to influence new handicap and mortality, whereas etiology and the SE Severity Score (STESS) were robust independent predictors.

Significance: Even without significant differences on outcome at discharge, LEV seems less efficient than VPA to control SE after benzodiazepines. A prospective comparative trial is needed to address this potentially concerning finding.

KEY WORDS: Epilepsy, Seizures, Intensive care neurology.

Status epilepticus (SE) represents a severe condition with significant mortality and morbidity (Coeytaux et al., 2000; Knake et al., 2001; Vignatelli et al., 2003), and its timely treatment is indicated to prevent potentially deleterious complications (Lowenstein & Alldredge, 1998). Unfortunately, high-level evidence is available only for the first-line medication; in particular, lorazepam has been shown to be more effective than phenytoin (PHT) or placebo (Treiman et al., 1998; Alldredge et al., 2001); therefore, intravenous benzodiazepines are recommended as an initial approach (Meierkord et al., 2010). However, because first-line therapy fails to control at least 35–45% of patients with SE (Treiman et al., 1998), additional treatments are needed, for whom convincing evidence is lacking. Historically, phenytoin (PHT) (Wallis et al., 1968; Pilz & Dreyer, 1969) has been used before valproic acid (VPA) (Sinha & Naritoku, 2000; Trinka, 2009) as a second-line agent. The Veterans Affairs study (Treiman et al., 1998) together with other smaller series (Misra et al., 2006; Gilad et al., 2008) showed that PHT is useful as first-line therapy, but comparative investigations using those compounds as second-line treatment after benzodiazepines are very scarce. A small prospective randomized study (Agarwal et al., 2007) analyzed PHT and VPA after diazepam failure and showed that both drugs were surprisingly highly effective (controlling SE in 88% and 84% of patients, respectively). More recently, levetiracetam (LEV) (Rossetti & Bromfield, 2006; Knake et al., 2008) and, to a much more limited extent, lacosamide (Kellinghaus et al., 2011) have also been described for this indication, but again without any comparison to other agents.

To address this relevant lack of information, we used our SE database to investigate the relative role of PHT, VPA,

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and LEV in the treatment of SE as second-line agents. We did not consider lacosamide, as it was marketed in Switzerland only in September 2009, whereas all other drugs were available before 2006.

Methods

Patients and procedures

We retrospectively analyzed data from a prospective registry including all patients treated at our center (tertiary hospital) over 4 years for SE between April 1, 2006 and March 31, 2010. Details on the registry were recently published in another study (Novy et al., 2010). Briefly, SE was defined as the continuous occurrence of seizures for >5 min, or repeated epileptic seizures without intercurrent baseline recovery. Seizures were diagnosed clinically, but formal electroencephalography (EEG) confirmation was required for nonconvulsive episodes. SE episodes were identified and screened by our neurologic consultants at the emergency unit and intensive care unit, and by the EEG staff. Subjects younger than 16 years old and patients with postanoxic SE were not included. We indentified all SE episodes in which a second-line treatment was prescribed.

Our protocol to treat SE starts with intravenous benzodiazepines (clonazepam 0.015 mg/kg or lorazepam 0.1 mg/kg), followed by a choice of PHT 20 mg/kg, VPA 20 mg/kg, or LEV 20 mg/kg; all are relayed by maintenance dosages (typically, 300–400 mg PHT, 1,000–2,500 mg VPA, or 1,000–3,000 mg LEV daily). The second-line treatment is typically administered within 1–30 min following benzodiazepines. Most of these drugs are given intravenously. Every case is discussed within 48 h with one or both senior epileptologists of our center to guide SE treatment after the application of the initial algorithm.

Variables

Age, gender, history of previous seizures, seizures type (partial vs. generalized), consciousness before treatment institution, treatments, and SE etiology were recorded prospectively. Consciousness was categorized as alert/confuse/somnolent versus stuporous/comatose. For each patient, a validated SE severity score (STESS) was calculated (Rossetti et al., 2008) and its scores categorized in ≥3 or <3 (Table 1). Etiology was considered "deadly" if leading to death if not specifically treated, as described previously (Rossetti et al., 2006), including: massive ischemic and hemorrhagic stroke, primary or secondary cerebral tumor, central nervous system (CNS) infection, severe autoimmune disease, AIDS with CNS complication, and metabolic disturbance sufficient to cause coma, eclampsia, and sepsis. We also categorized etiology as acute versus nonacute (Commission on Epidemiology and Prognosis, ILAE, 1993). The primary outcome was the failure of the second-line treatment, defined as the need to introduce a further compound to control SE. We considered SE as controlled if no change in antiepileptic medication was needed for at least 48 h after clinical and electrographic resolution. We developed a specific multilevel variable to define second-line treatment, where each compound represented one level of the variable (VPA being the reference, the second level was PHT, and the third was LEV). We also prospectively recorded, at hospital discharge, mortality (calculated using patients instead of episodes as denominator), new handicap (failure to return to baseline clinical conditions), or return to baseline.

Table 1. Status Epilepticus Severity Score (STESS), a favorable score is 0–2

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

[a]Complicating idiopathic generalized epilepsy.
Adapted from Rossetti et al. (2008).

Statistical analyses

Comparisons among the three treatment groups were performed using two-tailed Fisher's exact, chi-square, or analysis of variance (ANOVA) tests, as required. In order to adjust the results for possible confounders, variables with $p < 0.2$ were entered in stepwise logistic regressions using the outcome as dependent variable; goodness of fit was evaluated using a chi-square test. The population attributable fraction (PAF) of failure of the second-line treatment when using the worst acting agent was calculated using the formula (Miettinen, 1974; Hanley, 2001):

(Prevalence of patients exposed to the second-line treatment in the failure cases)
× ([odds ratio − 1]/odds ratio)

To perform a multivariate analysis and generate an adjusted estimate of the PAF of failure of the second-treatment, we determined the PAF for multiple levels of exposure defined as above.

Results

We indentified 198 SE episodes (representing 71% of 279 episodes in our database), occurring in 167 patients,

Table 2. Comparison of the groups of second-line treatment and the SE epilepticus characteristics

	VPA N = 59 (29.8%)	PHT N = 70 (35.4%)	LEV N = 58 (29.3%)	p-value (test)	Total N = 187 (%)
Deadly etiology	15 (25.4%)	39 (55.7%)	34 (58.6%)	<0.001 (χ^2)	88 (47.1%)
Acute etiology	27 (45.8%)	45 (64.3%)	39 (67.2%)	0.035 (χ^2)	111 (59.4%)
STESS ≥3	26 (44.1%)	49 (70.0%)	29 (50%)	0.007 (χ^2)	104 (55.6%)
Alert/confus/somnolent	28 (47.5%)	23 (32.9%)	29 (50%)	0.101 (χ^2)	70 (37.4%)
Stupor/coma	31 (52.5%)	47 (67.1%)	29 (50%)	0.101 (χ^2)	107 (57.2%)
GCSE + NCSEC	22 (37.3%)	41 (58.6%)	17 (29.3%)	0.002 (χ^2)	80 (42.8%)
No previous seizure	24 (40.7%)	48 (68.6%)	30 (51.7%)	0.006 (χ^2)	102 (54.5%)
Age: mean (SD)	64 (±18.9)	57.8 (±18.1)	66.1 (±14.9)	0.02 (ANOVA)	62.4 (±17.7)
Failure of second-line treatment	15 (25.42%)	29 (41.42%)	28 (48.27%)	0.032 (χ^2)	72 (38.5%)
New morbidity or death at discharge	25 (42.37%)	45 (64.28%)	39 (67.24%)	0.011 (χ^2)	109 (28.3%)
Mortality/patients	4/48 (8.4%)	17/64 (26.6%)	9/47 (19.1%)	0.045 (Fisher)	30/159 (18.7%)

GCSE, generalized convulsive status epilepticus; NCSE, nonconvulsive status epilepticus in coma; STESS, Status Epilepticus Severity Score; VPA, valproate; PHT, phenytoin; LEV, levetiracetam.

during which benzodiazepines were followed by a second-line agent. Only eight episodes (4%) lasted <30 min. Although in 11 episodes other oral agents were prescribed after failure of benzodiazepines (three received carbamazepine, three pregabalin, two lamotrigine, two gabapentin, and one phenobarbital), analysis was restricted to the 187 episodes in which PHT (70 episodes, 37%), VPA (59 episodes, 32%), or LEV (58 episodes, 31%) was used as second-line agents.

An overview of the treatment groups is presented in Table 2; several potentially important differences were observed. In the unadjusted analysis, patients treated with VPA had fewer unfavorable outcomes than the other two groups (failure of second-line agent, $p = 0.032$; new morbidity or death, $p = 0.011$; mortality, $p = 0.045$). VPA failed to control the SE in 25.4%, PHT in 41.4%, and LEV in 48.3%. In the 11 subjects who received others agents, this corresponded to 28% (3/11).

Patients with a deadly etiology ($p < 0.001$) and an acute etiology ($p = 0.035$) were more frequent in the LEV and PHT groups than in the VPA group, and subjects treated with VPA and LEV tended to have less severe SE episodes than patients of the PHT group ($p = 0.007$). The constitutive variables of the STESS (severe consciousness impairment, convulsive seizure, lack of previous seizures, higher age) were more frequently represented in the PHT group, except for age. Of note, treatment was started within an hour of symptoms onset in 48.5% of patients in the PHT, 30.5% in the VPA, and 29.5% in the LEV group ($p = 0.03$, chi-square; the difference between VPA and LEV being not significant). Discrepancies in SE severity and etiology may have played a major role regarding the outcomes; therefore, a multivariable approach was applied.

Logistic regression analyses were performed for the three outcomes, using VPA as the reference treatment (Table 3). All models showed an acceptable to excellent goodness of fit (second-line treatment failure: $p = 0.89$; new morbidity or mortality: $p = 0.38$; mortality: $p = 0.21$). After adjustments for SE severity and etiology, LEV was still related to a higher risk of second-line treatment failure as compared to VPA (OR 2.7, 95% CI 1.2–6.1). Treatment failures (PAF) attributable to the use of LEV corresponded to 16.8% (95% CI 6.0–31.4%), suggesting that 16.8% of second-line medication failures might have been avoided using VPA instead of LEV. PHT did not differ significantly from the other two compounds.

Table 3. Deadly etiology, Status Epilepticus Severity Score (STESS) ≥3, PHT and LEV compared with VPA with logistic regression for the different outcomes: failure of second-line treatment; new morbidity or death; and mortality

	OR	95% CI	p-Value
Failure of second-line treatment			
Deadly etiology	0.997	0.53–1.89	0.995
STESS ≥3	1.51	0.8–2.85	0.201
Treatment (ref VPA)			
PHT as second line	1.88	0.85–4.14	0.119
LEV as second line	2.69	1.19–6.08	**0.017**
New morbidity or death at discharge			
Deadly etiology	3.92	1.97–7.88	**<0.001**
STESS ≥3	3.83	1.95–7.52	**<0.001**
Treatment (ref VPA)			
PHT as second line	1.35	0.6–3.02	0.463
LEV as second line	1.98	0.86–4.57	0.109
Mortality			
Deadly etiology	3.69	1.47–9.3	**0.005**
STESS ≥3	3.56	1.32–9.61	**0.012**
Treatment (ref VPA)			
PHT as second line	1.34	0.43–4.12	0.607
LEV as second line	1.08	0.33–3.52	0.894

STESS, Status Epilepticus Severity Score; VPA, valproate; PHT, phenytoin; LEV, levetiracetam. Bold type, statistically significant values.

On the other side, the choice of the second-line treatment did not influence mortality and persistent morbidity at discharge (Table 3), whereas a STESS score ≥3 and a deadly etiology for the SE were strongly predictive for unfavorable outcome.

Discussion

As opposed to the few comparative studies investigating the administration of VPA and PHT in SE (Misra et al., 2006; Agarwal et al., 2007; Gilad et al., 2008), which despite several methodologic pitfalls suggest that these compounds are broadly comparable, LEV has not been tested against any other antiepileptic drug so far. This observational study suggests that the agent administered after benzodiazepines in patients with SE may influence the immediate treatment success, but not the outcome at hospital discharge: LEV seems to bear a higher risk of immediate treatment failure as compared to VPA, with 16.8% of treatment failures attributable to LEV, with PHT being in between.

It exists a paradox in the SE treatment, since practical and financial issues, and the position taken by regulatory authorities, render a prospective trial extremely difficult. A physician can choose among VPA, PHT, LEV, and even other compounds, in an almost complete absence of rational evidence, but cannot collect information to determine efficacy without getting informed consent from the patient, which in an emergency condition is extremely difficult. In order to attenuate the lack of information in this field, we, therefore, used a sort of "natural experiment," analyzing the real-world use of these compounds in SE and their efficacy,

In this cohort, PHT was prescribed slightly more often as a second-line drug, probably because of the historical experience with this substance (Wallis et al., 1968; Pilz & Dreyer, 1969); however, VPA and LEV were each used in almost 30% of episodes. This likely reflects clinician's preferences for these compounds in situations where local or cardiac toxicity of PHT (Craig, 2005), or the risk of pharmacokinetic interactions with PHT and VPA, might be at play (Knake et al., 2008).

Although treatment success rates after VPA were higher as compared to PHT and LEV in the univariate analysis, only the difference between VPA and LEV persisted after adjustment for etiology and SE severity (including age), two major predictors of SE outcome (Towne et al., 1994; Logroscino et al., 1997). Interestingly, the success rate among the 11 patients treated with other compounds was similar to that of VPA. It is unlikely that the observed differences resulted from systematic discrepancies in the loading or maintenance dosage of the second-line compounds. Actually, VPA was rather low-dosed in our hospital as compared to other series (Misra et al., 2006) and the most recent European guidelines (Meierkord et al., 2010), whereas PHT was given as recommended by the European guidelines (Meierkord et al., 2010); LEV was administered as previously reported in other centers (Knake et al., 2008; Berning et al., 2009) and the European guidelines (Meierkord et al., 2010), where loading doses of at least 1,000 mg and maintenance doses of about 2,000 mg are described. Furthermore, escalating LEV dosage beyond 3,000 mg/day has not been shown to provide any additional benefit (Rossetti & Bromfield, 2006). The fact that LEV was given orally in few subjects before its intravenous availability (June 2007) may theoretically have slowed its action; however, this occurred in only two patients, and they responded to the treatment. In fact, previous reports describe a definite effect after oral administration in SE (Rossetti & Bromfield, 2006).

STESS and deadly etiology were robust predictors for outcome at discharge, independently of the type of second-line treatment. This reflects convergent information from several studies (Towne et al., 1994; Logroscino et al., 1997; Rossetti et al., 2006), and suggests that various factors contribute to SE prognosis more than the specific antiepileptic therapy. In fact, differences in immediate SE control following the second-line drug might be "compensated" by the subsequent agent, suggesting that if the SE episode is per se treatable, it will respond to another drug. Again, it is tempting to assume that the biologic background represents the major prognostic determinant (Towne et al., 1994; Rossetti et al., 2006).

Our study has some limitations. Although we used a prospective database, data analysis was performed retrospectively for the purpose of this evaluation, and the treatment allocation was not randomized; therefore, we cannot exclude confounding factors. However, multivariable analyses were used to control for the most important known outcome predictors, including the STESS and the etiology; moreover, there was no significant difference in treatment delay between VPA and LEV. Less important predictors could not be assessed. These include adequacy of initial treatment with benzodiazepines, duration of SE, and timing of administration of second-line drugs. We did not specifically assess missed patients from the registry, but since in our hospital all subjects with a first seizure or SE suspicion have a neurologic consultation and an EEG, it is relatively unlikely that problems with case ascertainment had major influence on the results of this study. In our database, a second-line treatment was given more frequently (198/279 episodes = 70%) as compared to the first-line failure rates in published trials [35% for lorazepam (Lowenstein & Alldredge, 1998), 40% for lorazepam and 57% for diazepam (Alldredge et al., 2001), and 22% for lorazepam and 42% for diazepam (Leppik et al., 1983)]. We believe that several patients received a second-line agent shortly after benzodiazepines to prevent seizure recurrence (as it is commonly performed in clinical practice), leading to an overestimation of the efficacy of the three treatments. This reflects broadly used common practice (personal communications with several European and American SE special-

ists), and differs from the semiartificial trial settings. However, it is unlikely that a specific second-line agent was administered in case of "almost controlled" SE, generating a systematic bias. Furthermore, two senior epileptologists oversaw most of the treatment strategies, rendering unlikely a prescription bias by different physicians. The fact that in our series both PHT and VPA appeared less efficacious than previously reported (Agarwal et al., 2007) probably reflects a different etiologic and demographical profile (India vs. Switzerland). Finally, unfortunately our database does not allow extrapolating any estimation of specific side-effects related to the analyzed treatments, nor to retrieve specific drug dosages.

In conclusion, this study, which to the best of our knowledge represents the first comparison between PHT, VPA, and LEV in SE, suggests some caution in the use of LEV in this setting, pending a well-designed comparative trial. Despite several putative difficulties in patients' recruitment and organization, this approach appears clearly necessary to clarify this situation.

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Disclosure

Vincent Alvarez, Jean-Marie Januel and Bernard Burnand have nothing to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This work has been presented in part at the 21st ENS Meeting; Lisbon (P), May 28–31, 2011.

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BRIEF COMMUNICATION

Role of comorbidities in outcome prediction after status epilepticus

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Summary

Status epilepticus (SE) is associated with significant mortality and morbidity. A reliable prognosis may help better manage medical resources and treatment strategies. We examined the role of preexisting comorbidities on the outcome of patients with SE, an aspect that has received little attention to date. We prospectively studied incident SE episodes in 280 adults occurring over 55 months in our tertiary care hospital, excluding patients with postanoxic encephalopathy. Different models predicting mortality and return to clinical baseline at hospital discharge were compared, which included demographics, SE etiology, a validated clinical Status Epilepticus Severity Score (STESS), and comorbidities (assessed with the Charlson Comorbidity Index) as independent variables. The overall short-term mortality was 14%, and only half of patients returned to their clinical baseline. On bivariate analyses, age, STESS, potentially fatal etiologies, and number of preexisting comorbidities were all significant predictors of both mortality and return to clinical baseline. As compared with the simplest predictive model (including demographics and deadly etiology), adding SE severity and comorbidities resulted in an improved predictive performance (C statistics 0.84 vs. 0.77 for mortality, and 0.86 vs. 0.82. for return to clinical baseline); comorbidities, however, were not independently related to outcome. Considering comorbidities and clinical presentation, in addition to age and etiology, slightly improves the prediction of SE outcome with respect to both survival and functional status. This analysis also emphasizes the robust predictive role of etiology and age.

KEY WORDS: Predictors, Charlson Comorbidity Index, Prognosis, Etiology, Age.

Status epilepticus (SE) represents a severe medical condition (Neligan & Shorvon, 2011); some independent predictors of dismal outcome have been identified, such as acute or potentially fatal etiology, advanced age, de novo presentation, and impairment of consciousness before treatment (Towne et al., 1994; Logroscino et al., 1997; Rossetti et al., 2006). However, these variables encompass only a limited aspect of the clinical background. In fact, the role of previously existing medical problems has received far less attention.

We undertook this analysis to investigate how comorbidities influence SE outcome in addition to other known predictors.

Methods

Patients and procedures

We analyzed a prospective registry including all adult patients (16 years and older) with SE admitted to our tertiary hospital between April 1, 2006 and October 31, 2010 (55 months). Details may be found elsewhere (Novy et al., 2010). Briefly, SE was defined as the continuous occurrence of seizures for >30 min (until 2008), and 5 min (since 2008), as suggested by the operational definition (Lowenstein et al., 1999). Seizures were diagnosed clinically, but electroencephalography (EEG) confirmation (at least 20-min recordings with background reactivity evaluation) was required for nonconvulsive events. SE episodes were identified by the neurologic consultants at our emergency and intensive care units, and by the EEG medical staff. Patients with postanoxic SE were not included in the cohort. Only incident cases were considered, to allow every SE episode an equal chance to reach all possible outcomes. This study was approved by our ethics commission.

Variables

Demographics, history of previous seizures, worst seizures type, level of consciousness before treatment, pharmacologic treatments, and SE etiology were recorded prospectively. The Status Epilepticus Severity Score (STESS), a validated SE clinical severity score, including age, history of previous seizures, seizure type, and consciousness was calculated (0–6 points) (Rossetti et al., 2008) (Table S1) and categorized in ≥3 (bad outcome

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prediction) versus <3 (good outcome prediction). Etiology was considered "potentially fatal" if potentially leading to death and not specifically treated, as described previously (Rossetti et al., 2006).

The Charlson Comorbidity Index (CCI), a validated score of 19 different medical conditions (Table S2), was used to assess the comorbidities (Charlson et al., 1987). CCI was calculated after discharge, based on the medical files, by identification of all comorbid conditions present on admission (except SE etiology). The CCI was categorized in three groups: CCI = 0, CCI = 1–2, and CCI ≥3; in addition, we analyzed every medical condition as an individual variable. The clinical condition at hospital discharge represented the primary outcome; information on clinical condition was obtained prospectively and categorized into return to clinical baseline (premorbid functional and neurologic status), new impairment or death.

Statistical analyses

Potential predictors were analyzed for their relationship with the outcomes "return to baseline" and "mortality" using chi-square (χ^2) tests. Stepwise logistic regressions were performed to generate predictive models using potential predictors, including demographics, SE severity, etiology, and comorbidities. Age was dichotomized at 65 years; of note, because the STESS includes age, the latter was omitted in models considering this score. Discrimination power was assessed using the C statistics and 95% confidence intervals (Cis), and goodness of fit with the Hosmer-Lemeshow χ^2 test; the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values were used as a rough comparison of the models among them, whereas formal comparisons among receiver operating characteristic (ROC) curves were performed using a nonparametric approach. For multiple comparisons, we conservatively applied Bonferroni corrections to obtain a global $p < 0.05$. Analyses were performed with version 9 of the Stata software (StataCorp, College Station, TX, U.S.A.).

Results

Among 335 SE events recorded during the study period, we indentified 280 incident episodes. Demographics and most relevant clinical variables of the cohort are illustrated in Table 1. Twenty episodes (7%) lasted between 5 and 29 min. Gender was evenly distributed, the mean age (± standard deviation [SD]) was 59.3 (±18.5) years, and 59% of patients had a de novo SE episode. Slightly more than one half of the patients displayed a severely impaired consciousness (only 2.5% had a nonconvulsive status epilepticus in coma), or potentially fatal SE etiologies. Among the most frequent causes, 13.9% of SE were symptomatic of primary brain tumor or meningioma, 12.9% had a central nervous system hemorrhage, 9.7% were symptomatic of an old stroke; and 9.6% had a cryptogenic SE. In 55.4% of patients a severe SE was retained (STESS ≥3); 10.7% of patients received coma induction for SE treatment. About one-third of patients did not have any prior comorbidity, whereas one-third had a moderate, and the last third presented a high comorbidity index.

The overall short-term mortality was 14%, and only half of patients returned to baseline conditions at hospital discharge. Bivariate analyses demonstrated that age, STESS, potentially fatal etiologies, and an increased number of comorbidities were significant predictors of both outcomes, whereas gender was not (for more details, see Table S3).

With respect to in-hospital mortality, calibrations for all models were acceptable and are illustrated in Fig. 1A; the comparison of the six models did not show any statistically significant difference ($p = 0.1325$, χ^2) (for more details about model's calibration, see Table S4A). Pairwise analyses were performed using $p < 0.017$ (according to the Bonferroni's correction: 0.05/3) as a significant threshold. Compared to the simplest model (model 0), the model including the STESS (model 1, $p = 0.166$, χ^2) and the best model including CCI (model 3, $p = 0.064$, χ^2) were not sta-

Table 1. Tertiary care hospital SE patients' demographics and clinical characteristics

	Number (proportion)
Demographic data	
Gender (male)	139 (49.6%)
Age (SD)	59.3 (18.5)
Presence of previous seizures	115 (41%)
Severe conscious impairment (stuporous or comatose) before treatment	159 (56%)
Deadly etiology	129 (46%)
STESS ≥3	155 (55.4%)
Coma induction for SE treatment	30 (10.7%)
Charlson Comorbidity Score (%)	
0	75 (26.8)
1 or 2	100 (35.7)
≥3	105 (35.5)
Comorbidities (according to Charlson et al., 1987) (%)	
Cerebrovascular disease	61 (21.8)
Any tumor	58 (20.7)
Chronic pulmonary disease	31 (11)
Solid metastatic tumor	31 (11)
Congestive heart disease	25 (8.9)
Moderate/severe renal disease	23 (8.2)
Dementia	22 (7.9)
Myocardial infarction	21 (7.5)
Peptic ulcer	21 (7.5)
Peripheral vascular disease	18 (6.4)
Hemiplegia	16 (5.7)
Moderate/severe liver disease	14 (5)
Mild liver disease	11 (3.9)
Diabetes	9 (3.2)
HIV	6 (2.1)
Connective tissue disease	4 (1.4)
Lymphoma	4 (1.4)
Diabetes with organ damage	2 (0.7)
Leukemia	2 (0.7)

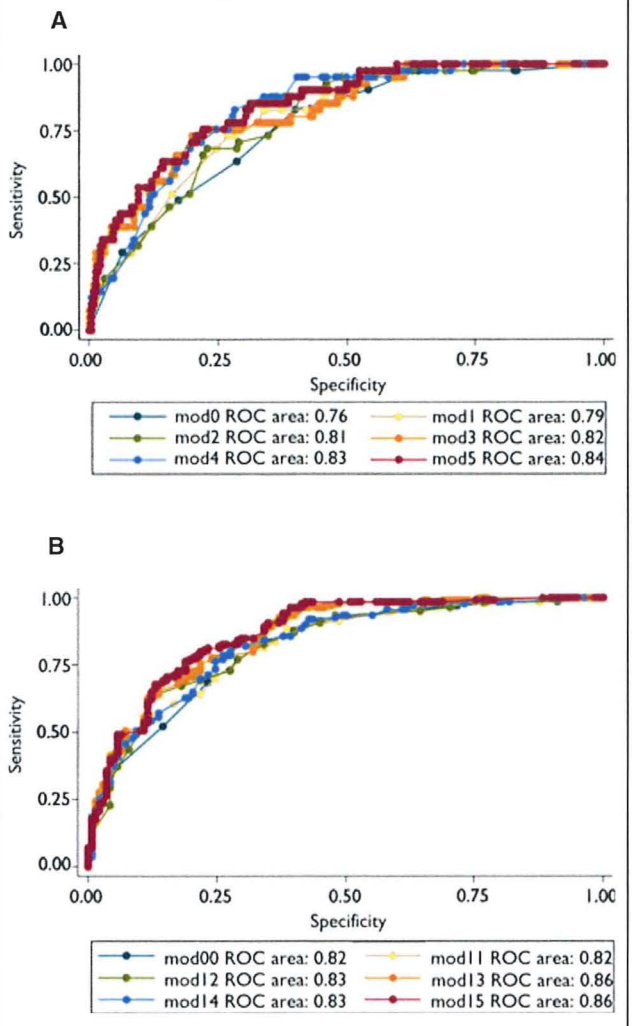

Figure 1.
Comparison of six predictive models (with model's construction). (**A**) For the outcome "mortality": *model 0*: Gender, age, potentially fatal etiology; *model 1*: Gender, potentially fatal etiology, STESS; *model 2*: Gender, age, potentially fatal etiology, categorized CCI; *model 3*: Gender, age, potentially fatal etiology, each variable of CCI; *model 4*: Gender, potentially fatal etiology, STESS, categorized CCI; *model 5*: Gender, potentially fatal etiology, STESS, each variable of CCI. (**B**) For the outcome "Return to base line": *model 00:* Gender, age, potentially fatal etiology; *model 11:* Gender, potentially fatal etiology, STESS; *model 12*: Gender, age, potentially fatal etiology, categorized CCI; *model 13:* Gender, age, potentially fatal etiology, each variable of CCI; *model 14:* Gender, potentially fatal etiology, STESS, categorized CCI; *model 15:* Gender, potentially fatal etiology, STESS, each variable of CCI.

tistically different. The model including both STESS and CCI was better (model 5, p = 0.0158, χ^2) as showed a slight improvement of the ROC curve area (0.77 vs. 0.84).

We used a similar approach for return to baseline clinical condition (Fig. 1B). All models' calibrations were acceptable, except for model 15 (for more details about model's calibration, see Table S4B). The comparison of the six models indicated some heterogeneity (p = 0.0403, χ^2). The best model, including CCI (model 13), was better than the simplest model (model 00, p = 0.0043, χ^2), corresponding to a modest improvement of the ROC curve area (0.82 vs. 0.86).

To summarize, the best predictive models included etiology, STESS, and each variable of the CCI for mortality (model 5), and demographics, etiology, and each variable of the CCI for return to clinical baseline conditions (model 13).

Discussion

This study shows that medical comorbidities increase relatively marginally the prediction accuracy of SE outcome, and confirms that age and etiology are robust outcome prognosticators in this setting.

Our results are in line with those of previous studies performed on different cohorts (Towne et al., 1994; Logroscino et al., 1997; Rossetti et al., 2006) that identified age and SE etiology as the main independent outcome predictors. In addition, one recent work suggested that patients with a higher number of comorbid conditions have a worse outcome (Koubeissi & Alshekhlee, 2007). However, this large data-based study, focused on convulsive SE, has important limitations: Its design included a retrospective identification of subjects with SE, and assessment of their comorbidities was based on International Classification of Diseases (ICD) diagnoses (Rossetti & Logroscino, 2008). Furthermore, the short-term mortality of 3% seems unusually low in this clinical setting, and concomitant medical diagnoses were identified only as independent prognostic factors, without any specific analysis addressing their added value in prognostic models including other major predictors.

Regarding etiology, because SE is often one of the clinical manifestations of brain injury, it seems logical that the nature of that injury will markedly influence prognosis. Massive and irreversible damage predicts per se a devastating outcome, whereas reversible conditions such as anticonvulsant drug withdrawal may herald a more favorable outcome after SE. As outlined previously (Rossetti et al., 2006; Novy et al., 2010), "acute etiologies" are less robust in predicting outcome than "potentially fatal" etiologies; this may be related to the fact that the latter encompass those acute and progressive symptomatic etiologies that are more dangerous for the patient.

Our study is limited to a hospital-based cohort, but since SE represents a condition that is predominantly treated at hospitals, this aspect should not affect our results. The second limitation lies in the fact that we investigated only the effect of comorbidities on prognosis at hospital discharge, but we cannot exclude that long-term prognosis may be influenced by comorbidities. The strength of our study builds on its prospective design, and the use of clearly

defined inclusion criteria. Our mortality rate (14%), which is in the middle range of population-based assessments in Europe and the United States over the last two decades—7% (Coeytaux et al., 2000) and 22% (DeLorenzo et al., 1996)—corroborates our findings. Finally, any score may not reflect exactly the clinical background of a patient, but because the CCI is widely used and validated, it seems to be a reasonable choice to represent patient's comorbidities.

In conclusion, comorbidities and the clinical presentation seem to affect the outcome of SE in a relatively marginal way, whereas age and etiology appear as robust and widely applicable predictors. This emphasizes the importance of a thorough search for the underlying cause of SE in the clinical setting. In addition, because the presence of comorbidities does not necessarily predict a bad outcome, this should not dissuade physicians from treating patients with SE and comorbid conditions appropriately. Obviously, comorbidities are important regarding contraindications and side effects of antiepileptic drugs. In this regard they may influence the outcome by influencing the utilization of specific treatments.

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Disclosure

Vincent Alvarez, Jean-Marie Januel, and Bernard Burnand have nothing to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Status Epilepticus Severity Score (STESS); a favorable score is 0–2.

Table S2. Charlson Comorbidity Index.

Table S3. Overview of the outcomes' predictors of SE in tertiary care patients (bivariate analyses).

Table S4. Summary of models construction, discrimination, calibration, and comparisons in patients with SE in tertiary care hospitals.

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Supporting information:

Table S1: Status Epilepticus Severity Score (STESS), a favorable score is 0–2. Adapted from Rossetti et al., 2008a

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

* complicating idiopathic generalized epilepsy

Table S2: Charlson Comorbidity Index. Adapted from Charlson et al., 1987

Assigned weights for diseases	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheric vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor (incl.):
	• Leukemia
	• Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Table S3: Overview of the outcomes' determinants of SE in tertiary care patients (bivariate analyses)

	Mortality			Return to baseline		
	yes = 41 (14%)*	**no = 239 (86%)***	**p value (χ2)**	**no = 140 (50%)***	**yes = 140 (50%)***	**p value (χ2)**
Age ≥ 65	26 (63.4%)**	96 (40.1%)**	**0.006**	84 (60%)**	38 (27.1%)**	**<0.001**
Male Gender	20 (48.8%)	119 (49.8%)	0.905	63 (45%)	76 (54.3%)	0.12
STESS ≥3	35 (85.4%)	120 (50.2%)	**<0.001**	104 (74.3%)	51 (36.4%)	**<0.001**
Potentially fatal etiology	34 (82.9%)	95 (39.7%)	**<0.001**	96 (68.6%)	33 (23.6%)	**<0.001**
Charlson Comorbitiy Index						
0	6 (14.6%)	69 (28.9%)		24 (17.1%)	51 (36.4%)	
1 & 2	8 (19.5%)	92 (38.5%)		47 (33.6%)	53 (37.9%)	
≥3	27 (69.9%)	78 (32.6%)	**<0.001**	69 (49.3%)	36 (25.7%)	**<0.001**

* Row percentages
** Column percentages

Table S4: Summary of models construction, discrimination, calibration and comparisons in tertiary care hospitals SE patients:

- 4A Determinants of mortality

MODELS	Model discrimination		Model Calibration		Model comparisons	
	C-statistic	(95% CI)	X^2	P	AIC	BIC
Model 0 : Gender, age, potentially fatal etiology	0.77	0.7 – 0.841	5.28	0.5	206	220
Model 1 : Gender, potentially fatal etiology, STESS	0.80	0.739 -0.862	5.38	0.716	198	212
Model 2 : Gender, age, potentially fatal etiology, categorized Charlson Comorbidity Index	0.81	0.742 -0.874	7.12	0.52	201	223
Model 3 : Gender, age, potentially fatal etiology, each variable of Charlson Comorbidity Index	0.82	0.757 – 0.887	11.39	0.18	216	285
Model 4 : Gender, potentially fatal etiology, STESS, categorized Charlson Comorbidity Index	0.83	0.769 – 0.885	6.73	0.56	193	215
Model 5 : Gender, potentially fatal etiology, STESS, each variable of Charlson Comorbidity Index	0.84	0.785 – 0.902	3.3	0.914	209	277

MODELS	Model discrimination		Model calibration		Model comparisons	
	C-statistic	(95% CI)	X^2	P	AIC	BIC
Model 00 : Gender, age, potentially fatal etiology	0.82	0.766 – 0.863	4.42	0.619	298	313
Model 11 : Gender, potentially fatal etiology, STESS	0.82	0.773 – 0.869	4.1	0.847	296	310
Model 12 : Gender, age, potentially fatal etiology, categorized Charlson Comorbidity Index	0.82	0.775 – 0.872	9.24	0.322	298	320
Model 13 : Gender, age, potentially fatal etiology, each variable of Charlson Comorbidity Index	0.86	0.818 – 0.902	11.62	0.169	294	366
Model 14 : Gender, potentially fatal etiology, STESS, categorized Charlson Comorbidity Index	0.83	0.781 – 0.876	4.17	0.841	294	316
Model 15 : Gender, potentially fatal etiology, STESS, each variable of Charlson Comorbidity Index	0.87	0.827 – 0.910	18.45	0.01	292	365