neurocritical care society Neurocrit Care (2013) 18:216–227
DOI 10.1007/s12028-012-9785-y

Calculating the Risk Benefit Equation for Aggressive Treatment of Non-convulsive Status Epilepticus

Matthew Ferguson · Matt T. Bianchi · Raoul Sutter · Eric S. Rosenthal · Sydney S. Cash · Peter W. Kaplan · M. Brandon Westover

Published online: 11 October 2012

Abstract
Objective To address the question: does non-convulsive status epilepticus warrant the same aggressive treatment as convulsive status epilepticus?
Methods We used a decision model to evaluate the risks and benefits of treating non-convulsive status epilepticus with intravenous anesthetics and ICU-level aggressive care. We investigated how the decision to use aggressive versus non-aggressive management for non-convulsive status epilepticus impacts expected patient outcome for four etiologies: absence epilepsy, discontinued antiepileptic drugs, intraparenchymal hemorrhage, and hypoxic ischemic encephalopathy. Each etiology was defined by distinct values for five key parameters: baseline mortality rate of the inciting etiology; efficacy of non-aggressive treatment in gaining control of seizures; the relative contribution of seizures to overall mortality; the degree of excess disability expected in the case of delayed seizure control; and the mortality risk of aggressive treatment.
Results Non-aggressive treatment was favored for etiologies with low morbidity and mortality such as absence epilepsy and discontinued antiepileptic drugs. The risk of aggressive treatment was only warranted in etiologies where there was significant risk of seizure-induced neurologic damage. In the case of post-anoxic status epilepticus, expected outcomes were poor regardless of the treatment chosen. The favored strategy in each case was determined by strong interactions of all five model parameters.
Conclusions Determination of the optimal management approach to non-convulsive status epilepticus is complex and is ultimately determined by the inciting etiology.

Keywords Non-convulsive status epilepticus · Risk benefit analysis · NCSE · Decision analysis

Electronic supplementary material The online version of this article (doi:10.1007/s12028-012-9785-y) contains supplementary material, which is available to authorized users.

M. Ferguson · M. T. Bianchi · E. S. Rosenthal · S. S. Cash · M. B. Westover
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

M. Ferguson
e-mail: gferguson1212@gmail.com

M. T. Bianchi
e-mail: mtbianchi@partners.org

E. S. Rosenthal
e-mail: erosenthal@partners.org

R. Sutter
Division of Neurosciences Critical Care, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: rsutter3@jhmi.edu

R. Sutter · P. W. Kaplan
Department of Neurology, Johns Hopkins Bayview Medical Center, Baltimore, MD, USA
e-mail: pkaplan@jhmi.edu

M. B. Westover (✉)
Wang 7 Neurology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA
e-mail: mb.westover@gmail.com; mwestover@partners.org

Introduction

The equation that has not yet been calculated is whether the small incidence of permanent cognitive side effects constitutes a greater morbidity than the small incidence of respiratory suppression, hypotension, cardiac

dysrhythmia, or even deaths which have followed the use of intravenous antiseizure medications [1].

Non-convulsive status epilepticus (NCSE) is an important consideration in the neurologic patient with impaired consciousness, yet the optimal approach to treatment remains a matter of debate [1–6]. By comparison, there is general agreement that refractory *convulsive* status epilepticus should be managed by aggressive measures, including intubation and high-dose intravenous anesthetic medications. The uncertainty surrounding management of NCSE involves several key clinical variables, including the morbidity and mortality expected from the inciting condition; the relative contributions of underlying etiology versus NCSE itself to the overall morbidity and mortality; the spectrum of electrographic patterns of NCSE and their differing potential to cause or exacerbate brain injury; the risks associated with aggressive ICU-level management (which interact with general medical health and age); and factors associated with non-aggressive approaches such as delayed diagnosis and/or resolution of NCSE.

To investigate the interplay of factors influencing NCSE management decisions, we develop a decision tree for the problem. We apply this model to four neurologic conditions commonly complicated by NCSE and known for having distinct clinical profiles in terms of treatment response, morbidity, and mortality [7, 8]: absence epilepsy, antiseizure-medication non-compliance, intraparenchymal hemorrhage (IPH), and hypoxic ischemic encephalopathy. Where published data are available, we use these data to set model parameters. Where data are lacking, we perform sensitivity analyses over a range of values to determine which values favor aggressive versus non-aggressive treatment. This analytic approach provides a practical framework in which to consider NCSE management strategies and highlights areas in critical need of further research.

Methods

Decision Model Structure

The model considers two treatment strategies for NCSE: (1) aggressive treatment, including admission to an intensive care unit (ICU), endotracheal intubation (if not already performed), and induction of pharmacological coma with close clinical and physiologic monitoring; and (2) non-aggressive treatment, limited to non-sedating anticonvulsants without specified admission to an ICU and without intubation or ventilation for the express purpose of achieving anesthetic levels that facilitate electrographic burst suppression. Aggressive treatment is assumed to immediately suppress seizure activity, whereas non-aggressive treatment incurs a longer duration of NCSE. Conceptually, the decision between aggressive and non-aggressive treatment occurs after 30 min of attempting to control NCSE with first-line non-sedating antiepileptic drugs (AEDs). Outcomes are expressed in terms of quality of life (QOL) based on long-term neurologic disability (see below). With the hypothesis that the marginal benefit of aggressive management would vary in a disease-specific manner, we separately considered four different etiologies for NCSE with distinct clinical characteristics: hypoxic-ischemic encephalopathy (HIE), IPH, discontinuation of antiepileptic drugs (dAED), and absence epilepsy. 3-month functional outcomes are presumed, a sufficient duration to permit stable rates of mortality and functional outcome to emerge.

We considered five variables to incorporate in our model of NCSE management: (1) baseline mortality rate for specific etiologies of NCSE, (2) efficacy of non-aggressive treatment, (3) impact of etiology on outcome, (4) excess disability attributable to delayed seizure control, and (5) mortality risk of aggressive treatment. Note that these variables represent "compound" factors, in that each is intended to capture the influence of multiple factors that may differ from patient to patient. For example, the baseline mortality and functional outcome in IPH survivors depends on hemorrhage volume and location, age, and pre-IPH cognitive impairment [9]. Sensitivity analysis of these five variables affords case-by-case clinical judgment to interact with the formal modeling presented here. Although we derived our base-case assumptions from population-level parameter values, in practice these values may be refined (formally or informally) based on patient-specific factors and clinical experience [9, 10]. Table 1 lists the values of these variables for the base-cases. The justification for these variable choices and their chosen values are given in the next section. A qualitative description of the relationships between model variables is provided in Fig. 1B.

Review of the Data and Choice of Model Parameters

Baseline Mortality Rates for Specific Etiologies of NCSE

Age, medical comorbidities, and duration of NCSE are important determinants of mortality in all forms of status epilepticus. While the inciting etiology is believed to play the dominant role [7, 11–16], overall mortality for each etiology reflects complex interactions between these factors [10, 17]. Baseline mortality rates in our model were adopted from published reports in which each base-case etiology was complicated by NCSE, as follows: ASE produces minimal if any long-term morbidity or mortality

Table 1 Data required in the analysis: probabilities, significance weights, and QOL

Etiology	Absence epilepsy	Discontinuation of anti-seizure medication	Intraparenchymal hemorrhage	Hypoxic ischemic encephalopathy
Model parameters				
%Baseline mortality	1	10	30	90
Weighting of etiology vs NCSE	1:10	1:10	5:1	10:1
%Mortality of aggressive treatment	20	20	20	20
%With disability incurred by delay	1	20	20	20
%Efficacy of non-aggressive treatment	99	70	25	10
Survivor baseline outcome distribution (%)				
Mild/No disability	100	100	44	16
Moderate disability	0	0	30	42
Severe disability	0	0	26	42

[18–20], thus we assumed a baseline mortality of <1 %. Baseline mortality for dAED was assumed to be 10 % [13], and for IPH complicated by NCSE, 30 % [21]. Prognosis for postanoxic status epilepticus (PSE) (with or without myoclonus) is generally poor; we assumed a baseline mortality of 90 % [22–24]. In the model, these values are taken as estimates of typical overall mortality in the *absence* of effective seizure treatment. However, expected mortality rates vary greatly in individual cases depending on case severity, e.g., mortality can exceed 90 % for large volume IPH [9, 25]. The effects of variation in baseline mortality rates are addressed by sensitivity analysis of the baseline mortality risk.

Baseline Functional Outcomes

As with mortality, our model assumes distinct distributions of outcomes in the absence of effective treatment for distinct etiologies. We classified outcomes by means of Glasgow Outcome Score (GOS) [26, 27], and assigned each of these a corresponding QOL using health state values from previously published decision analyses [28–30], as follows: GOS = 3 (functional dependence) was assigned QOL = 0.11; GOS = 4 (functional independence) was assigned QOL = 0.75; and GOS = 5 (good recovery without significant long-term disability) was assigned QOL = 1. Justifications for the distributions adopted for each etiology considered in our model are given below.

Absence status epilepticus (ASE), typified by spells in which patients exhibit a "trancelike" state with decreased/slowed responses [18, 19], and variable motor manifestations (e.g., myoclonus, rhythmic eyelid blinking, or quivering of the lips and face [18]), is generally considered to cause little if any lasting cognitive deficits [1, 18, 31], possibly because the key mechanism of epileptic activity is not excitotoxic [32, 33]. For example, patients with prolonged ASE have been reported in a duration exceeding 9 years without apparent neurocognitive sequelae [34]. Moreover, the inciting factors for ASE are relatively benign and typically reversible, e.g. menstruation, missed doses of medication, hypoglycemia, hyperventilation, flashing or bright lights, sleep deprivation, excessive physical exertion, or emotional stress [18, 35]. Accordingly, we assumed 100 % of survivors achieve a QOL = 1.

Similarly, we assumed 100 % good outcomes and 0 % with moderate or severe disability as the baseline outcome distribution of NCSE due to AED discontinuation (dAED) (i.e., in the case of rapid control of NCSE); in other words, we assume that the inciting factor in this situation is generally benign, and that any long-term morbidity among survivors is due to delayed seizure control. For IPH, we assumed a distribution of no, moderate, or severe long-term disability of 44, 30, and 26 %, respectively, based on published data [28], though outcome expectations may be refined based on individual case features (e.g., hemorrhage size). Finally, for PSE, based on a recent series of 111 patients with postanoxic coma with NCSE, we assumed a baseline outcome distribution of 16, 42, and 42 %, where the ordering is as above. % (no, moderate, or severe long-term disability) [78].

Contributions of NCSE to Mortality and Morbidity

ASE generally leads to no detectable morbidity or mortality [18–20, 31, 35]. By contrast, symptomatic nonconvulsive seizures and NCSE (e.g., after IPH, anoxia, missed AEDs, etc.) are associated with high mortality rates, approaching 70 %; [36]. Hospital stays are longer, and most survivors show significant deterioration on functional

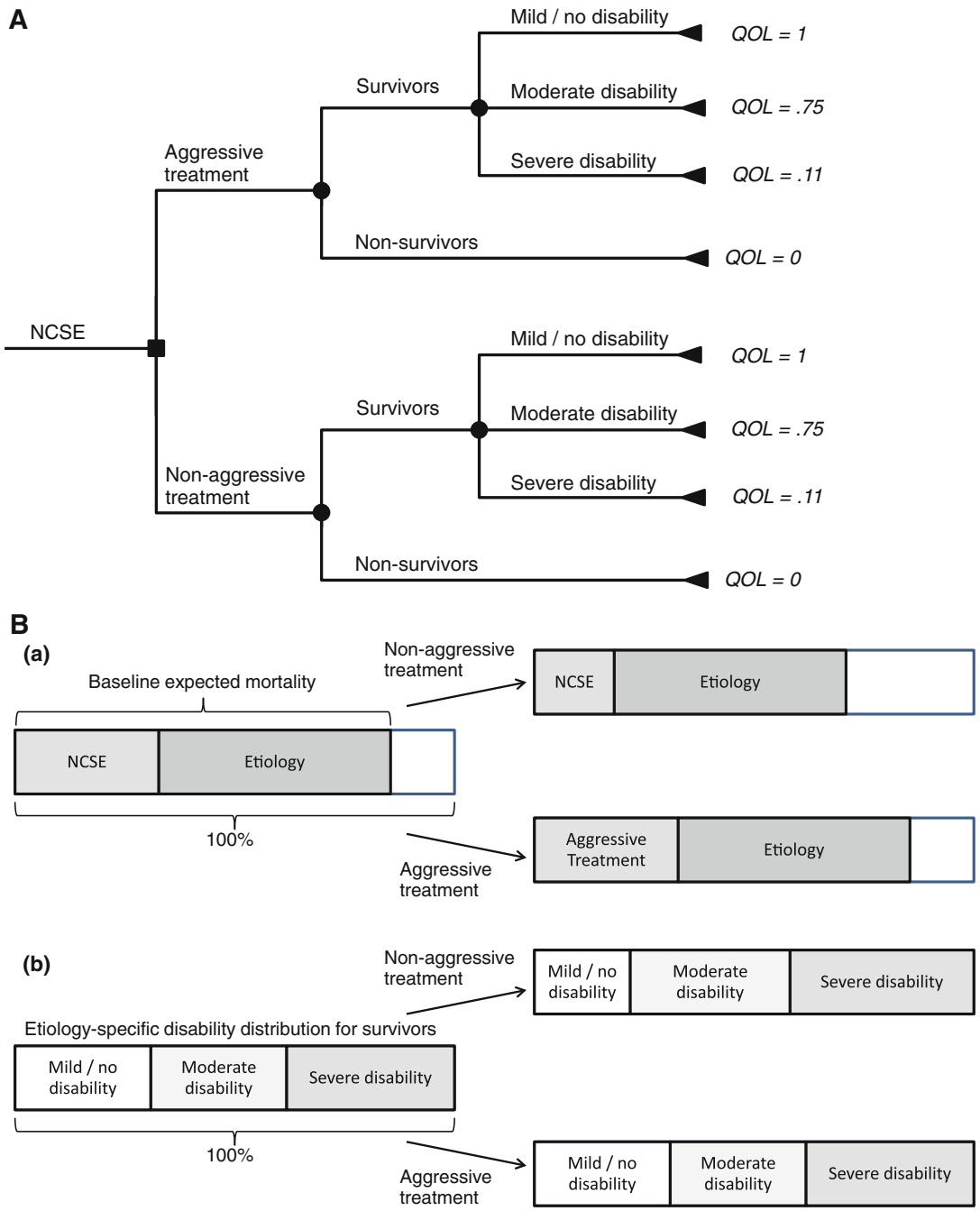

Fig. 1 **A.** Decision model structure. The model represents the possible outcomes for patients under both management strategies. Moving from *left* to *right*, the model considers two management options for patients with NCSE, aggressive and non-aggressive treatment. After a treatment is chosen, a patient may either survive or die with probabilities determined by baseline mortality risk and treatment strategy. Survivors may end up in 3 distinct disability classes with the distribution among classes depending again on management strategy and inciting etiology for NCSE: minimal or no disability (QOL = 1), moderate disability dysfunction (QOL = 0.75), or severe neurologic disability (QOL = 0.11). **B.** Modeling mortality and disability in NCSE. This figure qualitatively depicts the relationships between parameter values in the decision model. Actual parameter values assumed in the analysis for each etiology are given in Table 1. (*a*) The expected mortality for each inciting etiology when complicated by NCSE is divided into contributions from the inciting etiology and NCSE. Neither of the treatment options reduces mortality due to etiology. Non-aggressive treatment is assumed to reduce, but not abolish mortality due to NCSE, while aggressive treatment abolishes mortality due to NCSE while introducing mortality due to aggressive treatment. (*b*) Long-term neurologic disability among survivors is divided into classes of mild/no disability, moderate disability, and severe disability with the initial distribution among disability classes determined by inciting etiology of NCSE. The disability distribution among survivors of aggressive treatment is unchanged (i.e., we assume that aggressive treatment rapidly abolishes NCSE, hence there is no added morbidity due to prolonged seizure activity), while the outcomes among survivors of non-aggressive treatment are shifted toward more severe levels of disability due to deleterious effects of delayed control of NCSE. Whether aggressive versus non-aggressive treatment is optimal in any given case depends on the magnitudes of and interactions between these effects

outcome measures; [37] one study estimated that only 20 % had returned to baseline function at discharge [23]. The association of NCSE with increased morbidity and mortality persists after controlling for age, etiology, neurologic exam, and organ dysfunction [38–41]. Delayed diagnosis and prolonged duration of NCSE are linked with higher morbidity and mortality [11]. Existing data [13, 42, 43] suggest mortality rates of 3, 19, and 32 % for seizures lasting <30, 30–60 min, and 1–6 h, respectively, and a logarithmic increase in mortality up to 6 h thereafter, though once NCSE continues beyond 6 h its duration may become a weaker predictor of outcome [15, 44]. Convulsive and non-convulsive status epilepticus appear to act synergistically with acute brain pathology to produce worse outcomes in diverse forms of neurologic critical illness including stroke [45], IPH [46], subarachnoid hemorrhage (SAH) [47], and TBI [48]. Finally, much indirect evidence supports the hypothesis that NCSE may damage the brain, including cerebral microdialysis studies showing associations with NCSE and increased glutamate, glycerol, and lactate-pyruvate ratio; [49] increased neuron-specific enolase; [50, 51] increased intracranial pressure during non-convulsive seizures; [51] increased midline shift after IPH; [46] and the development of ipsilateral hippocampal and neocortical atrophy when seizures complicate traumatic brain injury (TBI) [52]. Many clinicians have concluded from this cumulative evidence that treating seizure and NCSE quickly and effectively may lead to better outcomes, and for these reasons advocate aggressive treatment [3, 53, 54].

Nevertheless, the degree to which NCSE *independently causes* morbidity and mortality beyond that expected from the inciting etiology is unknown and controversial [1, 4, 5, 54, 55] and likely varies with etiology, electrographic seizure pattern [2], and seizure duration [13]. For our model, we assumed that each etiology has a baseline mortality rate (see above), to which the underlying etiology and NCSE makes the following relative contributions. For ASE and dAED, we assumed that the inciting factor (e.g., missed medication doses, menstruation, emotional stress, etc.) played a relatively small role, and that NCSE played the dominant role in determining mortality; specifically, we assumed a tenfold greater contribution of NCSE to overall (untreated) mortality. Conversely, for IPH and PSE, we assumed that etiology played a tenfold greater role than NCSE. Sensitivity analysis was used to explore the implications of varying these values.

Generically, morbidity of prolonged seizures in survivors is assumed to depend on a combination of the underlying electrographic pattern reflecting different severities of NCSE [2] and the time taken to achieve seizure control [11, 13]. A convenient overall measure that implicitly combines both factors is the percentage of patients who suffer at least a 1-point drop on the GOS [26, 27], as suggested by Claassen et al. [56]. In the absence of etiology-specific data regarding these statistics, we assumed for our base-cases the following clinically plausible values for percent of patients with ≥ 1 point drop of GOS, and explored the consequences of deviations away from these values via sensitivity analyses: for ASE, 1 %; and for AED discontinuation, IPH, and PSE, 20 %. Note that these values denote the proportion of patients who acquire additional disability as a result of prolonged NCSE *beyond* the distribution of disability already expected from the underlying inciting etiology. For details, see Supplemental Methods.

Efficacy of Aggressive and Non-Aggressive Treatment

Our model assumes that in the absence of disease-related or treatment-related mortality, aggressive treatment with induction of burst suppression is 100 % effective, while non-aggressive management leads to a delay in seizure control and thereby incurs some additional mortality, the degree of which varies by etiology. ASE typically rapidly and completely resolves with low-dose benzodiazepine therapy given as intravenous, oral, buccal, or rectal bolus doses (e.g., diazepam, clonazepam, or lorazepam) [18, 35], or by intravenous valproate [18]; thus, we assume that the efficacy of treatment in preventing (the already small) mortality due to absence status epilepticus is 99 % (see Supplemental Methods for further details). In the absence of definitive data, based on the clinical experience, we assume the following plausible efficacy values for non-aggressive treatment of NCSE: in discontinuation of AEDs, 70 %; in IPH, 25 %; and in PSE, 10 %. The effects of these assumptions are investigated by sensitivity analysis.

Mortality Risks of Aggressive Management

Despite intensive efforts to minimize iatrogenesis, aggressive ICU-level medical care is fraught with potential complications, including ventilator-associated pneumonia, catheter-associated bloodstream infections, and other hospital-acquired infections [57], acute lung injury, and delirium [58], and is separately subject to withdrawal of care as a self-fulfilling prophecy based on patient or family preference [59]. Prolonged immobilization and deep sedation places patients at risk for ICU-acquired neuropathy and myopathy, deep vein thrombosis, and long-term neuropsychiatric disability [60–65]. ICU patients are vulnerable to increased medical errors because of underlying comorbidities and because of the complexity and highly technical nature of modern ICU care [66–68]. Patients undergoing aggressive treatment for NCSE are uniquely exposed to the risks of high-dose anesthetic drugs used to

induce burst suppression. Barbiturate anesthetics (e.g., pentobarbital and thiopental) have long elimination half lives and may accumulate, leading to prolonged ventilation times [69–71] and impaired immune function [72]. Hypotension complicates the use of all anesthetics used for refractory status epilepticus [73, 74]. All of these factors may substantially increase hospitalization duration, morbidity, and mortality [75].

The likelihood that exposure to aggressive ICU-level medical will directly lead to death varies widely among patients, depending on age (the elderly are more vulnerable) and underlying medical comorbidities [76, 77]. Although clinicians routinely make subjective assessments regarding patients' chances of tolerating aggressive care, no generally applicable objective risk assessment tool exists for this setting. For our base-case analyses, we assumed a 20 % risk of death as a result of ICU admission, representing a "high-risk" scenario, and performed sensitivity analysis to explore the implications of higher and lower levels of ICU mortality risk.

Results

Base-Case Results and One-Way Sensitivity Analyses

Base-case analyses were conducted separately for patients with either absence epilepsy, discontinuation of anti-seizure medication (dAED), IPH, or PSE as the inciting etiology of NCSE, where each case is characterized by clinical parameters in Table 1, and each case was subjected to 1-way sensitivity analysis for each of the five parameters (Fig. 2; Table 2).

For ASE, non-aggressive treatment is favored by a wide margin, and only under extreme and unrealistic assumptions (i.e., when aggressive treatment carries no risk or

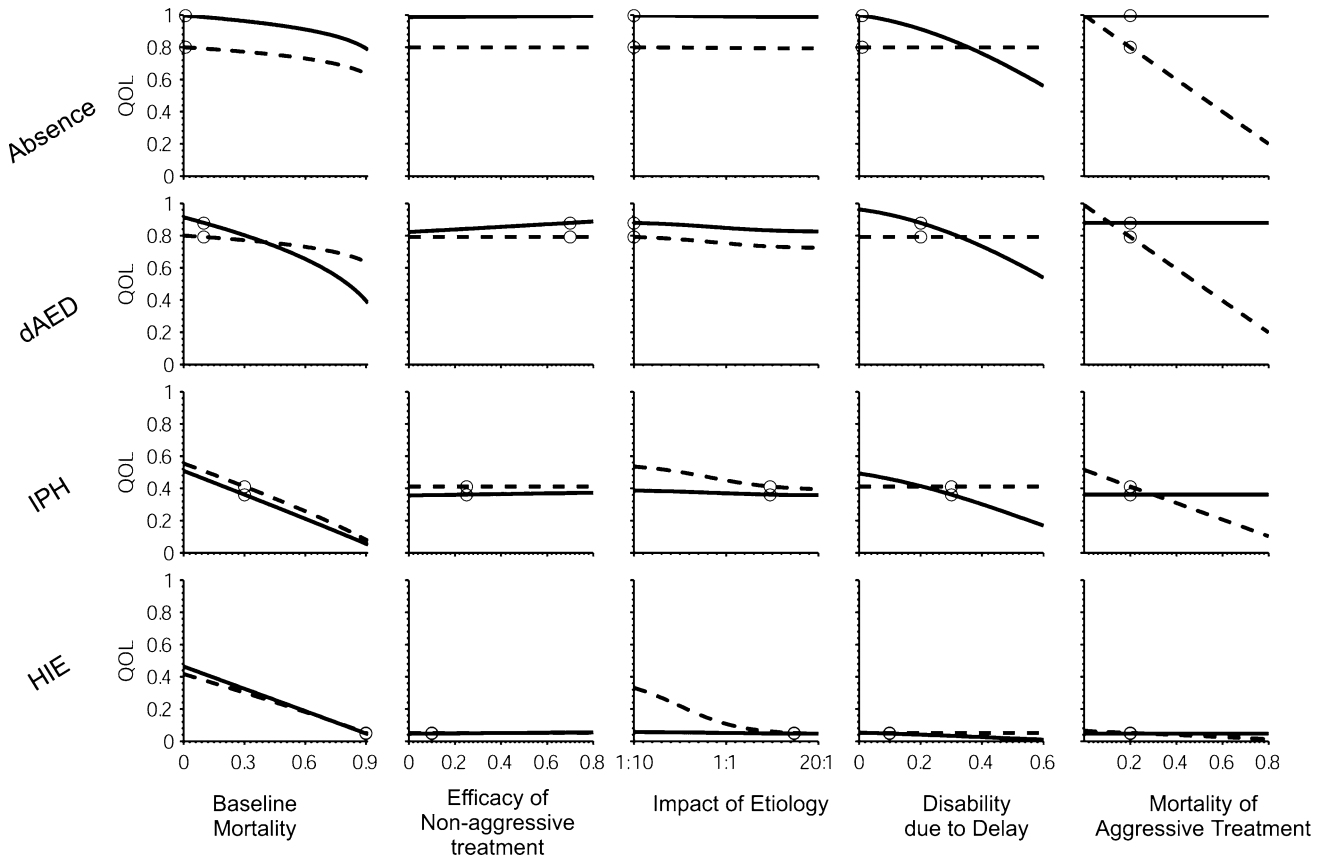

Fig. 2 One-way sensitivity analysis. From *top* to *bottom*, the etiology progresses from least to most severe: absence epilepsy (*Absence*), discontinued antiepileptic drugs (*dEAD*), intraparenchymal hemorrhage (*IPH*), and hypoxic ischemic encephalopathy (*HIE*). Across the columns, the parameter which is varied changes, from left to right: baseline mortality, efficacy of non-aggressive treatment, impact of etiology, disability due to delay and mortality of aggressive treatment. The solid line represents non-aggressive treatment and the *dotted line* represents aggressive treatment. The *y axis* shows the expected QOL. The circles represent our base-case values

Table 2 Results for base-case analyses

Etiology	Absence epilepsy	Discontinuation of anti-seizure medication	Intraparenchymal hemorrhage	Hypoxic ischemic encephalopathy
Preferred management	Non-aggressive	Non-aggressive	Aggressive	Aggressive
QOL difference between strategies (%)	20 (100 vs 80)	9 (88 vs 79)	5 (36 vs 41)	<1 (4.7 vs 5.1)
Crossover points				
%Baseline mortality	–	40	–	73
Weighting of etiology vs NCSE	–	–	–	–
%Mortality of aggressive treatment	–	–	–	49
%With disability incurred by delay	36	33	21	–
%Efficacy of non-aggressive treatment	–	11	30	26

delay leads to a high proportion of patients with functional disability) does the optimal treatment method switch to aggressive treatment. For NCSE due to discontinuation of anti-seizure medication, non-aggressive treatment is also favored over most parameter values. Aggressive treatment is preferred if baseline mortality increases, if seizure activity becomes more damaging or persistent, or if the risk associated with aggressive treatment substantially decreases. For IPH, aggressive treatment is favored for most of the parameter space though the preference is modest and subject to change with modest changes in model parameters. For example, non-aggressive treatment might still be preferred for IPH if the patient is particularly fragile and unlikely to survive aggressive management, or if the functional disability incurred by delayed seizure control is substantially lower, as might be the case for less malignant appearing EEG patterns which either cause minimal neurological damage or are rapidly controllable with non-aggressive treatment. For HIE, aggressive treatment is favored by a narrow margin. However, expected outcomes for these patients are uniformly poor regardless of which treatment is chosen because of the high baseline morbidity and mortality. This slight preference switches slightly in favor of non-aggressive treatment if baseline mortality decreases substantially, the mortality risk of aggressive treatment increases, or the efficacy of non-aggressive treatment substantially increases.

Regarding the general trends in response to parameter variation across etiologies, we make the following observations. First, QOL outcomes decline as expected with either management strategy when baseline mortality increases; however, the steepness of the QOL versus baseline mortality curves is uniquely modulated by the remaining variables. For example, the slope is shallow for ASE because both aggressive and non-aggressive treatment strategies are assumed effective. Second, outcomes associated with non-aggressive treatment improve as the efficacy of non-aggressive management options increases; however, the overall impact varies. For example, varying treatment efficacy has minimal impact on ultimate outcome in cases of ASE because mortality and long-term disability costs of delayed seizure control are assumed to be negligible. Increased treatment efficacy similarly has minimal impact in PSE, but here the reason is that even highly effective treatments have minimal impact because NCSE is assumed to play a minor role in determining mortality compared to the inciting etiology. Third, increasing the relative contribution of NCSE to baseline mortality tends to favor aggressive management, but again, the impact of such variation depends on the other model parameters. When the impact of etiology is low or, equivalently, when NCSE is the primary driver of mortality, stopping seizures rapidly may be worth the added risk of mortality from aggressive treatment, whereas when etiology plays a dominant role the risk of aggressive treatment outweighs the benefits of rapid seizure termination. Fourth, outcomes associated with non-aggressive treatment decrease for all etiologies as the risk of disability incurred by delayed seizure control increases, and consequently for each etiology a crossover point exists beyond which aggressive treatment becomes the preferred treatment modality (though in some cases, such as absence status epilepticus, this point is well outside the plausible clinical range). Finally, outcomes associated with aggressive treatment deteriorate as the mortality risk of aggressive treatment increases. This suggests that aggressive treatment should be avoided in fragile patients at high risk for harm. The difference in expected outcome with high-risk aggressive treatment versus non-aggressive treatment widens when outcome expected with non-aggressive management is good, as in ASE and dAED. For cases with high baseline mortality, such as IPH and especially PSE, the impact of treatment approach to NCSE on ultimate outcome is relatively small.

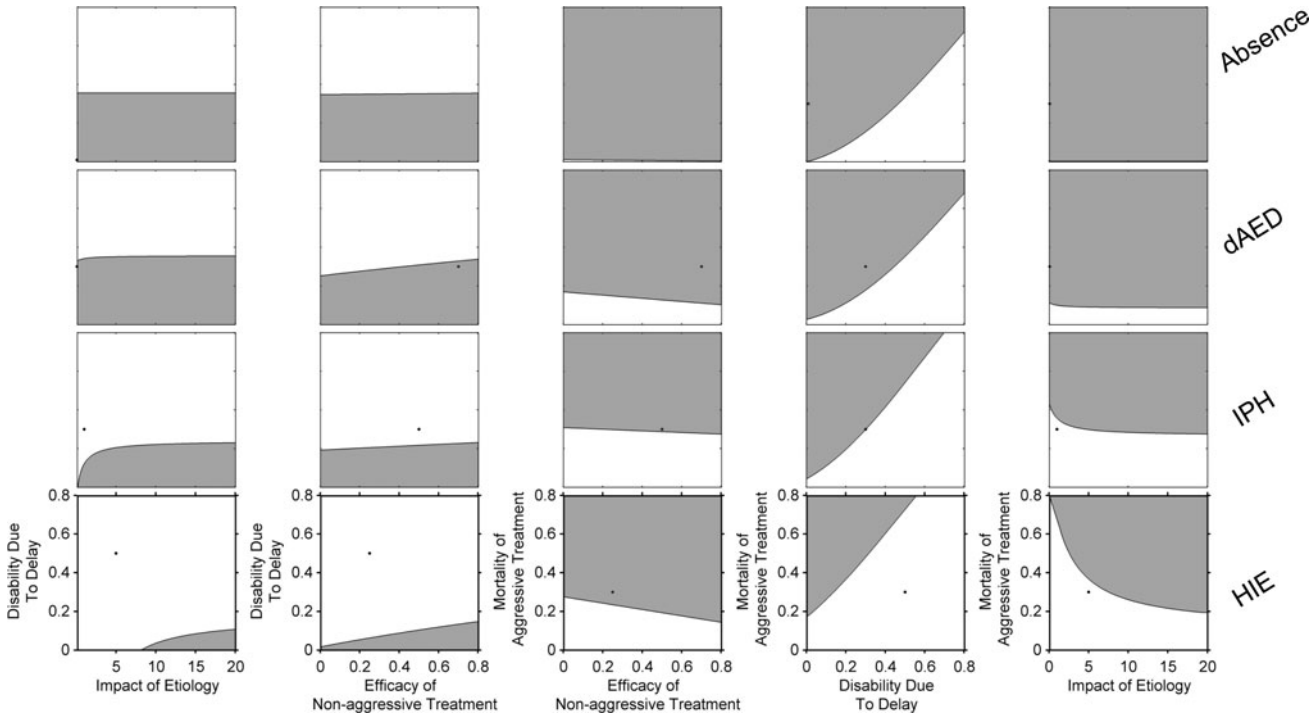

Fig. 3 Two-way sensitivity analysis. From top to bottom, the etiologies progress from least to most severe: absence epilepsy (*Absence*), discontinued antiepileptic drugs (*dEAD*), intraparenchymal hemorrhage (*IPH*), hypoxic ischemic encephalopathy (*HIE*). Across the columns, the parameters that vary are, from *left* to *right*: Impact of etiology versus disability due to delay, efficacy of non-aggressive treatment versus disability due to delay, efficacy of non-aggressive treatment versus mortality of aggressive treatment, disability due to delay versus mortality of aggressive treatment and impact of etiology versus mortality of aggressive treatment. The *gray space* represents the parameter space where non-aggressive treatment is favored and the white space represents the parameter space where aggressive treatment is favored. Note that the two-way sensitivity analysis does not quantify the expected QOL, instead shows which treatment option has a higher expected QOL, meaning the relative sizes of *gray and white regions* in Fig. 3 do not indicate that aggressive or non-aggressive treatment is favored by a larger margin, but that it is favored over a wider range of the two varied parameters

Two-Way Sensitivity Analyses

Two-way sensitivity analyses were performed on select pairs of variables to gain further insights into optimal NCSE management (Fig. 3).

Disability due to Delay Versus Impact of Etiology

The degree of disability incurred by delayed seizure control with non-aggressive treatment has a straightforward influence on optimal management strategy: when the penalty for non-aggressive treatment is too great (e.g., seizures are particularly malignant or difficult to control), aggressive treatment becomes favored. The impact of changing the relative contributions of etiology or NCSE to mortality is more subtle, in that this parameter's influence depends on the overall expected mortality. In the case of ASE, mortality is negligible, thus varying the weighting of etiology versus NCSE in overall mortality has almost no impact. For etiologies with higher associated mortality, larger weightings of etiology favor non-aggressive treatment, while weightings tilted toward NCSE imply a larger opportunity for efficacious therapeutic intervention, thus favoring aggressive management.

Disability due to Delay Versus Efficacy of Non-Aggressive Treatment

As the risk of disability associated with delayed seizure control increases, aggressive treatment will eventually become favorable (white area in the plots). Improving the efficacy of non-aggressive treatment will increasingly favor non-aggressive treatment, but only in circumstances in which there is substantial risk associated with delayed resolution of NCSE. For example, in ASE, there is almost no risk of death and thus improved treatment efficacy does not influence the optimal management strategy. For etiologies with higher overall mortality, improving the efficacy of non-aggressive treatment sufficiently will eventually make it the optimal treatment strategy.

Mortality of Aggressive Treatment Versus Efficacy of Non-Aggressive Treatment

The mortality associated with aggressive treatment has straightforward effects on the optimal management strategy. As patients become more susceptible to ICU complications, the mortality of aggressive treatment will increase, eventually favoring non-aggressive treatment (gray zone). Improved efficacy of non-aggressive choices also favors non-aggressive treatment. For ASE, non-aggressive treatment is favored almost universally, except where the risks of the ICU environment and efficacy of non-aggressive treatment are implausibly low. The dominance of non-aggressive treatment for this etiology suggests that any risk of aggressive treatment is unacceptable because of the benign nature of ASE. For other etiologies, as the morbidity associated with delayed control of NCSE increases, the parameter space which favors aggressive treatment increases (white region grows).

Mortality of Aggressive Treatment Versus Disability due to Delay

These plots illustrate the trade-offs between key risks associated with each treatment strategy. In the case of aggressive treatment, the primary risk involves ICU-related mortality; increasing the mortality risk of aggressive treatment favors non-aggressive management. For non-aggressive management, the primary risk is delayed control of seizures, which manifests as increased long-term functional disability. Increased disability associated with delayed seizure control during non-aggressive treatment favors aggressive treatment.

Mortality of Aggressive Treatment Versus Impact of Etiology

This two-way sensitivity analysis again demonstrates that essentially no degree of risk is sufficiently small to favor aggressive management of ASE. The inciting factors behind episodes of ASE do not supply enough risk of morbidity and mortality to warrant the risks of aggressive treatment. As more severe etiologies expose patients to greater risks of morbidity and mortality, aggressive treatment becomes favored over a larger parameter space since aggressive management is assumed to be the most effective in eliminating the morbidity and mortality incurred by ongoing NCSE. Aggressive treatment is especially favored when NCSE (over etiology) is a major driver of overall mortality.

Discussion

The Value of Decision Modeling for NCSE Management

We applied the principles of decision analysis to model a difficult clinical problem facing physicians managing patients with NCSE. Our analysis illuminates the decision by providing a framework in which data from the current medical literature regarding the various competing risks and benefits associated with aggressive treatment of NCSE are synthesized and weighed against each other in a coherent fashion. Our analysis shows that the decision to elect for aggressive care should be driven primarily by etiological factors, rather than the mere presence of NCSE alone.

We demonstrated that sensitivity analysis has strong utility in modeling the interactions of these multiple risks to make logical and pragmatic decisions for individual patients, even when the confidence of each parameter is imperfect. Our analysis shows that in specific circumstances, a benign etiology of NCSE may dictate that aggressive treatment is unwarranted, while for other etiologies, the prognosis may be sufficiently intermediate such that aggressive management can offer net benefit.

Clinicians must and do make subjective risk estimates as a matter of routine. Accordingly, we advocate that clinicians reckon with the complexity of NCSE by transforming the dialog about *whether to treat* NCSE aggressively into a conversation about *when to treat* aggressively. Our model provides a systematic approach to making pragmatic patient-specific assessments by quantifying QOL outcomes across a range of plausible parameter values, enabling decisions which are tailored to patient-specific factors assembled from the clinical literature.

A Multifactorial Decision Framework is Essential

An important implication of our analysis is that no single variable determines the optimal management of NCSE. In some cases, NCSE can be the driving force behind morbidity and mortality, but in other cases it may be an epiphenomenon. In the latter setting, tolerance for aggressiveness treatment risk is driven by the fragility of the patient and inciting etiology. None of the five variables we isolated as essential to the understanding of NCSE management decisions commands complete control of the model. Instead, all five variables contribute significantly to patient outcome and accounting for all of them is essential to choosing the best management approach to particular cases of NCSE.

The Importance of Etiology

Our model utilizes five variables to predict the optimal treatment for NCSE, and these variables are determined by the inciting etiology of NCSE. This suggests that understanding etiology-specific risks in relation to NCSE is crucial to defining optimal individualized management. This perspective emphasizes the importance of considering clinical context rather than focusing on electrophysiologic findings alone, particularly when the relative implication of specific EEG patterns is not precisely known.

Limitations and Future Directions

The main strength of our model is that it identifies, relates, and weighs the key determinants of NCSE treatment outcomes in a manner which also allows clinical judgment to inform the process. Nevertheless, adequate quantitative knowledge of several key values in the model is lacking in the medical literature. For example, while the risks of intubation and general anesthesia are well studied in a surgical context, their impact on morbidity and mortality when used for extended periods in conjunction with prolonged ICU care remains uncertain. More generally, while our analysis has attempted to determine the optimal decision at a population level based on the best available parameter estimates from the current literature, the optimal decision in clinical practice will often depend on individual patient factors which are difficult to quantify. This uncertainty is in part addressed by our sensitivity analyses, which provide a mechanism for clinician judgment and patient-specific considerations to provide flexible implementations of our model. It is important to recognize that in some cases the optimal decision may switch within the range of parameter uncertainty (see Fig. 2). This fact not only emphasizes the continued importance of patient-specific clinical judgment but also highlights the need in critical care for improved tools to tailor risk and benefit estimates to individual patients. Examples of progress along these lines include the recently developed Status Epilepticus Severity Score (STESS) developed by Rossetti et al. [10] and the FUNC score for predicting outcomes in IPH developed by Rost et al. [9].

Implications for Practice

Should non-intubated patients with NCSE be rapidly and aggressively treated with intubation and high-dose anesthetics, or managed less urgently with less powerful drugs, even when delays in achieving seizure control might incur brain damage? A key conclusion of our analysis is that this decision is fundamentally complex. No single, simple management algorithm (e.g., "NCSE → intubate and burst suppress") is tenable. In our view, the downsides of aggressive NCSE management are not as widely appreciated as they should be and it was partly in response to what we view as tendencies in the recent literature toward oversimplification of management that we undertook the present study: (1) the tendency to emphasize the potential benefits and downplay the risks of aggressive seizure treatment; and (2) the tendency to view the debate regarding aggressive versus non-aggressive management of NCSE solely in terms of whether or not NCSE causes brain damage. In this work, we have shown that, even in cases where NCSE is likely to cause brain damage, aggressive treatment may yet confer greater overall risk. Appreciation of the complexity of management decisions in NCSE should help physicians taking care of patients in neuro-ICUs and neurology wards to resist the tendency to apply "one-size-fits-all" treatment algorithms, and to carefully seek in all cases the optimal risk–benefit balance.

Disclosures MBW receives research support from the NIH/NINDS (NS062092) and American Brain Foundation. MTB receives research support from the National Center for Research Resources: Harvard Clinical and Translational Science Center and the Center for Integration of Medicine and Innovative Technology (CIMIT). ESR receives research support from the Center for Integration of Medicine and Innovative Technology (CIMIT), the NIH/NIBIB (5U54EB007954-04), the Department of Defense (W81XWH-08-2-0154), and the Andrew David Heitman Neuroendovascular Research Foundation.

References

1. Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. J Clin Neurophysiol. 1999;16(4):341–52. discussion 353.
2. Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. J Clin Neurophysiol. 2005;22(2):79–91.
3. Young GB, Jordan KG. Do nonconvulsive seizures damage the brain?–Yes. Arch Neurol. 1998;55(1):117.
4. Aminoff MJ. Do nonconvulsive seizures damage the brain?–No. Arch Neurol. 1998;55(1):119–20.
5. 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(6):377–82.
6. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol. 2006;13(5):445–50.
7. Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. Neurology. 2003;61(8):1066–73.
8. Rossetti AO, Logroscino G, Liaudet L, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology. 2007;69(3):255–60.
9. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. Stroke. 2008;39(8):2304–9.

10. Rossetti AO, Logroscino G, Milligan TA, et al. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol. 2008;255(10):1561–6.
11. Young BG, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring an investigation of variables associated with mortality. Neurology. 1996;47(1):83–9.
12. Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Arch Neurol. 2005;62(11):1698–702.
13. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia. 1994;35(1):27–34.
14. Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Short-term mortality after a first episode of status epilepticus. Epilepsia. 1997;38(12):1344–9.
15. 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(6):1566–71.
16. Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. Neurology. 2007;69(9):886–93.
17. Alvarez V, Januel J-M, Burnand B, Rossetti AO. Role of comorbidities in outcome prediction after status epilepticus. Epilepsia. 2012;53(5):e89–92.
18. Shorvon S, Walker M. Status epilepticus in idiopathic generalized epilepsy. Epilepsia. 2005;46(Suppl 9):73–9.
19. Andermann F, Robb JP. Absence status. A reappraisal following review of thirty-eight patients. Epilepsia. 1972;13(1):177–87.
20. Agathonikou A, Panayiotopoulos CP, Giannakodimos S, Koutroumanidis M. Typical absence status in adults: diagnostic and syndromic considerations. Epilepsia. 1998;39(12):1265–76.
21. Claassen J, Jetté N, Chum F, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology. 2007;69(13):1356–65.
22. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;67(2):203–10.
23. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia. 2010;51(2):251–6.
24. Oddo M, Rossetti AO. Predicting neurological outcome after cardiac arrest. Curr Opin Crit Care. 2011;17(3):254–9.
25. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32(4):891–7.
26. Kosty J, Macyszyn L, Lai K, et al. Relating quality of life to Glasgow outcome scale health states. J Neurotrauma. 2012;29(7):1322–7.
27. Nichol AD, Higgins AM, Gabbe BJ, et al. Measuring functional and quality of life outcomes following major head injury: common scales and checklists. Injury. 2011;42(3):281–7.
28. Eckman MH, Rosand J, Knudsen KA, Singer DE, Greenberg SM. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. Stroke. 2003;34(7):1710–6.
29. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: a decision analysis. Arch Neurol. 2011;68(5):573–9.
30. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Intern Med. 1996;156(16):1829–36.
31. Shirasaka Y. Lack of neuronal damage in atypical absence status epilepticus. Epilepsia. 2002;43(12):1498–501.
32. Meldrum BS. Concept of activity-induced cell death in epilepsy: historical and contemporary perspectives. Prog Brain Res. 2002;135:3–11.
33. Guerrini R, Aicardi J, Arzimanoglou A. Aicardi's epilepsy in children. 3rd ed. Philadelphia: Lippincott Williams; 2004.
34. Gökyiğit A, Calişkan A. Diffuse spike-wave status of 9-year duration without behavioral change or intellectual decline. Epilepsia. 1995;36(2):210–3.
35. Panayiotopoulos CP. The epilepsies: seizures, syndromes and management: based on the ILAE classifications and practice parameter guidelines. Oxfordshire: Bladon; 2005. http://www.ncbi.nlm.nih.gov/books/NBK2606/. Accessed 2 October 2012.
36. Drislane FW, Lopez MR, Blum AS, Schomer DL. Detection and treatment of refractory status epilepticus in the intensive care unit. J Clin Neurophysiol. 2008;25(4):181–6.
37. Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol. 2002;59(2):205–10.
38. DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia. 1998;39(8):833–40.
39. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. Crit Care Med. 2009;37(6):2051–6.
40. Delanty N, French JA, Labar DR, Pedley TA, Rowan AJ. Status epilepticus arising de novo in hospitalized patients: an analysis of 41 patients. Seizure. 2001;10(2):116–9.
41. Vignatelli L, Rinaldi R, Baldin E, et al. Impact of treatment on the short-term prognosis of status epilepticus in two population-based cohorts. J Neurol. 2008;255(2):197–204.
42. DeLorenzo RJ, Garnett LK, Towne AR, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia. 1999;40(2):164–9.
43. Waterhouse EJ, Garnett LK, Towne AR, et al. Prospective population-based study of intermittent and continuous convulsive status epilepticus in Richmond, Virginia. Epilepsia. 1999;40(6):752–8.
44. Cooper AD, Britton JW, Rabinstein AA. Functional and cognitive outcome in prolonged refractory status epilepticus. Arch Neurol. 2009;66(12):1505–9.
45. Waterhouse EJ, Vaughan JK, Barnes TY, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. Epilepsy Res. 1998;29(3):175–83.
46. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. Neurology. 2003;60(9):1441–6.
47. Dennis LJ, Claassen J, Hirsch LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. Neurosurgery. 2002;51(5):1136–43. discussion 1144.
48. Vespa PM, Nuwer MR, Nenov V, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg. 1999;91(5):750–60.
49. Vespa P, Prins M, Ronne-Engstrom E, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. J Neurosurg. 1998;89(6):971–82.
50. DeGiorgio CM, Heck CN, Rabinowicz AL, et al. Serum neuron-specific enolase in the major subtypes of status epilepticus. Neurology. 1999;52(4):746–9.
51. Vespa PM, Miller C, McArthur D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med. 2007;35(12):2830–6.

52. Vespa PM, McArthur DL, Xu Y, et al. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. Neurology. 2010;75(9):792–8.
53. Foreman B, Hirsch LJ. Epilepsy emergencies: diagnosis and management. Neurol Clin. 2012;30(1):11–41, vii.
54. Jordan KG, Hirsch LJ. In nonconvulsive status epilepticus (NCSE), treat to burst-suppression: pro and con. Epilepsia. 2006;47(Suppl 1):41–5.
55. Young GB, Claassen J. Nonconvulsive status epilepticus and brain damage: further evidence, more questions. Neurology. 2010;75(9):760–1.
56. Claassen J, Lokin JK, Fitzsimmons B-FM, Mendelsohn FA, Mayer SA. Predictors of functional disability and mortality after status epilepticus. Neurology. 2002;58(1):139–42.
57. Grundmann H, Bärwolff S, Tami A, et al. How many infections are caused by patient-to-patient transmission in intensive care units? Crit Care Med. 2005;33(5):946–51.
58. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62.
59. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. Neurology. 2001;56(6):766–72.
60. Ali NA, O'Brien JM Jr, Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med. 2008;178(3):261–8.
61. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
62. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006;174(5):538–44.
63. Angus DC, Musthafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;163(6):1389–94.
64. Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 2003;31(4):1226–34.
65. De Jonghe B, Sharshar T, Lefaucheur J-P, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002;288(22):2859–67.
66. Forster AJ, Kyeremanteng K, Hooper J, Shojania KG, van Walraven C. The impact of adverse events in the intensive care unit on hospital mortality and length of stay. BMC Health Serv Res. 2008;8:259.
67. Garrouste-Orgeas M, Timsit JF, Vesin A, et al. Selected medical errors in the intensive care unit results of the IATROREF study: parts I and II. Am J Respir Crit Care Med. 2010;181(2):134–42.
68. Wunsch H. Is there a starling curve for intensive care? Chest. 2012;141(6):1393–9.
69. Bayliff CD, Schwartz ML, Hardy BG. Pharmacokinetics of high-dose pentobarbital in severe head trauma. Clin Pharmacol Ther. 1985;38(4):457–61.
70. Cordato DJ, Mather LE, Gross AS, Herkes GK. Pharmacokinetics of thiopental enantiomers during and following prolonged high-dose therapy. Anesthesiology. 1999;91(6):1693–702.
71. Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? Epilepsia. 2007;48(Suppl 8):52–5.
72. Kress HG, Segmüller R. Intravenous anesthetics and human neutrophil granulocyte motility in vitro. Anaesthesist. 1987;36(7):356–61.
73. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002;43(2):146–53.
74. 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(12):792–8.
75. Naidech AM, Bendok BR, Tamul P, et al. Medical complications drive length of stay after brain hemorrhage: a cohort study. Neurocrit Care. 2009;10(1):11–9.
76. Fuchs L, Chronaki CE, Park S, et al. ICU admission characteristics and mortality rates among elderly and very elderly patients. Intensive care med. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22797350. Accessed 28 July 2012.
77. Añon JM, Gómez-Tello V, González-Higueras E, et al. Prognosis of elderly patients subjected to mechanical ventilation in the ICU. Med Intensiva. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22592112. Accessed 28 July 2012.
78. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol. 2010;67(3):301–7.