Seizures and the Neurosurgical Intensive Care Unit

Panayiotis N. Varelas, MD, PhD[a,b,*],
Marianna V. Spanaki, MD, PhD, MBA[a],
Marek A. Mirski, MD, PhD[c,d]

KEYWORDS

• Seizures • Neurosurgical intensive care unit • Antiepileptic drugs

KEY POINTS

- Although prophylaxis is often not recommended, prompt treatment of seizures, especially recurrent or prolonged, improves the clinical outcome.
- Seizures occurring in the neurosurgical intensive care unit (NICU) are of diverse structural causes and metabolic disturbances, each with a distinct risk of seizures.
- Several, but not all, new anticonvulsants hold promise as successful agents to treat NICU-related seizures.

INTRODUCTION

The neurosurgical intensive care unit (NICU) is a complex environment. Seizures occur more often in this unit than in general or other specialty ICUs, partly because of the patient population but also because of the enhanced neurologic monitoring undertaken in such units with specialty trained personnel. Both primary neurologic as well as non-neurologic causes of seizures may occur, often in combination, leading to complex clinical evaluations to ascertain the probable cause. Therefore, to avoid confusion and frustration, the neurosurgeon, neuro-intensivist, or consulting neurologist should have an algorithmic approach to the problem.

This topic is vast. In this review, the authors present the most common causes of seizures encountered in the NICU, suggest treatment algorithms, and end with the most recent information regarding the newest antiepileptic drugs (AEDs). The interested reader can find additional information in other review articles[1] or specialized textbooks on this subject.[2]

INCIDENCE

The incidence of seizures in the general ICUs ranges from 3.3% to 34.0%, depending on the ICU population and the detection method. When a routine electroencephalogram (EEG) is used, the incidence is lower than when continuous EEG monitoring is used. Varelas and colleagues[3] reported that out of 129 emergent EEGs ordered in ICUs, 49 (38%) showed some ictal (12%) or interictal (26%) epileptiform activity. Independent variables predicting seizures in the ICU were age, cardiopulmonary arrest, and use of prolonged EEG for detection.

The specific patient population admitted to the ICU may also play a role. For example, in an NICU, 34% of patients had nonconvulsive seizures on continuous EEG, and 76% of them were in nonconvulsive status epilepticus (NCSE).[4]

[a] Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202-2689, USA; [b] Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202-2689, USA; [c] Department of Neurology, Johns Hopkins Hospital, 600 North Wolfe Street, Meyer 8-140, Baltimore, MD 21287, USA; [d] Department of Anesthesiology and Critical Care, Johns Hopkins Hospital, 600 North Wolfe Street, Meyer 8-140, Baltimore, MD 21287, USA

* Corresponding author. Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, K-11, Detroit, MI 48202-2689.
E-mail address: varelas@neuro.hfh.edu

Neurosurg Clin N Am 24 (2013) 393–406
http://dx.doi.org/10.1016/j.nec.2013.03.005
1042-3680/13/$ – see front matter

Box 1
Common causes of critical care seizures

Neurologic pathology
Neurovascular
- Ischemic stroke
- Hemorrhagic stroke
  - Subarachnoid hemorrhage
  - Intracerebral hemorrhage
- Arteriovenous malformation
- Cerebral sinus thrombosis
- Hyperperfusion syndrome

Tumor
- Primary
- Metastatic

Central nervous system (CNS) infection
- Abscess
- Meningitis
- Encephalitis

Encephalitis (noninfectious)
- Paraneoplastic limbic
  - N-methyl-d-aspartate–receptor antibodies
- Nonparaneoplastic limbic
  - Voltage–gated K+ channel antibodies (VGKC/LGII)

Inflammatory disease
- Vasculitis
- Acute disseminated encephalomyelitis

Traumatic head injury
- Depressed skull fragments
- Cerebral contusion
- Extra-axial hemorrhage
  - Subdural hematoma
  - Epidural hematoma
  - Hygroma (?)

Primary epilepsy
Primary CNS metabolic disturbance (inherited)

Complications of critical illness
Hypoxia/ischemia
Drug/substance toxicity
- Antibiotics
- Antiviral agents
- Antidepressants
- Antipsychotics
- Bronchodilators
- Local anesthetics
- Immunosuppressives
- Cocaine
- Amphetamines
- Phencyclidine

Drug/substance withdrawal
- Barbiturates
- Benzodiazepines
- Opioids
- Alcohol

Infection (febrile seizures)
Metabolic abnormalities
- Hypophosphatemia
- Hyponatremia
- Hypoglycemia
- Renal/hepatic dysfunction

Data from Mirski MA, Varelas PN. Seizures and status epilepticus in the critically ill. Crit Care Clin 2008;24:115–47, ix.

CAUSE AND PATHOPHYSIOLOGY

Seizures in the NICU can be caused either by primary neurologic pathology or as a complication of critical illness (**Box 1**). Although in general ICUs the latter may be more common, in neurologic and neurosurgical patients, structural pathology may be the leading cause. In several patients, however, both can be present. In this case, it is difficult to decide which one of the two is the major contributor, but correcting the nonstructural disorder usually brings seizures under control.

The mechanisms by which nonstructural abnormalities induce seizures are, in many cases, unknown. Drugs precipitate seizures by either preventing γ-aminobutyric acid (GABA) binding to the $GABA_A$ receptor,[5] such as with antibiotics, or via antagonism at the Na^+ channels, such as with the local anesthetics. Depending on the level of potassium, hyperkalemia may depolarize the neuronal membranes or inactivate the Na^+ and Ca^{++} channels, leading to an increased threshold for membrane depolarization. Hyponatremia and low osmolarity, as a consequence of increased cellular edema and increased neuronal excitability, may also lead to seizures. During alkalosis, increased inward Na^+ and Ca^{++} channel currents and during hypomagnesemia decreased N-methyl-d-aspartate receptor antagonism promote cell depolarization.[6]

SEIZURES AFTER STROKE

Seizures after Ischemic Stroke

The most common cause of seizures in patients older than 60 years is ischemic stroke,[7] although the overall risk is fairly low, ranging from 4.4% to 13.8% depending on the subgroups of patients included in the analysis and the follow-up period.[8,9] These seizures can be divided into early (24 hours to 4 weeks, depending on the definition used by the study) and late (usually after the first 4 weeks). Early seizures occur in 1.8% to 15.0% of patients[10,11] and are thought to be caused by excitatory or inhibitory alterations in the penumbral tissue.[12] They are not associated with higher mortality at 1 month and 1 year or with an unfavorable functional outcome, as in a large recent registry from France.[13] Thrombolysis with tissue plasminogen activator (t-PA), however, may lead to worse outcomes in 3 months in the group with seizures compared with the group without seizures.[14] Additionally, patients receiving endovascular treatment and developing early poststroke seizures have worse outcomes and higher mortality compared with seizure-free patients.[15] Late seizures (after 4 weeks) have been reported in 2.5% to 15.0% of poststroke cases[16–18] and are thought to emanate from gliosis and the development of a meningocerebral cicatrix. These patients with late-onset seizures are at an almost 3 times higher risk for subsequent stroke.[19]

Status epilepticus (SE) comprises one-fourth to one-sixth of poststroke seizures and is significantly correlated with infarcts in the posterior temporal region.[20] Interestingly, if SE is the first epileptic manifestation after stroke, it is usually not followed by other seizures. If, however, SE follows early or late seizures, the chances are high that it will recur as SE or seizures.[21] Using data from the Nationwide Inpatient Sample, Bateman and colleagues[22] estimated that generalized convulsive SE developed in 0.2% of the acute ischemic strokes, in 0.3% of the intracerebral hemorrhages, and was associated with higher rates of adverse outcomes.

Management of patients with ischemic stroke and seizures in the NICU should not be different than that for seizures from other causes. The most recent guidelines from the American Heart Association and the American Stroke Association do not recommend prophylactic use of AEDs and recognize that there are few data pertaining to the efficacy of these drugs in the treatment of poststroke seizures.[23] Some studies report protection from seizures with AEDs only during the period that these drugs are administered but have no carryover effect in preventing late-onset seizures following AED discontinuation.[24] However, some patients may be at a higher risk for seizures, such as those with stroke after cardioembolism (seizures occurring within the first 24 hours),[9] those with high admission glucose[13] or after thrombolysis with t-PA,[14] with large infarcts, cortical involvement or hemorrhagic component,[8,11,17,25] with watershed distributions[26] and affecting temporal and parietal branches of the middle cerebral artery (late seizures) or temporal and occipital branches of the middle cerebral artery (early seizures).[20] Additional factors for poststroke seizures and a possible need for longer AED administration are preexisting dementia,[27] late poststroke seizures (an independent predictor of epilepsy),[8,17] and SE following poststroke seizures.[21] In a study of 204 patients with stroke-related seizures, seizure recurrence was observed in 13.8% of the early seizure (<15 days), in 54.7% of the late-seizure (1–24 months), and in 34.0% of the very-late-seizure (>24 months) group. Interestingly, 25% of the very late seizures were related to lacunar strokes and very mild disability.[28]

Regarding the choice of AEDs, the available data are also not very helpful; randomized studies comparing AEDs to placebo for primary or secondary prevention of seizures are missing.[29] New-generation AEDs, such as lamotrigine, gabapentin, and levetiracetam, in low doses would be reasonable choices, especially for elderly patients, because of their improved safety profile and fewer interactions with other drugs, including anticoagulants, compared with first-generation AEDs.[24] Topiramate may have additional neuroprotective properties against cerebral ischemia,[30] in contrast with phenytoin, barbiturates, and benzodiazepines, that may have a negative effect on recovery from stroke.[31] Overall, poststroke seizures are usually easily controlled and monotherapy usually suffices.[24]

Seizures after Intracerebral Hemorrhage

The risk for seizures is 2 to 7 times higher with intracerebral hemorrhage (ICH) than with ischemic stroke.[8,25,32] This difference was evident in the study by Vespa and colleagues,[33] whereby 28% of patients with ICH developed seizures despite being given prophylactic AEDs. Only 6% of those with ischemic stroke had seizures in the absence of AEDs.

The incidence of post-ICH seizures varies between 0% and 28%, with studies using continuous EEG monitoring (CEEG) reporting higher range percentages.[33–36] In patients with electrographic seizures, CEEG will detect them within 1 hour in

56% and within 2 days in 94% of the time.[36] Supporting cortical localization as a principal risk, lobar or subcortical ICHs have the highest incidence of seizures; those in the posterior fossa have almost zero.[8,34] In a large Italian study, hyperlipidemia conferred a lower risk for seizures after ICH.[25] After surgical evacuation of the hematoma, seizures occur even more frequently. In a study of 110 patients with evacuated thrombus, 41.8% of patients had seizures, 29.6% of which were clinical and 16.3% were electrographic. ICH volume, presence of subarachnoid hemorrhage (SAH) and subdural hemorrhage predicted early seizures; subdural hematoma and increased admission international normalized ratio predicted late seizures.[37]

As with ischemic stroke, it is unclear if seizures should be treated prophylactically. The current guidelines suggest administration of AEDs only if clinical or electrographic seizures occur. They also recommend CEEG in patients with depressed mental status out of proportion to the degree of brain injury to detect them.[38] Patients with alcoholism with ICH who have a 3-fold increased risk for SE[39] should also be treated with AEDs that increase GABAergic inhibition (for example, benzodiazepines). If late seizures occur (after 2 weeks from onset), long-term AEDs should be prescribed because of the greater risk of epilepsy.[40–42] However, it is unknown which AEDs should be used. In a prospective study of 98 patients with ICH, phenytoin (and not levetiracetam) was associated with more fever, worse National Institute of Health's stroke scale at 14 days, and worse modified Rankin scale up to 3 months. Interestingly, even excluding the 7 patients who did have seizures from the analysis did not change the results.[43]

Seizures after SAH

At the onset of SAH, many patients have motor manifestations and loss of consciousness, which may not be seizures but represent opisthotonos or posturing from acute hydrocephalus or loss of cerebral blood flow momentarily.[2,44] However, early seizures in 1.1% to 16.0% and late seizures in 5.1% to 14.0% of patients with SAH have also been reported.[45–47] In a recent review of 25 studies with 7000 patients, early postoperative seizures occurred in 2.3% and late postoperative seizures in 5.5% of patients (on average 7.45 months after the bleed). Late seizures were more likely with middle cerebral artery aneurysms, Hunt/Hess grade III, and clipping.[48] Because rebleeding from an unprotected aneurysm during seizures is a serious concern, most neurosurgeons prefer to administer AEDs until the aneurysm is secured. However, rebleeding may also manifest as a new seizure.[45,49] Therefore, if there is a prolonged change in the neurologic status or new blood in the ventriculostomy after a seizure, imaging of the brain should be considered. Because CEEG detects NCSE in 8% of patients with SAH, it should be used in those NICU patients with otherwise unexplained coma or neurologic deterioration after SAH[50] or if sedated. In a recent study from Sweden, 7% of sedated patients had seizures, and one was in NCSE for 5 hours.[51]

The therapeutic management of the ruptured aneurysm may also correlate with the incidence of seizures. Coiling, theoretically, may be associated with a lower risk for seizures because of less cortical injury. In a large prospective study, no seizures were witnessed in the periprocedural period (within 30 days) and only 1.7% patients developed late de novo seizures.[52] Further data from the International Subarachnoid Aneurysm Trial have shown a relative risk for seizures of 0.52 with coiling compared with clipping.[53] However, others have found that treatment of only unruptured aneurysms with clipping was associated with a higher risk of seizures or epilepsy compared with coiling, but this difference was not evident in ruptured aneurysms.[54]

The evidence for prophylactic use of AEDs is not compelling.[55] Some experts advocate withholding AEDs on several grounds in the early period because many seizures are unpreventable (occur at onset or during the prehospital period).[56] AED use may precipitate fever, and their use has been correlated to a worse Glasgow Outcome Scale–measured outcome, higher incidence of cerebral vasospasm, neurologic deterioration or cerebral infarction,[57] as well as cognitive and functional disability with phenytoin.[58] Additionally, early perioperative seizures are not predictive of subsequent epilepsy,[59] and such seizures do not lead to a worse outcome after a minimum 1-year follow-up.[60] Others, however, advocate AED use for patients with onset seizures (given only during the hospitalization period),[45,47] rebleeding,[47] subdural hematoma or cerebral infarction at any time point,[61] thick subarachnoid clot, or just periprocedurally[62] but not after coiling of the aneurysm.[52] In a recent review, a 3-day treatment seems to provide similar seizure prevention with better outcome than longer treatment.[63] The American Heart Association's most recent guidelines support prophylactic AEDs in the immediate posthemorrhagic period and routine use of AEDs only in patients with high risk for delayed seizures, such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or middle cerebral artery aneurysm.[64]

It is also unclear which AED should be preferred when seizures occur. Most of the data are derived from phenytoin use, an AED that can reduce the bioavailability of nimodipine, a drug frequently used in these patients.[65] Despite fewer available data, newer AEDs may have a similar[66] or improved profile.[67,68]

The recently reported association of cortical spreading depolarizations (recorded via electrocorticography) with delayed ischemic neurologic deficits despite the absence of vasospasm, opens new horizons in our understanding of electric epiphenomena after SAH.[69–71] The clinical improvement with hypertension in patients with SAH and vasospasm may also be related to spreading depolarizations, because, in animals, a reverse correlation between spreading depression and blood pressure has been reported.[72]

Seizures and Cerebral Venous and Sinus Thrombosis

Seizures are very common after cerebral venous and sinus thrombosis, occurring in 29% to 50% of patients, frequently as an inaugural manifestation.[73,74] Early seizures (within 2 weeks from onset) occur in 34% to 44% of patients and are predicted by presenting seizures, motor or sensory deficits, parenchymal lesion on admission (hemorrhage, infarct, focal edema), and the presence of cortical vein thrombosis.[73–75] Late seizures occur in 9.5% of patients and may be more common in those patients with early seizures.[74] Although randomized controlled studies for prophylactic use of AEDs are not available, these drugs may be prescribed in those patients at high risk for early seizures because they may be associated with higher morbidity and early mortality.[73–75] In a recent retrospective study, however, whereby all patients with seizures received AEDs, seizures were not associated with death or 6-month worse outcomes.[76]

Reperfusion-Hyperperfusion Syndrome and Seizures

Reperfusion-hyperperfusion syndrome (RHS) is an uncommon complication of carotid endarterectomy, carotid angioplasty, and stenting.[77,78] Seizures occur either immediately after revascularization procedures (usually because of distal embolization) or later (7 hours to 14 days)[77–81] and are considered a delayed manifestation of RHS. Transient periodic lateralizing epileptiform discharges have also been reported after internal carotid stenting in a patient with previous ICH[82] and NCSE after superficial temporal to middle cerebral artery anastomosis, successfully treated with AEDs.[83] The use of prophylactic AEDs remains controversial; early onset seizures are treated almost without exception in addition to tight blood pressure control as an adjunct to a likely procedural complication (ICH, severe edema, ischemic stroke). The management of late seizures also includes AEDs in addition to tight blood pressure control, to a level of equalizing transcranial Doppler-measured velocities ipsilateral and contralateral to the treated carotid artery.[79]

TRAUMATIC BRAIN INJURY AND SEIZURES

The incidence of posttraumatic seizures varies widely, with estimates of 2% to 12% in civilian populations and up to 53% in military populations.[84,85] Traumatic brain injury (TBI) accounts for 10% to 20% of symptomatic epilepsy in the general population and 5% of epilepsy in general.[86,87] In a study, however, using CEEG in the NICU, 22% of post-TBI patients had seizures (52% of which were nonconvulsive). One-third of these patients were in SE with minimal clinical signs, such as facial twitching or eye fluttering, and all died.[88] Hippocampal atrophy on volumetric magnetic resonance imaging (MRI), suggesting an anatomic damaging effect, has also been associated with nonconvulsive posttraumatic seizures.[89]

Clinical studies divide seizures into immediate (<24 hours), early (within 1 week, with a seizure incidence of 2.1%–16.9%), or late (with an incidence of 1.9% to >30.0%).[86,87,90] Independent risk factors for late seizures or posttraumatic epilepsy include early seizures, coma or loss of consciousness for more than 24 hours, dural penetration, biparietal or multiple contusions, intracranial hemorrhage, depressed skull fracture not surgically treated, and at least one nonreactive pupil.[87,91] In a recent study, diffuse axonal injury on MRI was not correlated with posttraumatic epilepsy, but cerebral contusions were.[92] Early seizures occur in 25% of patients not treated with AEDs and are associated with seizures immediately following trauma, depressed skull fracture, intracerebral hematoma, or subdural hematoma. The risk is lower (15%–20% range) if the patients had a penetrating head injury, epidural hematoma, cortical contusion, and had a Glasgow Coma scale score of 10 or less.[91] Although early seizures are independently associated with an unfavorable outcome, their effect is much lower than other variables, such as severity of brain injury or older age.[93] Injury surrogate markers have been associated with seizures. In a study of 20 patients with moderate to severe TBI monitored with microdialysis and CEEG, 10 patients had post-TBI seizures, which resulted in episodic increases in intracranial

pressure (ICP) and lactate/pyruvate ratio. Both remained elevated beyond postinjury hour 100 in the subgroup with seizures (compared with the subgroup without), suggesting long-lasting effects.[94]

If early and, especially, late posttraumatic seizures occur, AEDs should be used. The treatment of post-TBI seizures in the ICU is not different from the treatment of any other seizures. Prophylactic AED administration is more controversial. In a systematic review of randomized trials, prophylactic AEDs were effective in reducing early seizures; but there was no evidence that they reduced the occurrence of late seizures or had any effect on death and neurologic disability.[95] The current practice parameters by the American Academy of Neurology (AAN)[96] and the Brain Trauma Foundation[97] advocate prophylactic treatment only during the first 7 days from a head injury. Regarding the choice of AEDs, phenytoin has been shown to decrease the incidence of early posttraumatic seizures[97] and be more cost-effective than levetiracetam.[98] Levetiracetam was equally effective as phenytoin in preventing early seizures in a prospective study of 32 patients with severe TBI but was associated with an increased seizure tendency on 1-hour EEG.[99] Valproic acid, compared with phenytoin, did not seem to benefit and actually showed a trend toward higher mortality.[100] Lastly, vagus nerve stimulation may reduce seizures in patients with refractory posttraumatic epilepsy.[101]

BRAIN TUMORS AND SEIZURES

Many patients admitted to the NICU with brain tumors have seizures (in up to 35% of all tumor cases[102]) and the incidence is both pathology and location dependent. In high-grade, rapidly progressive tumors, such as glioblastoma, or metastatic tumors, seizures occur in 25% to 35% of cases, which is lower than the reported 70% incidence in slower-growing tumors, such as astrocytomas or meningiomas, and 90% in oligodendrogliomas. The locations with the highest incidence are the temporoparietal regions with cortical gray involvement.[103]

Although patients with brain tumors and seizures should be treated with AEDs, prophylactic treatment is controversial. AEDs may interfere with corticosteroids, chemotherapy, and radiation treatment and induce more frequent and serious allergic reactions in such patients.[104] Therefore, the AAN's practice parameter does not support prophylactic AEDs in patients with newly diagnosed brain tumors. Postoperatively, patients who have not experienced a seizure should have tapering and discontinuation of AEDs within a week (particularly those patients who are medically stable and have AED-related side effects).[105] Patients who have brain metastases may have less propensity to develop seizures; based on recently published guidelines, they should also not be on prophylactic AEDs.[106,107]

If seizures occur, the newer-generation AEDs, such as gabapentin, lacosamide, levetiracetam, oxcarbazepine, pregabalin, topiramate, and zonisamide, are preferred because they have fewer drug interactions, especially with chemotherapy, and cause fewer side effects.[108] In a small case series of 25 patients with brain tumor–related epilepsy, oxcarbazepine monotherapy at a mean dosage of 1230 mg/d led to significant improvement in mood and seizure-freedom rate.[109] Perioperative oral or intravenous (IV) levetiracetam administration in patients with primary brain tumors also led to seizure freedom 100% in the presurgery and 84% to 88% in the early late postsurgery phases.[110]

If a primary or metastatic brain tumor is causing SE, a combination of IV phenytoin, IV levetiracetam (median dosage 3 g/d), and by-mouth pregabalin (median dosage 375 mg/d) led to 70% control, on average, 24 hours after the addition of the third AED.[111] In another small case series, pregabalin controlled non-convulsive (NC) seizures or NCSE in 67% of 9 patients with brain tumors.[112]

Older AEDs may also have a role in treating brain tumor–related seizures. In a recent study of patients with glioblastoma, valproic acid improved the survival of patients on temozolomide/radiotherapy compared with those receiving an enzyme-inducing AED or no AED.[113] It is unclear if this valproic effect is through increased temozolomide bioavailability or its action as a histone deacetylase inhibitor.[114]

DRUG-INDUCED SEIZURES

Drugs rank low as precipitants of seizures in the NICU.[5,115] Antibiotics, such as the penicillins, cephalosporins, carbapenems (especially imipenem), aztreonam, fluoroquinolones, isoniazid, and metronidazole, can precipitate seizures when administered intrathecally[116] or at high doses in patients with renal insufficiency[5] or undergoing continuous renal replacement therapy.[117] Peak concentration periods of the drug may also provoke electrographic changes. During infusion of cefepime and CEEG, 23.7% of patients had continuous epileptiform discharges compared with only 3.75% during meropenem infusion.[118] Because of their specific action through GABA receptors, it is important to remember that first-line

AEDs should be GABAergic agonists, such as benzodiazepines or barbiturates. In case of isoniazid intoxication, the addition of IV pyridoxine is important because the drug antagonizes B6 transformation to pyridoxal phosphate, an essential cofactor for GABA synthesis.[5]

Intrathecal administration of baclofen may provoke seizures or convulsive or nonconvulsive SE in patients with multiple sclerosis.[119] Similarly, intrathecal absorption of the locally used hemostatic agent tranexamic acid can lead to seizures.[120] These seizures are self-limiting and easily controlled with AEDs.

Rapid opioid withdrawal may provoke seizures, which appear on average, 2 to 4 days following discontinuation.[121] Normeperidine, a metabolite of meperidine, is a strong proconvulsant. This drug should probably be avoided in the NICU.[122]

ELECTROLYTE AND METABOLIC ABNORMALITIES

Hyponatremia is the most frequent ICU electrolyte abnormality associated with new-onset seizures (in 18.2% of ICU patients[121]). Acute hyponatremia is associated with a higher risk for seizures than chronic hyponatremia.[123] Correction of Na^+ levels is adequate treatment if structural intracranial pathology is not present. The rate of Na^+ correction with hypertonic solutions can be faster in acute cases (up to 1–2 mEq/L/h of Na^+ increase until seizures are under control) than in chronic cases, when it should be less than 0.5 mEq/L/h.[124]

Disturbances in glucose levels have become common in NICU patients with implementation of tighter glucose control than in the past. Both focal and generalized seizures can be caused by hyperglycemia and hypoglycemia. Seizures related to nonketotic hyperosmolar hyperglycemia may present as speech arrest, visual disturbances, or be related to limb movement (*reflex seizures*).[125,126] Seizures associated with hypoglycemia are frequently preceded by signs of sympathetic excitation. There is no role for AEDs, and only correction of the glucose abnormality will bring the seizures under control.[2]

TREATMENT OF NICU SEIZURES

Seizures complicating critically ill neurosurgical patients should not be considered benign phenomena. During seizures or SE, ICP increases in parallel with cerebral blood flow, brain temperature, and lactate/pyruvate ratio and is correlated with dramatic reductions of brain tissue oxygen tension.[94,127] Although there is no broad acceptance that seizures lead to worse outcomes, most intensivists will treat NICU seizures emergently targeting the ensuing immediate brain metabolic stress and potentially the long-standing secondary effects.

The management of NICU seizures basically follows the same general rules, which guide treatment of noncritically ill patients (**Box 2**). A new staged approach to the treatment of SE has been proposed and included in **Box 2**.[128–131] Because the NICU admits the most resistant-to-treatment seizures, familiarity of the medical and nursing staff with the process of diagnosis and treatment is essential. Urgency without panic is important when seizures are recurrent or SE is present because the duration of seizures is related to resistance to treatment and overall outcome.[132]

Newer Antiepileptic Agents and Their Potential Use in the NICU

Several newer AEDs have currently found their place in the epileptologist's armamentarium. Their use in the NICU is limited because of a lack of parenteral preparations and no approved status beyond adjunct therapy. Therefore, their use should be limited to those patients who are able to swallow or with a nasogastric tube and with proven gastric emptying and absorption of the drug. Indications for their administration include (1) continuation of home regimen; (2) adjunct treatment to older parenteral AEDs, when there is a failure to control seizures; (3) specific organ dysfunction or disease prohibiting the use of other parenteral AEDs; (4) proven allergy to older AEDs; and (5) reason for limited interactions with other crucial drugs, such as chemotherapeutic or immunosuppressive agents, as in patients with brain tumors[108] or after transplantation.[133]

Gabapentin is renally metabolized and has moderate anticonvulsant effects. In the ICU, gabapentin may be considered in patients with hepatic failure or porphyria.[134] Used as a monotherapy, in a dose range from 900 mg/d for patients weighing less than 75 kg to 1200 mg/d for patients weighing more than 75 kg, gabapentin controlled late poststroke seizures in 82% of cases, with higher success among patients who had partial seizures as compared with those with generalized seizures.[135]

Lamotrigine has been approved as an adjunctive therapy or monotherapy in partial or generalized epilepsy and in the Lennox-Gastaut syndrome. Few human data regarding its use in SE exist, and caution should be exerted because cases of new-onset NCSE[136] and myoclonic SE[137] have been reported with its use.

Box 2
Management of seizures in the ICU

1. Brief single seizure (<60 seconds)

   Observe; eliminate cause if identified. Consider a course of chronic therapy: phenytoin 15 to 20 mg/kg or fosphenytoin 15 to 20 mg/kg phenytoin equivalents (PE) loading dose and 300 to 400 mg/d. The goal serum level is 10 to 20 mcg/mL or free level 1 to 2 mcg/mL. Consider IV/oral valproic acid 600 to 3000 mg/d or oral carbamezapine 600 to 1200 mg/d for patients who are phenytoin intolerant. Seizure precautions include padding bed rails and increased observation.

2. Prolonged or more than 1 seizure

   Check oxygen saturation and vital signs. Immediately administer IV benzodiazepine-lorazepam 1 to 2 mg, diazepam 10 to 20 mg, or midazolam 2 to 5 mg with concurrent loading dose phenytoin or fosphenytoin (PE) 15 to 20 mg/kg and maintenance as discussed earlier. Administer valproic acid IV 400 to 600 mg every 6 hours if patients are phenytoin intolerant. Perform similar seizure precautions.

3. Recurrent or refractory seizures of more than 5 minutes or more than 2 discrete seizures between which there is no recovery of consciousness (meeting criteria for SE)

   Stage 1: Emergent initial measures

   Preserve airway and oxygenation by oxygen face mask or intubation, as needed.

   Establish IV access.

   Order EEG to be available during therapy.

   Measure finger-stick blood glucose. Administer 1 A of DW 50% IV if less than 60 mg/100 dL and 100 mg thiamine IV.

   Send to the laboratory the following: antiepileptic blood levels, electrolytes, complete blood count, liver function tests, arterial blood gases, toxicology screen (urine and blood).

   At the same time with the abovementioned stage, complete the following: immediate benzodiazepines (IV lorazepam 0.07–0.1 mg/kg or diazepam 0.15–0.25 mg/kg IV). If there is no IV access, administer diazepam 20 mg per rectum or midazolam 10 mg intramuscularly, buccally, or intranasally.

   Stage 2: Urgent control

   The phenytoin loading dose is 20 mg/kg IV at 50 mg/min or fosphenytoin 20 mg/kg PE IV at 150 mg/min.

   If patients are allergic to phenytoin, administer valproate 25 to 40 mg/kg IV load at 1.5 to 3.0 mg/kg/min or levetiracetam 30 to70 mg/kg IV (500 mg/min) or phenobarbital 20 mg/kg IV (rate 100 mg/min).

   If the seizures continue, administer phenytoin or fosphenytoin (additional 5 mg/kg–10 mg/kg or 5 mg/kg–10 mg/kg PE). The goal serum level is 20 mg dL to 25 mg/dL. If there is a phenytoin allergy, administer an additional valproate load of 20 mg/kg IV.

   The EEG is connected and running.

   Stage 3: Refractory SE

   If patients are NCSE and not yet intubated, one or more of phenytoin, valproic acid, levetiracetam, phenobarbital (that has not been administered in stage 2), or lacosamide can be tried.

   Perform intubation and mechanical ventilation.

   Provide hemodynamic support by pressors and IV fluid boluses.

   Administer propofol 2 mg/kg IV bolus and 150 μg/kg/min to 200 μg/kg/min infusion, or thiopental 2 to 3 mg/kg IV bolus and 0.3 mg/kg/min to 0.4 mg/kg/min infusion, or midazolam 0.2 mg/kg IV bolus, which can be repeated every 5 minutes up to a total of 2 mg/kg, followed by an infusion of 0.1 to 0.2 mg/kg/h.

   If seizures continue, administer pentobarbital 10 mg/kg IV load at up to 50 mg/min, which can be repeated several times until an EEG burst-suppression pattern with 20 to 30 seconds suppression goal is achieved. Start at the same time continuous infusion 1 mg/kg/h and titrate up to 10 mg/kg/h for the same goal.

Stage 4: Alternative therapies for super-refractory SE (in order from the first to the last resort)

- Ketamine 0.5 to 4.5 mg/kg bolus IV and up to 5 mg/kg/h infusion
- Isoflurane, desflurane, gabapentin, or levetiracetam (in acute intermittent porphyria)
- Topiramate 2 to 25 mg/kg/d (children) or up to 300 to 1600 mg/d (adults) per orogastric tube
- Magnesium infusion 4 g bolus IV, 2 to 6 g/h infusion
- Pyridoxine 180 to 600 mg/d IV or per orogastric tube
- Steroids 1 g/d IV for 3 days, followed by 1 mg/kg/d for 1 week or
- Intravenous immunoglobulin 0.4 g/kg/d IV for 5 days or plasmapheresis
- Hypothermia 32°C to 35°C for less than 48 hours
- Ketogenic diet 4:1
- Neurosurgical resection of epileptic focus
- Electroconvulsive therapy
- Vagal nerve or deep brain stimulation or transcranial magnetic stimulation

Data from Refs.[2,128–131]

Topiramate is used in both children and adults with SE.[138,139] The dose administered in adults via nasogastric tube is high, ranging from 300 mg/d to 1600 mg/d. In a recent study of 35 patients with refractory SE treated with topiramate as an adjunct AED, the response rate was 86% (as the third AED) and remained stable at 67% after administration as the fourth, fifth, sixth, or seventh AED. Overall, SE was terminated in 71% of patients within 72 hours after the first administration of topiramate.[140]

Zonisamide controlled intractable SE in siblings with Lafora body disease[141]; but because no parenteral form is available in the United States, its use is limited in the adult NICU as an adjunctive treatment of resistant partial seizures.[142]

Oxcarbazepine is a 10-keto carbamazepine analogue, with a safer clinical profile than carbamazepine. There are no data to support its use in the NICU, and the higher risk for hyponatremia may also be a limiting factor. However, it has been successfully used to treat seizures associated with porphyria cutanea tarda.[143]

Oxcarbazepine monotherapy may improve seizure freedom rate in patients with brain tumor–related epilepsy.[109]

Levetiracetam has a distinct advantage for the ICU use because it is not metabolized through the cytochrome P450 system and its metabolites are inactive and renally excreted. There is no need for drug level monitoring, and there are no significant interactions with other common ICU medications, including other AEDs. It may be used either as an approved adjunct therapy or as an alternative AED in the setting of hepatic insufficiency or porphyria.[144] In renal failure, a 50% dosage is suggested. Levetiracetam may be used to control seizures or SE, and there are some data showing comparable effects with benzodiazepines without the risk for artificial ventilation or hypotension common with the latter. For example, in a recent open-label randomized study of 79 patients with convulsive SE or subtle SE that compared levetiracetam 20 mg/kg IV over 15 minutes with lorazepam 0.1 mg/kg over 2 to 4 minutes, SE was controlled by levetiracetam in 76.3% and by lorazepam in 75.6% of patients.[145] In a review of studies using levetiracetam after benzodiazepines in 334 patients with SE, its efficacy ranged from 44% to 94%.[146] Overall, more than 700 patients with SE have been treated with an initial dosage of 2 to 3 g/d and an estimated success rate around 70%.[147] In a retrospective study of 181 episodes of SE not responding to the benzodiazepine first-line treatment, however, levetiracetam failed more often than valproic acid as a second-line AED in controlling SE.[148]

Lacosamide is also available in an IV formulation and may be a safe and effective alternative for the treatment of seizures in the ICU, based on a series of 24 critically ill patients treated for seizures or refractory SE.[149] In a recent review of 136 episodes of refractory SE, it had a success rate of 56% after a bolus dose of 200 to 400 mg over 3 to 5 minutes.[150] In an accidental intrathecal administration of 60 mg baclofen, lacosamide, in addition to levetiracetam, controlled seizures that occurred in the ICU.[151]

Pregabalin (a renally excreted, orally administered antiepileptic), when added as the second to fourth AED, controlled NC seizures or NCSE in 52% of 21 critically ill patients with NC seizures or NCSE. In this study, 67% of patients with brain

tumors responded compared with none after a hypoxic injury.[112]

Retigabine is a unique AED because it opens voltage-gated K+ channels of the Kv7 subfamily. Because it is not metabolized through cytochrome P450, it has limited interaction with other hepatically metabolized drugs.[152]

REFERENCES

1. Mirski MA, Varelas PN. Seizures and status epilepticus in the critically ill. Crit Care Clin 2008; 24:115–47, ix.
2. Varelas PN. Seizures in critical care. A guide to diagnosis and therapeutics. 2nd edition. Humana Press; 2010.
3. Varelas PN, Hacein-Bey L, Hether T, et al. Emergent electroencephalogram in the intensive care unit: indications and diagnostic yield. Clin EEG Neurosci 2004;35:173–80.
4. Jordan KG. Continuous EEG monitoring in the neuroscience intensive care unit and emergency department. J Clin Neurophysiol 1999;16:14–39.
5. Wallace KL. Antibiotic-induced convulsions. Crit Care Clin 1997;13:741–62.
6. Somjen GG. Ion regulation in the brain: implications for pathophysiology. Neuroscientist 2002;8: 254–67.
7. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975;16:1–66.
8. Bladin CF, Alexandrov AV, Bellavance A, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol 2000;57:1617–22.
9. Szaflarski JP, Rackley AY, Kleindorfer DO, et al. Incidence of seizures in the acute phase of stroke: a population-based study. Epilepsia 2008;49:974–81.
10. Arboix A, Comes E, Massons J, et al. Relevance of early seizures for in-hospital mortality in acute cerebrovascular disease. Neurology 1996;47:1429–35.
11. Reith J, Jorgensen HS, Nakayama H, et al. Seizures in acute stroke: predictors and prognostic significance. The Copenhagen Stroke Study. Stroke 1997;28:1585–9.
12. Sun DA, Sombati S, DeLorenzo RJ. Glutamate injury-induced epileptogenesis in hippocampal neurons: an in vitro model of stroke-induced "epilepsy". Stroke 2001;32:2344–50.
13. Hamidou B, Aboa-Eboule C, Durier J, et al. Prognostic value of early epileptic seizures on mortality and functional disability in acute stroke: the Dijon Stroke Registry (1985-2010). J Neurol 2012. [Epub ahead of print].
14. Alvarez V, Rossetti AO, Papavasileiou V, et al. Acute seizures in acute ischemic stroke: does thrombolysis have a role to play? J Neurol 2013; 260:55–61.
15. Jung S, Schindler K, Findling O, et al. Adverse effect of early epileptic seizures in patients receiving endovascular therapy for acute stroke. Stroke 2012;43:1584–90.
16. Lancman ME, Golimstok A, Norscini J, et al. Risk factors for developing seizures after a stroke. Epilepsia 1993;34:141–3.
17. Lamy C, Domigo V, Semah F, et al. Early and late seizures after cryptogenic ischemic stroke in young adults. Neurology 2003;60:400–4.
18. Berges S, Moulin T, Berger E, et al. Seizures and epilepsy following strokes: recurrence factors. Eur Neurol 2000;43:3–8.
19. Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. Lancet 2004; 363:1184–6.
20. De Reuck J, De Groote L, Van Maele G, et al. The cortical involvement of territorial infarcts as a risk factor for stroke-related seizures. Cerebrovasc Dis 2008;25:100–6.
21. Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke: report on a hospital-based stroke cohort. Neurology 2000;54:350–4.
22. Bateman BT, Claassen J, Willey JZ, et al. Convulsive status epilepticus after ischemic stroke and intracerebral hemorrhage: frequency, predictors, and impact on outcome in a large administrative dataset. Neurocrit Care 2007;7:187–93.
23. Jauch EC, Saver JL, Adams HP Jr, 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 2013;44:870–947.
24. Gilad R. Management of seizures following a stroke: what are the options? Drugs Aging 2012; 29:533–8.
25. Beghi E, D'Alessandro R, Beretta S, et al. Incidence and predictors of acute symptomatic seizures after stroke. Neurology 2011;77:1785–93.
26. Denier C, Masnou P, Mapoure Y, et al. Watershed infarctions are more prone than other cortical infarcts to cause early-onset seizures. Arch Neurol 2010;67:1219–23.
27. Cordonnier C, Henon H, Derambure P, et al. Influence of pre-existing dementia on the risk of post-stroke epileptic seizures. J Neurol Neurosurg Psychiatry 2005;76:1649–53.
28. De Reuck J, Sieben A, Van Maele G. Characteristics and outcomes of patients with seizures according to the time of onset in relation to stroke. Eur Neurol 2008;59:225–8.
29. Kwan J, Wood E. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database Syst Rev 2010;(1):CD005398.
30. Leker RR, Neufeld MY. Anti-epileptic drugs as possible neuroprotectants in cerebral ischemia. Brain Res Brain Res Rev 2003;42:187–203.

31. Goldstein LB. Potential effects of common drugs on stroke recovery. Arch Neurol 1998;55:454–6.
32. Giroud M, Gras P, Fayolle H, et al. Early seizures after acute stroke: a study of 1,640 cases. Epilepsia 1994;35:959–64.
33. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. Neurology 2003;60:1441–6.
34. Faught E, Peters D, Bartolucci A, et al. Seizures after primary intracerebral hemorrhage. Neurology 1989;39:1089–93.
35. Tatu L, Moulin T, El Mohamad R, et al. Primary intracerebral hemorrhages in the Besancon stroke registry. Initial clinical and CT findings, early course and 30-day outcome in 350 patients. Eur Neurol 2000;43:209–14.
36. Claassen J, Jette N, Chum F, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology 2007;69:1356–65.
37. Garrett MC, Komotar RJ, Starke RM, et al. Predictors of seizure onset after intracerebral hemorrhage and the role of long-term antiepileptic therapy. J Crit Care 2009;24:335–9.
38. Morgenstern LB, Hemphill JC 3rd, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010;41:2108–29.
39. Passero S, Rocchi R, Rossi S, et al. Seizures after spontaneous supratentorial intracerebral hemorrhage. Epilepsia 2002;43:1175–80.
40. Cervoni L, Artico M, Salvati M, et al. Epileptic seizures in intracerebral hemorrhage: a clinical and prognostic study of 55 cases. Neurosurg Rev 1994;17:185–8.
41. Qureshi AI, Tuhrim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. N Engl J Med 2001;344:1450–60.
42. Yang TM, Lin WC, Chang WN, et al. Predictors and outcome of seizures after spontaneous intracerebral hemorrhage. Clinical article. J Neurosurg 2009;111:87–93.
43. Naidech AM, Garg RK, Liebling S, et al. Anticonvulsant use and outcomes after intracerebral hemorrhage. Stroke 2009;40:3810–5.
44. Haines SJ. Decerebrate posturing misinterpreted as seizure activity. Am J Emerg Med 1988;6:173–7.
45. Pinto AN, Canhao P, Ferro JM. Seizures at the onset of subarachnoid haemorrhage. J Neurol 1996;243:161–4.
46. Hasan D, Schonck RS, Avezaat CJ, et al. Epileptic seizures after subarachnoid hemorrhage. Ann Neurol 1993;33:286–91.
47. Butzkueven H, Evans AH, Pitman A, et al. Onset seizures independently predict poor outcome after subarachnoid hemorrhage. Neurology 2000;55:1315–20.
48. Raper DM, Starke RM, Komotar RJ, et al. Seizures after aneurysmal subarachnoid hemorrhage: a systematic review of outcomes. World Neurosurg 2012. [Epub ahead of print].
49. Hart RG, Byer JA, Slaughter JR, et al. Occurrence and implications of seizures in subarachnoid hemorrhage due to ruptured intracranial aneurysms. Neurosurgery 1981;8:417–21.
50. Dennis LJ, Claassen J, Hirsch LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. Neurosurgery 2002;51:1136–43 [discussion: 44].
51. Lindgren C, Nordh E, Naredi S, et al. Frequency of non-convulsive seizures and non-convulsive status epilepticus in subarachnoid hemorrhage patients in need of controlled ventilation and sedation. Neurocrit Care 2012;17:367–73.
52. Byrne JV, Boardman P, Ioannidis I, et al. Seizures after aneurysmal subarachnoid hemorrhage treated with coil embolization. Neurosurgery 2003;52:545–52 [discussion: 50–2].
53. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366:809–17.
54. Hoh BL, Nathoo S, Chi YY, et al. Incidence of seizures or epilepsy after clipping or coiling of ruptured and unruptured cerebral aneurysms in the nationwide inpatient sample database: 2002-2007. Neurosurgery 2011;69:644–50 [discussion: 50].
55. Naval NS, Stevens RD, Mirski MA, et al. Controversies in the management of aneurysmal subarachnoid hemorrhage. Crit Care Med 2006;34:511–24.
56. Rhoney DH, Tipps LB, Murry KR, et al. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. Neurology 2000;55:258–65.
57. Rosengart AJ, Huo JD, Tolentino J, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. J Neurosurg 2007;107:253–60.
58. Naidech AM, Kreiter KT, Janjua N, et al. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. Stroke 2005;36:583–7.
59. Lin CL, Dumont AS, Lieu AS, et al. Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;99:978–85.
60. Lin YJ, Chang WN, Chang HW, et al. Risk factors and outcome of seizures after spontaneous

aneurysmal subarachnoid hemorrhage. Eur J Neurol 2008;15:451–7.
61. Claassen J, Peery S, Kreiter KT, et al. Predictors and clinical impact of epilepsy after subarachnoid hemorrhage. Neurology 2003;60:208–14.
62. Baker CJ, Prestigiacomo CJ, Solomon RA. Short-term perioperative anticonvulsant prophylaxis for the surgical treatment of low-risk patients with intracranial aneurysms. Neurosurgery 1995;37:863–70 [discussion: 70–1].
63. Lanzino G, D'Urso PI, Suarez J. Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2011;15:247–56.
64. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012;43:1711–37.
65. Wong GK, Poon WS. Use of phenytoin and other anticonvulsant prophylaxis in patients with aneurysmal subarachnoid hemorrhage. Stroke 2005; 36:2532 [author reply].
66. Mink S, Muroi C, Seule M, et al. Levetiracetam compared to valproic acid: plasma concentration levels, adverse effects and interactions in aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 2011;113:644–8.
67. Szaflarski JP, Sangha KS, Lindsell CJ, et al. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. Neurocrit Care 2010;12: 165–72.
68. Shah D, Husain AM. Utility of levetiracetam in patients with subarachnoid hemorrhage. Seizure 2009;18:676–9.
69. Bosche B, Graf R, Ernestus RI, et al. Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. Ann Neurol 2010;67:607–17.
70. Sakowitz OW, Santos E, Nagel A, et al. Clusters of spreading depolarizations are associated with disturbed cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. Stroke 2013;44:220–3.
71. Woitzik J, Dreier JP, Hecht N, et al. Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2012;32:203–12.
72. Sukhotinsky I, Yaseen MA, Sakadzic S, et al. Perfusion pressure-dependent recovery of cortical spreading depression is independent of tissue oxygenation over a wide physiologic range. J Cereb Blood Flow Metab 2010;30:1168–77.
73. Masuhr F, Busch M, Amberger N, et al. Risk and predictors of early epileptic seizures in acute cerebral venous and sinus thrombosis. Eur J Neurol 2006;13:852–6.
74. Ferro JM, Correia M, Rosas MJ, et al. Seizures in cerebral vein and dural sinus thrombosis. Cerebrovasc Dis 2003;15:78–83.
75. Ferro JM, Canhao P, Bousser MG, et al. Early seizures in cerebral vein and dural sinus thrombosis: risk factors and role of antiepileptics. Stroke 2008;39:1152–8.
76. Kalita J, Chandra S, Misra UK. Significance of seizure in cerebral venous sinus thrombosis. Seizure 2012;21:639–42.
77. Coutts SB, Hill MD, Hu WY. Hyperperfusion syndrome: toward a stricter definition. Neurosurgery 2003;53:1053–8 [discussion: 1058–60].
78. Breen JC, Caplan LR, DeWitt LD, et al. Brain edema after carotid surgery. Neurology 1996;46: 175–81.
79. Jorgensen LG, Schroeder TV. Defective cerebrovascular autoregulation after carotid endarterectomy. Eur J Vasc Surg 1993;7:370–9.
80. Ho DS, Wang Y, Chui M, et al. Epileptic seizures attributed to cerebral hyperperfusion after percutaneous transluminal angioplasty and stenting of the internal carotid artery. Cerebrovasc Dis 2000;10: 374–9.
81. Kieburtz K, Ricotta JJ, Moxley RT 3rd. Seizures following carotid endarterectomy. Arch Neurol 1990;47:568–70.
82. Marino D, Vatti G, Rufa A, et al. Transient periodic lateralised epileptiform discharges (PLEDs) following internal carotid artery stenting. Epileptic Disord 2012;14:85–9.
83. Hamamura T, Morioka T, Sayama T, et al. Cerebral hyperperfusion syndrome associated with nonconvulsive status epilepticus following superficial temporal artery-middle cerebral artery anastomosis. Case report. Neurol Med Chir (Tokyo) 2010;50:1099–104.
84. Salazar AM, Jabbari B, Vance SC, et al. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. Neurology 1985;35:1406–14.
85. Lee ST, Lui TN, Wong CW, et al. Early seizures after moderate closed head injury. Acta Neurochir (Wien) 1995;137:151–4.
86. Herman ST. Epilepsy after brain insult: targeting epileptogenesis. Neurology 2002;59:S21–6.
87. Pitkanen A, Bolkvadze T. Head trauma and epilepsy. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Source Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
88. 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;91:750–60.
89. Vespa PM, McArthur DL, Xu Y, et al. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. Neurology 2010;75: 792–8.
90. Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia 2003;44(Suppl 10):11–7.
91. Temkin NR. Risk factors for posttraumatic seizures in adults. Epilepsia 2003;44(Suppl 10):18–20.
92. Scheid R, von Cramon DY. Clinical findings in the chronic phase of traumatic brain injury: data from 12 years' experience in the Cognitive Neurology Outpatient Clinic at the University of Leipzig. Dtsch Arztebl Int 2010;107:199–205.
93. Wiedemayer H, Triesch K, Schafer H, et al. Early seizures following non-penetrating traumatic brain injury in adults: risk factors and clinical significance. Brain Inj 2002;16:323–30.
94. 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;35:2830–6.
95. Schierhout G, Roberts I. Prophylactic antiepileptic agents after head injury: a systematic review. J Neurol Neurosurg Psychiatry 1998;64:108–12.
96. Chang BS, Lowenstein DH. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2003;60:10–6.
97. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XIII. Antiseizure prophylaxis. J Neurotrauma 2007;24(Suppl 1):S83–6.
98. Cotton BA, Kao LS, Kozar R, et al. Cost-utility analysis of levetiracetam and phenytoin for posttraumatic seizure prophylaxis. J Trauma 2011;71: 375–9.
99. Jones KE, Puccio AM, Harshman KJ, et al. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. Neurosurg Focus 2008;25:E3.
100. Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. J Neurosurg 1999;91: 593–600.
101. Englot DJ, Rolston JD, Wang DD, et al. Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy. J Neurosurg 2012;117:970–7.
102. Le Blanc FE, Rasmussen T. Cerebral seizures and brain tumors. In: Magnus O, de Haas AM, Vinken PJ, et al, editors. Handbook of clinical neurology. Amsterdam: North-Holland Publishing; 1974. p. 295–301.
103. Sirven JI, Wingerchuk DM, Drazkowski JF, et al. Seizure prophylaxis in patients with brain tumors: a meta-analysis. Mayo Clin Proc 2004; 79:1489–94.
104. Aguiar D, Pazo R, Duran I, et al. Toxic epidermal necrolysis in patients receiving anticonvulsants and cranial irradiation: a risk to consider. J Neurooncol 2004;66:345–50.
105. Glantz MJ, Cole BF, Forsyth PA, 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: 1886–93.
106. Bhangoo SS, Linskey ME, Kalkanis SN. Evidence-based guidelines for the management of brain metastases. Neurosurg Clin N Am 2011;22:97–104, viii.
107. Mikkelsen T, Paleologos NA, Robinson PD, et al. The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:97–102.
108. Maschio M. Brain tumor-related epilepsy. Curr Neuropharmacol 2012;10:124–33.
109. Maschio M, Dinapoli L, Sperati F, et al. Oxcarbazepine monotherapy in patients with brain tumor-related epilepsy: open-label pilot study for assessing the efficacy, tolerability and impact on quality of life. J Neurooncol 2012;106:651–6.
110. Bahr O, Hermisson M, Rona S, et al. Intravenous and oral levetiracetam in patients with a suspected primary brain tumor and symptomatic seizures undergoing neurosurgery: the HELLO trial. Acta Neurochir (Wien) 2012;154:229–35 [discussion: 35].
111. Swisher CB, Doreswamy M, Gingrich KJ, et al. Phenytoin, levetiracetam, and pregabalin in the acute management of refractory status epilepticus in patients with brain tumors. Neurocrit Care 2012; 16:109–13.
112. Swisher CB, Doreswamy M, Husain AM. Use of pregabalin for nonconvulsive seizures and nonconvulsive status epilepticus. Seizure 2013;22:116–8.
113. Weller M, Gorlia T, Cairncross JG, et al. Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma. Neurology 2011;77:1156–64.
114. Tsai HC, Wei KC, Tsai CN, et al. Effect of valproic acid on the outcome of glioblastoma multiforme. Br J Neurosurg 2012;26:347–54.
115. Rhoney DH, Varelas PN. Drug-induced seizures in critically ill patients. In: Varelas PN, editor. Seizures in critical care. A guide to diagnosis and therapeutics. 2nd edition. New York: Humana Press; 2010. p. 307–40.
116. Boswell MV, Wolfe JR. Intrathecal cefazolin-induced seizures following attempted discography. Pain Physician 2004;7:103–6.
117. Smith NL, Freebairn RC, Park MA, et al. Therapeutic drug monitoring when using cefepime in

continuous renal replacement therapy: seizures associated with cefepime. Crit Care Resusc 2012; 14:312–5.
118. Naeije G, Lorent S, Vincent JL, et al. Continuous epileptiform discharges in patients treated with cefepime or meropenem. Arch Neurol 2011;68:1303–7.
119. Schuele SU, Kellinghaus C, Shook SJ, et al. Incidence of seizures in patients with multiple sclerosis treated with intrathecal baclofen. Neurology 2005; 64:1086–7.
120. Yeh HM, Lau HP, Lin PL, et al. Convulsions and refractory ventricular fibrillation after intrathecal injection of a massive dose of tranexamic acid. Anesthesiology 2003;98:270–2.
121. Wijdicks EF, Sharbrough FW. New-onset seizures in critically ill patients. Neurology 1993;43:1042–4.
122. Armstrong PJ, Bersten A. Normeperidine toxicity. Anesth Analg 1986;65:536–8.
123. Cluitmans FH, Meinders AE. Management of severe hyponatremia: rapid or slow correction? Am J Med 1990;88:161–6.
124. Soupart A, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications. Clin Nephrol 1996;46:149–69.
125. Hennis A, Corbin D, Fraser H. Focal seizures and non-ketotic hyperglycaemia. J Neurol Neurosurg Psychiatry 1992;55:195–7.
126. Tiras R, Mutlu A, Ozben S, et al. Forced eye closure-induced reflex seizure and non-ketotic hyperglycemia. Ann Saudi Med 2009;29:313–5.
127. Ko SB, Ortega-Gutierrez S, Choi HA, et al. Status epilepticus-induced hyperemia and brain tissue hypoxia after cardiac arrest. Arch Neurol 2011;68: 1323–6.
128. Shorvon S. Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation. Epilepsia 2011;52(Suppl 8):53–6.
129. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;134:2802–18.
130. Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135:2314–28.
131. Trinka E, Hofler J, Zerbs A. Causes of status epilepticus. Epilepsia 2012;53(Suppl 4):127–38.
132. Towne AR, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus. Epilepsia 1994;35:27–34.
133. Shepard PW, St Louis EK. Seizure treatment in transplant patients. Curr Treat Options Neurol 2012;14:332–47.
134. Pandey CK, Singh N, Bose N, et al. Gabapentin and propofol for treatment of status epilepticus in acute intermittent porphyria. J Postgrad Med 2003;49:285.
135. Alvarez-Sabin J, Montaner J, Padro L, et al. Gabapentin in late-onset poststroke seizures. Neurology 2002;59:1991–3.
136. Trinka E, Dilitz E, Unterberger I, et al. Non convulsive status epilepticus after replacement of valproate with lamotrigine. J Neurol 2002;249:1417–22.
137. Guerrini R, Belmonte A, Parmeggiani L, et al. Myoclonic status epilepticus following high-dosage lamotrigine therapy. Brain Dev 1999;21:420–4.
138. Towne AR, Garnett LK, Waterhouse EJ, et al. The use of topiramate in refractory status epilepticus. Neurology 2003;60:332–4.
139. Tarulli A, Drislane FW. The use of topiramate in refractory status epilepticus. Neurology 2004;62:837.
140. Hottinger A, Sutter R, Marsch S, et al. Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. CNS Drugs 2012;26:761–72.
141. Yoshimura I, Kaneko S, Yoshimura N, et al. Long-term observations of two siblings with Lafora disease treated with zonisamide. Epilepsy Res 2001; 46:283–7.
142. Brodie MJ, Ben-Menachem E, Chouette I, et al. Zonisamide: its pharmacology, efficacy and safety in clinical trials. Acta Neurol Scand Suppl 2012;(194): 19–28.
143. Gaida-Hommernick B, Rieck K, Runge U. Oxcarbazepine in focal epilepsy and hepatic porphyria: a case report. Epilepsia 2001;42:793–5.
144. Zaatreh MM. Levetiracetam in porphyric status epilepticus: a case report. Clin Neuropharmacol 2005;28:243–4.
145. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol 2012;259:645–8.
146. Zelano J, Kumlien E. Levetiracetam as alternative stage two antiepileptic drug in status epilepticus: a systematic review. Seizure 2012;21:233–6.
147. Trinka E. What is the evidence to use new intravenous AEDs in status epilepticus? Epilepsia 2011; 52(Suppl 8):35–8.
148. Alvarez V, Januel JM, Burnand B, et al. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia 2011;52:1292–6.
149. Cherry S, Judd L, Muniz JC, et al. Safety and efficacy of lacosamide in the intensive care unit. Neurocrit Care 2012;16:294–8.
150. Hofler J, Trinka E. Lacosamide as a new treatment option in status epilepticus. Epilepsia 2013;54(3): 393–404.
151. Berger B, Vienenkoetter B, Korporal M, et al. Accidental intoxication with 60 mg intrathecal baclofen: survived. Neurocrit Care 2012;16:428–32.
152. Czuczwar P, Wojtak A, Cioczek-Czuczwar A, et al. Retigabine: the newer potential antiepileptic drug. Pharmacol Rep 2010;62:211–9.