Status Epilepticus

3

Emily J. Gilmore and Emad Nourollahzadeh

Case Example

A 75-year-old male with history of hypertension, atrial fibrillation on warfarin, and diabetes mellitus type II and distant history of ischemic stroke, who recently underwent a renal transplant, was admitted to the SICU for management of high blood pressure, confusion, and multiple falls. On hospital day 1, the nurse pages you to bedside for an acute change in the patient's mental status; he is now "unresponsive." What are the first steps in the diagnostic workup and management of this patient's neurological deterioration? We will review this particular case at the end of this chapter.

Introduction

Patients that are critically ill such as those in the surgical ICU are at a high risk for seizures [1, 2]. Moreover, seizures in critically ill patients are mainly nonconvulsive, and, thus, status epilepticus is readily underdiagnosed [1–12]. It is essential for an intensivist to be familiar with the seizure evaluation paradigm in patients with fluctuating neurological symptoms or in those with an unexplained impairment of level of consciousness. Prompt recognition and early treatment of seizures and status epilepticus are critical as prolonged seizures lead to increased morbidity and mortality [13]. Extensive work has shown that seizures – including nonconvulsive seizures – in the acutely injured brain can initiate a variety of adverse physiological effects, such as increases in cerebral blood flow, intracranial pressure, metabolic demand, and mass effect. Additional deleterious effects include acute elevations in lactate, glutamate, and neuron-specific enolase levels as well as delayed hippocampal atrophy and chronic epilepsy [14, 15].

E.J. Gilmore, MD (✉) • E. Nourollahzadeh, MD, MSc
Neurocritical Care and Emergency Neurology, Yale New Haven Hospital, New Haven, CT 06520, USA
e-mail: emily.gilmore@yale.edu; emad.nourollah-zadeh@yale.edu

Classifications and Definitions

Seizure is the occurrence of abnormal and synchronous neuronal activity that can lead to various clinical manifestations [16]. It is useful to recognize and classify specific seizure types, as it can help guide both the diagnostic workup and treatment. The latest classification by the International League Against Epilepsy (ILAE) divides seizures into three broad categories of generalized, focal, or unknown according to clinical and EEG manifestations. Generalized seizures involve bilateral networks within the cortical or subcortical areas of the brain, while focal seizures originate from networks limited to one hemisphere [17]. An electrographic seizure is defined by [18]:

1. A paroxysmal pattern that evolves in morphology, frequency, and/or spatial distribution OR
2. Generalized spike-wave discharges ≥3/s
3. Clearly evolving discharges of any type that reach a frequency >4/s (can be focal or generalized)
4. A paroxysmal electrographic pattern (which does not meet the above criteria) that is different from the background EEG pattern and is associated with a clinical correlate

Convulsive status epilepticus (SE) is operationally defined as ongoing seizure activity for more than 5 min or two or more seizures between which the patient does not return to baseline [19]. Where convulsive SE has clinical motor manifestations (tonic or rhythmic jerking of the extremities), nonconvulsive SE often manifests as decreased level of arousal without overt signs of ongoing ictal activity [20]. Though the definition of nonconvulsive status epilepticus can be rather nebulous, attempts at standardization exist [21]. A commonly used definition of nonconvulsive status epilepticus in critically ill patients is >30 min of ictal EEG activity within a single hour of recording.

When SE fails to cease after the administration of two intravenous antiepileptic drugs (AEDs), it is denoted as

N.D. Martin, L.J. Kaplan (eds.), *Principles of Adult Surgical Critical Care*, DOI 10.1007/978-3-319-33341-0_3

refractory SE, which occurs in 43 % of patients with SE and is associated with increased length of hospital stay, morbidity, and mortality [8, 22, 23].

Epidemiology

In the United States, the annual incidence of SE has increased from 3.5 to 12.5 per 100,000 between 1979 and 2010 [24], while the mortality rate has remained stable around 20 %. Moreover, 31–43 % of patients with SE ultimately progress to refractory SE, which is further associated with a worse prognosis [23, 25]. The data on seizure prevalence strictly among surgical ICU patients is limited and likely underestimated as the majority of seizures in the critically ill are nonconvulsive and would be undiagnosed without cEEG monitoring. In the few studies that include SICU patients, between 5 and 11 % of patients with encephalopathy can be in nonconvulsive SE when screened by cEEG [2, 3]. This rate is expectedly higher (~19 %) among encephalopathic neurological ICU patients with acute brain injury screened with cEEG [5, 9, 13, 26, 27].

Etiology

The causes of seizure and more specifically status epilepticus can be broad in the critically ill patient and include those with prior history of epilepsy (22–34 %), remote history of a structural brain lesion (24 %, i.e., ischemic or hemorrhagic stroke, tumor, etc.), acute stroke (22 %), hypoxic/ischemic encephalopathy (10 %), metabolic derangements (10 %), and alcohol withdrawal (10 %) along with other causes as shown in Table 3.1 [28].

It is important to remember that there are a host of clinical scenarios in the ICU that may mimic seizures, be associated with seizures, or lower the threshold for developing seizures. There are a handful of life-threatening diagnoses that can mimic nonconvulsive SE and should be considered in the setting of acute neurological deterioration.

Table 3.1 Causes of status epilepticus in adults [24, 28]

Etiology	Frequency
Epilepsy history	22–34 %
Medication noncompliance	
Refractory epilepsy	
Remote structural lesion	24 %
Tumor	
Traumatic brain injury	
Stroke	
Intracerebral hemorrhage	
Vascular malformations, etc.	
Ischemic stroke	22 %
Hypoxic/anoxic encephalopathy	10 %
Metabolic abnormalities	10 %
Hyponatremia (usually <120 meq/L)	
Hypoglycemia or hyperglycemia	
Liver or renal-related failure	
Hypothyroidism	
Alcohol withdrawal	10 %
Other	
PRES (posterior reversible encephalopathy syndrome)	
Infection (sepsis or CNS infection)	
Toxins	
Medications/illicit drugs	

Pathophysiology

In general terms, seizures occur due to instability of neuronal membranes and the inability to inhibit rapid synchronous discharges. Seizures are sustained due to an imbalance between increased excitation and decreased inhibition. The most common excitatory neurotransmitter is glutamate, which acts on the N-methyl-D-aspartate (NMDA) receptor. On the other hand, the most common inhibitory neurotransmitter is gamma-aminobutyric acid (GABA), which can bind to GABA-A receptors to inhibit excitation; this is the site of action for many antiepileptic drugs (AEDs) such as benzodiazepines, barbiturates, and propofol [29]. In addition, voltage-gated sodium channels, which are blocked by various AEDs (e.g., phenytoin, carbamazepine, and topiramate) to selectively inhibit rapidly firing neurons [30], and subtypes of calcium channels, which are targeted by zonisamide, valproate sodium, and lamotrigine, are also involved in seizure propagation [31].

Neurochemical Changes

The first few minutes of seizure onset are characterized by modulation of ionic channels, neurotransmitter release, and rearrangement of receptors on neuronal synapses via endocytosis or exocytosis, which leads to an increased number of excitatory NMDA receptors and a decreased number of inhibitory GABA-A receptors. As status epilepticus continues, the number and/or sensitivity of GABA-A receptors is thought to decrease; in fact, potency of benzodiazepines decreases by 20-fold within just 30 min of chemically induced status epilepticus animal models [32]. This highlights the importance of recognizing seizures as a neurological emergency in which early diagnosis and treatment initiation can improve clinical outcomes. Subsequently within hours to days, there will be seizure-induced neuronal damage and ultimately neuronal death (apoptosis and/or

necrosis) secondary to excitotoxicity [33–35]. The neuronal injury can be shown by nonspecific markers such as elevation of neuron-specific enolase or imaging findings of cerebral edema (vasogenic or cytotoxic) on FLAIR or diffusion-weighted imaging sequences or chronic atrophy especially in the hippocampus [36–38].

Physiological Changes

Within 30 min of convulsive status epilepticus, robust catecholamine release occurs leading to various systemic changes including increased blood pressure, fever, tachycardia, arrhythmias, leukocytosis, lactic acidosis, hyperglycemia, increased pulmonary vascular resistance, and pulmonary edema [29, 39–41]. Early in status epilepticus, cerebral physiology remains relatively stable through a host of intrinsic autoregulatory mechanisms that result in increased cerebral blood flow (CBF) as well as increased oxygen and glucose uptake [29]. However, after 30–60 min, SE typically becomes nonconvulsive and the early compensatory mechanisms fail, leading to excitotoxic damage and compounded neurological injury.

Diagnosis

Diagnosing seizures and status epilepticus can be challenging due to varied clinical manifestations that can represent both positive and negative phenomena (Table 3.2) [42]. Seizure onset is typically abrupt; however, there are several entities that may mimic seizures and status epilepticus, particularly when they are nonconvulsive (Table 3.3) [43]. After early management (see Fig. 3.1), the diagnosis of seizures must be further investigated with a scalp electroencephalogram (EEG). The underlying etiology should be worked up by checking rapidly reversible causes such as hypoglycemia, electrolyte imbalances, as well as renal and hepatic dysfunction. Other laboratory data such as toxicology and CSF analysis or advanced neuroimaging (CT or MR angiography/venography or MRI) may be required depending on the patient's specific history and neurological examination.

Table 3.2 Clinical manifestations of seizure [42]

Cognitive/language/behavioral
Memory loss
Decreased level of consciousness
(Fluctuating or persistent; with severity ranging from confusion to coma)
Echolalia, aphasia, mutism, and perseveration
Psychosis, hallucinations, catatonia, and delusions
Cry and laughter
Motor
Tonic and/or clonic activity and posturing
Eye deviation, blinking, facial twitching, and nystagmus
Autonomic
Tachycardia or bradycardia
Skin flushing, nausea, vomiting, miosis, mydriasis, and hippus

Table 3.3 Seizure mimics [43]

Movement disorders
Chorea, dystonia, tics, myoclonus, and asterixis
Psychogenic non-epileptic seizures
Syncope
Cardiogenic
Cataplexy (narcolepsy related)
Herniation syndromes (posturing)
Delirium
Ischemic events
"Limb shaking" TIA due to severe carotid stenosis
Posterior circulation strokes

Neurological and Physical Examination and History

When evaluating any patient with neurological dysfunction, a full neurological examination is helpful; however, in emergency situations one can do a focused neurological exam to guide subsequent management. At the minimum, in the noncomatose patient, this includes an assessment of mental status (orientation, attention, and concentration), language, memory, and lateralizing motor signs. In a comatose patient, an assessment of level of consciousness with verbal or noxious stimuli (alert, lethargic, stuporous, or comatose) and a cranial nerve examination are paramount. During inspection look for subtle oral, facial, or limb twitching, pupillary changes, and the presence of gaze deviation. Patients in nonconvulsive SE can have pupillary abnormalities, including asymmetry and hippus; however, if their pupils are dilated, pinpoint, or unreactive, other life-threatening neurological emergencies should be entertained, prompting an emergent neurology or neurosurgical consultation. Additionally, in nonconvulsive SE the eyes may be open, but the patient is mute (e.g., eye open mutism), and the eyes may be deviated with or without head version. Not all eye deviation is secondary to seizure and can be seen in cortical, thalamic, and brain stem lesions. In general, with ongoing seizures the eyes will deviate away from the brain lesion (especially if frontal), but with stroke or other lesions, they will deviate toward the side of the lesion. The exception to this rule involves lesions to the paramedian pontine reticular formation, in which lesions in the pons may cause contralateral eye deviation. Facial, eye, or limb twitches may be observed and may be induced with stimulation (SIRPIDs – stimulus-induced rhythmic, periodic, or ictal discharges – only occasionally with clinical correlate). Tone may be symmetrically or asymmetrically

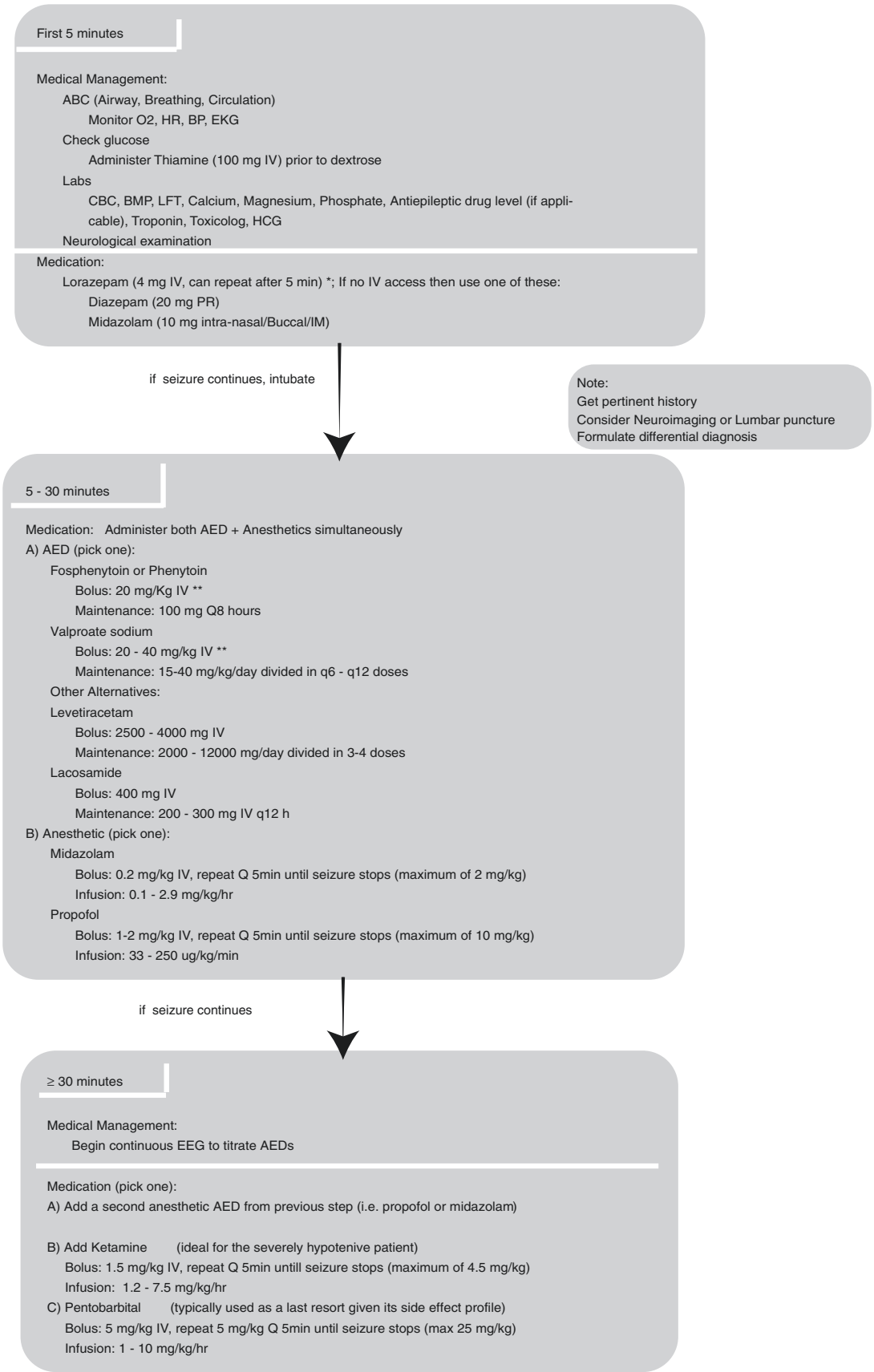

Fig. 3.1 Convulsive status epilepticus treatment algorithm for adults adopted at Yale-New Haven Hospital. *AED* antiepileptic drug, *BMP* basic metabolic profile, *BP* blood pressure, *Ca* calcium, *CBC* complete blood count, *EKG* electrocardiogram, *HCG* human chorionic gonadotropin, *HR* heart rate, *IM* intramuscular, *IV* intravenous, *LFT* liver function test, *O2* oxygen, and *Mg* magnesium. * This is based on 0.1 mg/kg dosing of lorazepam (divided into two doses) for an average adult (about 70 kg). ** Loading dose does not require adjustment for hepatic/renal insufficiency. Post-load serum drug level should be drawn 2 h post-phenytoin/fosphenytoin/valproate sodium

increased with hyperreflexia and clonus. "Awake" patients are more likely to exhibit automatisms (e.g., picking, lip smacking) and behavioral changes (perseveration, agitation, emotional lability, aggressiveness).

Stupor and coma can result from diseases affecting bilateral cerebral hemispheres, thalami, or the brain stem. As a rule, unilateral hemispheric lesions do not produce stupor or coma unless there is sufficient mass effect to raise the intracranial pressure or compress the contralateral hemisphere or brain stem (i.e., partial or complete herniation syndromes). Brain stem lesions produce coma by affecting the reticular activating system. Metabolic disorders impair consciousness by diffuse effects on both the reticular formation and the cerebral cortex.

Brain Imaging

Brain imaging after urgent treatment of status epilepticus, computed tomography (CT) of the head is indicated in almost all patients. If the etiology remains inconclusive, then magnetic resonance imaging (MRI) of the brain may be indicated to assess for diagnosis such as ischemic stroke, encephalitis (i.e., infectious, autoimmune, or neoplastic), or posterior reversible encephalopathy syndrome (PRES). It should be noted that prolonged status epilepticus could also lead to MRI findings in various anatomical locations (typically in the hippocampus, cortex, corpus callosum, thalamus); importantly, these findings may be reversible with appropriate management.

EEG

Early management of status epilepticus must rely on its clinical diagnosis and should not be delayed to obtain a cEEG. However, cEEG monitoring can both confirm and allow one to tailor therapeutics in critically ill patients. Scalp EEG detects seizures only when it involves a relatively large area of cortex (>10 cm^2) as it measures the summation of excitatory and inhibitory postsynaptic potentials of pyramidal neurons [44, 45]. Thus, scalp EEG may be falsely negative in seizures with small or deep foci. In patients who fail to fully regain consciousness, it is imperative to monitor for nonconvulsive SE and/or seizures due to their high prevalence of 15 % and 48 %, respectively [8]. Another important factor to consider is the duration of cEEG monitoring as routine 1 h EEGs can miss up to 50 % of seizures [7]. In critically ill patients, the recommended monitoring duration is 12–24 h for non-comatose patients and 24–48 h for comatose patient as seizure detection can reach up to 95 % and 87 %, respectively [5, 7]. The cEEG should also be continued until the patient is seizure-free for 24 h or has a reliable neurological exam to follow for clinical seizures. The latest Neurocritical Care Society (NCS) and the European Society of Intensive Care Medicine (ESICM) recommend cEEG in all patients with an unexplained alteration of consciousness either with an acute brain injury or comatose ICU patients without an acute brain injury (especially those with sepsis, renal/hepatic failures), in patients with CSE without return to baseline after 60 min, in patients undergoing hypothermia induction and within 24 h of their rewarming, and lastly in comatose subarachnoid hemorrhage patients in order to detect delayed cerebral ischemia (DCI) [46]. The guidelines set forth by the American Clinical Neurophysiology Society (ACNS) mostly mirror the aforementioned recommendations. Moreover, ACNS also suggests the use of cEEG in other settings such as monitoring of sedation or suppressive therapy (to avoid oversedation and undesirable side effects of anesthetic agents) and lastly the use of cEEG to help with prognostication in various neurological diseases [14].

Management

Upon diagnosis, seizures should be managed as a neurological emergency given the association of prolonged seizures and worse outcome. Management includes patient positioning, airway/breathing/circulation (ABC) management, antiepileptic drug (AED) administration, and diagnostic workup of the underlying etiology to further tailor treatment. As seen in Fig. 3.1, these steps should be prioritized and performed within 5–10 min as per the latest subspecialty guideline recommendations from the NCS [47].

Antiepileptic Drugs in Convulsive SE

Prompt AED administration must be prioritized given its association with improved seizure cessation and outcome [48]. It is essential to note that delayed treatment in convulsive SE is twice more likely to lead to systemic complications (respiratory failure, hypotension, and arrhythmia) than treatment with AEDs such as benzodiazepines (see Table 3.4 for list of AEDs) [15, 49]. Benzodiazepines are generally recognized as the first-line AEDs in the treatment of convulsive SE and are superior to phenytoin and phenobarbital [47, 48]. In patients with intravenous (IV) access, lorazepam is the preferred drug of choice. In those without IV access, intramuscular midazolam can be administered, which has a similar efficacy as lorazepam [50]. Furthermore, rectal diazepam is also an acceptable alternative to above agents.

In the critically ill, almost all patients should receive a second-line AEDs unless there is a reversible etiology and the patient has returned to baseline. Second-line AEDs

should be given intravenously and include fosphenytoin/phenytoin, valproate sodium, levetiracetam, phenobarbital, or midazolam [47]. The selection of a second-like AED depends on institutional accessibility, patient's comorbidities, and the type of epilepsy if known and applicable. Typically, fosphenytoin/phenytoin is a preferred choice due to accessibility; however, it is associated with cardiovascular side effects (e.g., hypotension and arrhythmias) and may exacerbate seizures in those with a history of primary generalized epilepsy (PGE). Valproate sodium has been shown to be at least as effective and perhaps superior to fosphenytoin/phenytoin based on two trials; furthermore, valproate sodium is a good choice for the treatment of PGE and has less cardiovascular side effects [51, 52]. Another commonly used AED is levetiracetam due to its efficacy, benign side effect profile, and minimal interactions with other medications [53, 54]. As discussed earlier, the failure of a second-line AED defines SE as refractory and requires the initiation of a third-line AED, typically as a bolus dose followed by an infusion of anesthetic such as midazolam, propofol, ketamine, or pentobarbital. These agents should be titrated to seizure cessation (and not burst suppression) with the help of cEEG. In one study there was no difference in mortality between refractory SE treated by continuous propofol, midazolam, or pentobarbital [55]. Pentobarbital is generally used as a last resort in cases of superrefractory SE (nonconvulsive SE > 48 h) due to its significant systemic side effects. Once seizure suppression is achieved, anesthetic AEDs should be slowly tapered off after 24–48 h to prevent rebound seizures; the taper is typically performed over 24 h [47]. It should be noted that the treatment of status epilepticus (NCSE or CSE) with anesthetic AEDs to reach therapeutic coma (i.e., either seizure cessation or burst suppression on cEEG) has been shown to be associated with worse outcome [56]. Further prospective, randomized trials are needed to validate these findings.

Finally, in certain clinical situations, immune medicated therapies (e.g., high-dose steroids, IVIg, plasma exchange) as well as hypothermia and electroconvulsive therapy may be instituted to manage super-refractory cases.

Antiepileptic Drugs in Nonconvulsive SE and Ictal-Interictal Patterns

Currently, there are no prospective trials to guide or support an algorithmic treatment of nonconvulsive SE. However, given the association with increased mortality, it is reasonable to treat generalized nonconvulsive SE with the same urgency and aggressiveness as convulsive SE. Lastly, there are certain EEG patterns (e.g., lateralized rhythmic or periodic discharges) that are not clearly seizures but suggest different degree of cortical hyperexcitability based on their prevalence, frequency, morphology, spread, and evolution; these patterns could simply be markers of brain injury or severity of illness; however, they have the potential to progress to frank seizure. Currently, there is no clear consensus on the treatment of

Table 3.4 List of commonly used AEDs in status epilepticus [15, 49]

Medication	Loading dose	Maintenance dose	Clearance	Side effects/comments
Lorazepam	4 mg, repeat after 5 min	N/A	Hepatic	Hypotension
Diazepam	20 mg (PR)	N/A	Hepatic	Prolonged half-life
Phenytoin & fosphenytoin	20 mg/kg*	100 mg Q8 hr	Hepatic	Hypotension, arrhythmias, hepatic dysfunction. Monitor free levels if albumin low, or if patient is on valproate sodium
Valproate sodium	20–40 mg/kg**	15–40 mg/kg/d (divided in q6–12 doses)	Hepatic	Platelet dysfunction, thrombocytopenia, pancreatitis, and tremor
Levetiracetam	2,500–4,000 mg	2,000–12,000 mg/d (divided in q6–12 doses)	Renal	Somnolence, behavioral disturbances, and agitation
Lacosamide	400 mg	200–300 mg q12 hr	Renal/hepatic	Bradycardia, prolonged PR interval
Midazolam	0.2 mg/kg, Q5 min prn (max 2 mg/kg)	0.1–2.9 mg/kg/hr	Hepatic	Hypotension, accumulates in fat
Propofol	1–2 mg/kg, Q5 min prn (max 10 mg/kg)	33–250 μg/kg/min	Hepatic	Hypotension, propofol infusion syndrome
Ketamine	1.5 mg/kg, Q5 min prn (max 4.5 mg/kg)	1.2–7.5 mg/kg/hr	Hepatic	Hypertension, rise in ICP (unlikely)
Pentobarbital	5 mg/kg (at 50 mg/min), repeat 5 mg/kg boluses Q5 min prn (max 25 mg/kg)	1–10 mg/kg/hr	Hepatic	Hypotension, gastroparesis, cardiac suppression, and thrombocytopenia

d day, *hr* hour, *ICP* intracranial pressure, *min* minute, *PR* per rectum, and *prn* pro re nata (as needed)

*Target serum phenytoin level is 20 ug/ml (total level) or 2–3 ug/ml (free level)

**Target serum valproate sodium level is 80–120 ug/ml

these patterns; however, most patients are placed on prophylactic AEDs to prevent the emergence of bona fide seizures.

Seizure Prophylaxis in Intracranial Pathologies

Any intracranial process can potentially be a risk factor for a new-onset seizure; however, different diseases are associated with various rates of seizure occurrence. The use of AEDs in neurocritical care patients is controversial, and in this section we will discuss risks and benefits of seizure prophylaxis for common critically ill neurology patients.

Traumatic Brain Injury (TBI)

Seizures in TBI are classified as early or late depending on whether they occur before or after 7 days, respectively. In patients with severe TBI (i.e., GCS ≤8 and/or with parenchymal/subdural hemorrhage, depressed skull fractures, or brain contusions), the incidence of early seizure ranges between 20 and 25 % [57]. In patients with penetrating TBI, the incidence of early seizure is up to 50 %. In a randomized trial, it was shown that patients with severe TBI had significantly lower incidence of early seizures when treated with phenytoin compared to placebo (3.6 % and 14.2 %, respectively); however, phenytoin was associated with decreased functional performance at 1 month [58, 59]. In another randomized trial, valproate sodium was shown to be as effective as phenytoin in preventing early seizures; however, there was a trend toward higher mortality in patients treated with valproate sodium [60]. For this reason, valproate sodium is not used in seizure prophylaxis of patients with TBI. Lastly, levetiracetam has been investigated in small prospective and randomized trials, which showed to be as effective as phenytoin in early seizure prophylaxis. Furthermore, treatment with levetiracetam was associated with improved disability rating scores and Glasgow Outcome Scale [61, 62]. Currently, the Brain Trauma Foundation (BTF) and American Academy of Neurology (AAN) recommend 7 days of seizure prophylaxis in severe TBI patients to minimize the occurrence of early seizures [63, 64]. In many institutions there is a trend toward using levetiracetam (dose ranging from 500 to 1,500 mg twice daily) due to its bioavailability, side effect profile, and minimal drug interactions. Seizure prophylaxis is not recommended for late-onset seizures (>7 days) in severe TBI patients since the incidence of late-onset seizure has not shown to be reduced by any of the investigated AEDs [65, 66]. Lastly, seizure prophylaxis is not routinely recommended for mild to moderate TBI due to low risk of post-traumatic seizures of 0.7 and 1.2 %s [57].

Brain Tumors

Generally about 25–45 % of patients with brain tumor will develop new-onset seizures, with some of the high-risk features including the tumor type (primary tumor vs. metastasis) and location (temporal lobe) [67, 68]. Given the high seizure incidence, prophylaxis has been extensively investigated in multiple randomized controlled trials and meta-analyses. The latest guideline from AAN in 2000 recommends that patients with newly diagnosed brain tumors should not routinely receive AEDs for seizure prophylaxis. This recommendation was based on multiple studies, including four randomized controlled trials, mainly investigating older AEDs (phenytoin, valproate sodium, and phenobarbital) [67]. Since then, there have been multiple meta-analyses with similar findings of older AEDs being ineffective for seizure prophylaxis in patients with primary or metastatic brain tumors [69, 70]. The use of these AEDs is further complicated by their significant drug interaction with chemotherapeutic agents. Further investigation is required to assess the efficacy of newer AEDs such as levetiracetam. However, in patients undergoing tumor resection, the use of levetiracetam for perioperative seizure prophylaxis is reasonable [71].

Ischemic Stroke

In the patients older than 60 years, the most common cause of a new-onset unprovoked seizure is an ischemic stroke [72]. The incidence of stroke-related seizure varies greatly among studies, but it is typically less than 10 % and similar to TBI in that it can occur early or late after stroke onset [73]. There is no clear correlation between stroke size or subtype and the risk of seizure development [74]. As of the most recent American Heart Association/American Stroke Association (AHA/ASA) guideline, the prophylactic use of AEDs is not recommended due to a paucity of data [73].

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH), especially if cortical, is more epileptogenic than ischemic stroke with the post-ICH incidence of seizure ranging from 2.7 to 17 % with the majority occurring close to ICH onset [75]. The incidence of ICH-related seizure is even higher when cEEG is utilized at 28–31 %, likely representing a reporting bias from the use of a more sensitive diagnostic tool [27, 76]. Seizure

prophylaxis in ICH is controversial, however, as two studies (primarily using phenytoin) showed worsened mortality and functional outcome associated with seizure prophylaxis [77, 78]. The latest AHA/ASA guideline recommends against seizure prophylaxis in patients with ICH [75]. It should be noted that in ICH patients with out of proportion or fluctuating neurological exam, it is imperative to screen for seizures using cEEG. In one study, acute seizure after ICH was an independent predictor of increased midline shift [27].

Aneurysmal Subarachnoid Hemorrhage (aSAH)

Patients with aSAH can present with seizure-like events (e.g., posturing); it is estimated that the incidence of seizures spans from 6 to 18 % and typically occurs early in the course [79, 80]. Some of the risk factors for seizure occurrence are location of aneurysm (middle cerebral artery), thickness of aSAH on imaging, the presence of ICH, ischemic stroke or rebleeding, poor neurological exam, history of hypertension, and mode of aSAH (i.e., treatment with clipping) [81]. In the acute phase of aSAH when the aneurysm is still unsecured, seizures can potentially be catastrophic as it can lead to rebleeding [82, 83]. Unfortunately, there are no randomized trials to assess the utility of seizure prophylaxis in this population, and most of studies have focused on the use of phenytoin, which was again associated with worse neurological outcomes [84, 85]. Thus, seizure prophylaxis is only recommended in the acute setting of aSAH for 3–7 days as per both AHA/ASA and NCS guidelines [81, 86]. The drug of choice in most institution remains to be levetiracetam for the aforementioned reasons.

Case Example Explanation

What would be your initial approach to the management of this patient?

The first step in the management of an "unresponsive" patient includes the assessment of ABCs and appropriate stabilization (see Fig. 3.1). This should be followed by a succinct neurological examination to serve as a guide in diagnosis and management. The differential diagnosis should be formulated based on the patient's clinical presentation, comorbidities, and neurological examination. In this particular case, the patient's sudden onset of "unresponsiveness" points to an etiology such as a vascular event (e.g., ischemic/hemorrhagic stroke) or seizures.

After your initial assessment, the patient is hemodynamically appropriate but on neurological examination does not follow commands with eyes closed despite noxious stimulation. Further examination reveals normal cranial nerves, a symmetric motor exam with localization of all extremities, and normal muscle tone. However, you note a right-sided gaze deviation that lasted for 30 s. What are the next steps?

Etiologies such as posterior circulation strokes (i.e., affecting brain stem or bilateral thalami) or herniation syndromes due to mass effect (e.g., intracerebral hemorrhage) must always be considered given the urgency and narrow window of their treatment. However, in this patient such etiologies are lower on the differential given normal cranial nerves and symmetric motor examination. The right-sided gaze deviation can be a clue that is typically either due to seizure or a structural lesion causing gaze deviation away or toward the lesion, respectively. This is due to hyper-excitation (in seizure) or inhibition (in structural lesion) of the frontal eye field center that plays a role in controlling horizontal eye movements. In this particular case, given the patient's normal motor and cranial nerve exam, the right gaze deviation most likely signifies seizure.

After sending appropriate labs (Fig. 3.1), you decide to administer lorazepam. The patient, however, is now unable to protect his airway and requires intubation. The patient's gaze deviation has now resolved, and a CT of his head shows subtle hypodensities in bilateral occipital lobes, consistent with vasogenic edema. It has now been 20 min since the patient was last noted to be at his neurologic baseline. What are the next steps in management?

In the setting of hypertension, immunosuppressive therapy, and radiographic findings consistent with vasogenic edema, PRES is the most likely etiology of his new-onset seizure (Table 3.1). At this point, the patient should be presumed to be in nonconvulsive status epilepticus and treated with a similar urgency as that for convulsive SE (see Fig. 3.1). The patient should be started on an anesthetic AED (e.g., propofol) as well as the administration of a second-line AED. The choice of AED should be tailored based on the drug's side effect profile and patient's comorbidities as shown in Table 3.4. In this patient, levetiracetam may be an ideal agent since, unlike valproate sodium and phenytoin, it does not interact with warfarin. In tandem, the patient should be monitored with continuous EEG for 24–48 h to confirm and/or to tailor AED treatment. Importantly, the patient's blood pressure should also be controlled given the presumptive diagnosis of PRES.

The labs all return normal and on cEEG patient is noted to be in NCSE. This prompts you to bolus and increase the maintenance dose of propofol, which achieves the desired effect. After 24 h of seizure freedom, propofol may be tapered off leading to liberation from mechanical ventilation after returning the patient to his baseline neurological examination.

References

1. Towne AR, Waterhouse EJ, Boggs JG, Garnett LK, Brown AJ, Smith Jr JR, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;54(2):340–5.
2. Kamel H, Betjemann JP, Navi BB, Hegde M, Meisel K, Douglas VC, et al. Diagnostic yield of electroencephalography in the medical and surgical intensive care unit. Neurocrit Care. 2013;19(3):336–41.
3. Kurtz P, Gaspard N, Wahl AS, Bauer RM, Hirsch LJ, Wunsch H, et al. Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med. 2014;40(2):228–34.
4. 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.
5. Pandian JD, Cascino GD, So EL, Manno E, Fulgham JR. Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. Arch Neurol. 2004;61(7):1090–4.
6. Gilmore EJ, Gaspard N, Choi HA, Cohen E, Burkart KM, Chong DH, et al. Acute brain failure in severe sepsis: a prospective study in the medical intensive care unit utilizing continuous EEG monitoring. Intensive Care Med. 2015;41(4):686–94.
7. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743–8.
8. DeLorenzo RJ, Waterhouse EJ, Towne AR, Boggs JG, Ko D, DeLorenzo GA, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia. 1998;39(8):833–40.
9. Jordan KG. Neurophysiologic monitoring in the neuroscience intensive care unit. Neurol Clin. 1995;13(3):579–626.
10. Privitera M, Hoffman M, Moore JL, Jester D. EEG detection of nontonic-clonic status epilepticus in patients with altered consciousness. Epilepsy Res. 1994;18(2):155–66.
11. Benbadis SR, Tatum WO. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;55(9):1421–3.
12. Foreman B, Hirsch LJ. Epilepsy emergencies: diagnosis and management. Neurol Clin. 2012;30(1):11–41, vii.
13. Young GB, 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.
14. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. J Clin Neurophysiol: Off Publ Am Electroencephalographic Soc. 2015;32(2):87–95.
15. Hirsch LJ, Gaspard N. Status epilepticus. Continuum. 2013;19(3 Epilepsy):767–94.
16. Fisher RS, van Emde BW, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470–2.
17. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51(4):676–85.
18. Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol: Off Publ Am Electroencephalographic Soc. 2013;30(1):1–27.
19. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(1):120–2.
20. Shorvon S. What is nonconvulsive status epilepticus, and what are its subtypes? Epilepsia. 2007;48 Suppl 8:35–8.
21. Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia. 2013;54 Suppl 6:28–9.
22. Bleck TP. Refractory status epilepticus. Curr Opin Crit Care. 2005;11(2):117–20.
23. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J Neurol Neurosurg Psychiatry. 2005;76(4):534–9.
24. Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care. 2014;20(3):476–83.
25. Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol. 2002;59(2):205–10.
26. Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, 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.
27. Vespa PM, O'Phelan K, Shah M, Mirabelli J, Starkman S, Kidwell C, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. Neurology. 2003;60(9):1441–6.
28. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol. 2006;5(3):246–56.
29. Fountain NB, Lothman EW. Pathophysiology of status epilepticus. J Clin Neurophysiol: Off Publ Am Electroencephalogr Soc. 1995;12(4):326–42.
30. Perucca E. An introduction to antiepileptic drugs. Epilepsia. 2005;46 Suppl 4:31–7.
31. Meldrum BS. Update on the mechanism of action of antiepileptic drugs. Epilepsia. 1996;37 Suppl 6:S4–11.
32. Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J Neurosci: Off J Soc Neurosci. 1997;17(19):7532–40.
33. Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relation to ictal physiological events. Arch Neurol. 1973;28(1):10–7.
34. Sloviter RS. Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. Science. 1987;235(4784):73–6.
35. Fujikawa DG. The temporal evolution of neuronal damage from pilocarpine-induced status epilepticus. Brain Res. 1996;725(1):11–22.
36. Rabinowicz AL, Correale JD, Bracht KA, Smith TD, DeGiorgio CM. Neuron-specific enolase is increased after nonconvulsive status epilepticus. Epilepsia. 1995;36(5):475–9.
37. Chu K, Kang DW, Kim JY, Chang KH, Lee SK. Diffusion-weighted magnetic resonance imaging in nonconvulsive status epilepticus. Arch Neurol. 2001;58(6):993–8.
38. Lazeyras F, Blanke O, Zimine I, Delavelle J, Perrig SH, Seeck M. MRI, (1)H-MRS, and functional MRI during and after prolonged nonconvulsive seizure activity. Neurology. 2000;55(11):1677–82.
39. Tomlinson FH, Anderson RE, Meyer FB. Effect of arterial blood pressure and serum glucose on brain intracellular pH, cerebral and cortical blood flow during status epilepticus in the white New Zealand rabbit. Epilepsy Res. 1993;14(2):123–37.
40. Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. Am J Med. 1980;69(5):657–66.
41. Simon RP. Physiologic consequences of status epilepticus. Epilepsia. 1985;26 Suppl 1:S58–66.
42. Jirsch J, Hirsch LJ. Nonconvulsive seizures: developing a rational approach to the diagnosis and management in the critically ill

population. Clin Neurophysiol: Off J Int Fed Clin Neurophysiol. 2007;118(8):1660–70.
43. Smith PE. Epilepsy: mimics, borderland and chameleons. Pract Neurol. 2012;12(5):299–307.
44. Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia. 2005;46(5):669–76.
45. Smith SJ. EEG in the diagnosis, classification, and management of patients with epilepsy. J Neurol Neurosurg Psychiatry. 2005;76 Suppl 2:ii2–7.
46. Le Roux P, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocrit Care. 2014;21 Suppl 2:S1–26.
47. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.
48. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339(12):792–8.
49. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345(9):631–7.
50. Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012;366(7):591–600.
51. Gilad R, Izkovitz N, Dabby R, Rapoport A, Sadeh M, Weller B, et al. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. Acta Neurol Scand. 2008;118(5):296–300.
52. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. Neurology. 2006;67(2):340–2.
53. Zelano J, Kumlien E. Levetiracetam as alternative stage two antiepileptic drug in status epilepticus: a systematic review. Seizure. 2012;21(4):233–6.
54. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol. 2012;259(4):645–8.
55. 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.
56. Marchi NA, Novy J, Faouzi M, Stahli C, Burnand B, Rossetti AO. Status epilepticus: impact of therapeutic coma on outcome. Crit Care Med. 2015;43(5):1003–9.
57. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med. 1998;338(1):20–4.
58. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med. 1990;323(8):497–502.
59. Dikmen SS, Temkin NR, Miller B, Machamer J, Winn HR. Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. JAMA. 1991;265(10):1271–7.
60. Temkin NR, Dikmen SS, Anderson GD, Wilensky AJ, Holmes MD, Cohen W, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. J Neurosurg. 1999;91(4):593–600.
61. Jones KE, Puccio AM, Harshman KJ, Falcione B, Benedict N, Jankowitz BT, et al. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. Neurosurg Focus. 2008;25(4):E3.
62. Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. Neurocrit Care. 2010;12(2):165–72.
63. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. XIII. Antiseizure prophylaxis. J Neurotrauma. 2007;24 Suppl 1:S83–6.
64. Chang BS, Lowenstein DH. Quality Standards Subcommittee of the American Academy of N. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003;60(1):10–6.
65. Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst Rev. 2001(4):CD000173.
66. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia. 2001;42(4):515–24.
67. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;54(10):1886–93.
68. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 2007;6(5):421–30.
69. Sirven JI, Wingerchuk DM, Drazkowski JF, Lyons MK, Zimmerman RS. Seizure prophylaxis in patients with brain tumors: a meta-analysis. Mayo Clin Proc. 2004;79(12):1489–94.
70. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev. 2008(2):CD004424.
71. Iuchi T, Kuwabara K, Matsumoto M, Kawasaki K, Hasegawa Y, Sakaida T. Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study. J Neurol Neurosurg Psychiatry. 2015;86:1158–62.
72. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia. 1996;37(3):224–9.
73. Jauch EC, Saver JL, Adams Jr HP, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke J Cereb Circ. 2013;44(3):870–947.
74. Gupta SR, Naheedy MH, Elias D, Rubino FA. Postinfarction seizures. A clinical study. Stroke J Cereb Circ. 1988;19(12):1477–81.
75. Morgenstern LB, Hemphill 3rd JC, Anderson C, Becker K, Broderick JP, Connolly Jr ES, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke J Cereb Circ. 2010;41(9):2108–29.
76. Claassen J, Jette N, Chum F, Green R, Schmidt M, Choi H, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology. 2007;69(13):1356–65.
77. Messe SR, Sansing LH, Cucchiara BL, Herman ST, Lyden PD, Kasner SE, et al. Prophylactic antiepileptic drug use is associated with poor outcome following ICH. Neurocrit Care. 2009;11(1):38–44.
78. Naidech AM, Garg RK, Liebling S, Levasseur K, Macken MP, Schuele SU, et al. Anticonvulsant use and outcomes after intracerebral hemorrhage. Stroke J Cereb Circ. 2009;40(12):3810–5.
79. Butzkueven H, Evans AH, Pitman A, Leopold C, Jolley DJ, Kaye AH, et al. Onset seizures independently predict poor outcome after subarachnoid hemorrhage. Neurology. 2000;55(9):1315–20.

80. Rhoney DH, Tipps LB, Murry KR, Basham MC, Michael DB, Coplin WM. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. Neurology. 2000;55(2):258–65.
81. Connolly Jr ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke J Cereb Circ. 2012;43(6):1711–37.
82. Kvam DA, Loftus CM, Copeland B, Quest DO. Seizures during the immediate postoperative period. Neurosurgery. 1983;12(1):14–7.
83. Matthew E, Sherwin AL, Welner SA, Odusote K, Stratford JG. Seizures following intracranial surgery: incidence in the first post-operative week. Can J Neurol Sci J Can Sci Neurol. 1980;7(4):285–90.
84. Naidech AM, Kreiter KT, Janjua N, Ostapkovich N, Parra A, Commichau C, et al. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. Stroke J Cereb Circ. 2005;36(3):583–7.
85. Rosengart AJ, Huo JD, Tolentino J, Novakovic RL, Frank JI, Goldenberg FD, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. J Neurosurg. 2007;107(2):253–60.
86. Diringer MN, Bleck TP, Claude Hemphill 3rd J, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211–40.