Chapter 12
Seizures and Status Epilepticus

Catherine Harris and Emily Gilmore

12.1 Introduction

Seizures are a common phenomenon in intensive care units (ICU). The prevalence of seizures in the ICU, including patients with brain injury, varies widely in studies from 7% to 68% [1–4]. In patients without a primary neurological disorder, the prevalence is much less at 8–11% [1–4]. Seizures in critically ill patients can be provoked or unprovoked, focal or generalized, and with (convulsive or myoclonic) or without (nonconvulsive) prominent motor features. The majority of ICU seizures are classified as nonconvulsive and may be

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secondary to focal injury, as seen in ischemic and hemorrhagic stroke, encephalitis, or diffuse injury (as seen in traumatic brain injury, aneurysmal subarachnoid hemorrhage, and hypoxic-ischemic encephalopathy). Seizures occur when there is excessive neuronal excitability. The focus of electrical activity comes from the neurons of the cortex and possibly the brain stem, although brain stem origin has not been well established. Most excessive electrical activity causing a seizure will stop on its own in a couple of minutes. Seizures lasting more than 5 min are less likely to stop spontaneously and require urgent treatment.

A thorough description and classification of seizures can help clinicians determine etiology and guide treatment:

- *Provoked* vs. *unprovoked*. Provoked seizures can be the result of primary neurological disorders, systemic disorders, or drugs that lower the seizure threshold, outlined in Table 12.1. Unprovoked seizures occur without a clear precipitating event.
- *Focal* vs. *generalized.* Generalized seizures include tonic-clonic, absence, myoclonic, clonic, tonic, or atonic. Focal seizures can occur with or without impairment in consciousness. Semiology of focal and generalized seizures are outlined in Table 12.1.
- *Discrete* vs. *continuous.* Seizures should be described in reference to the time course of seizure activity. Descriptions of seizures should include onset, duration and frequency, or if the seizures are continuous or intermittent.

Seizures present with a spectrum of clinical manifestation and severity. The following terms are used frequently to define the spectrum of seizure activity [5, 7, 8]:

Table 12.1 Seizure semiology [5, 6]

Semiology for focal-onset seizures	
Frontal lobe	Disinhibited behaviors
	Confusion
	Automatisms
Temporal lobe	Confusion
	Auditory hallucinations
	Chewing, lip smacking
Parietal lobe	Paresthesias (warmth, cold, tingling, numbness)
	Loss of awareness
	Confusion
Occipital lobe	Scotomas
	Visual hallucinations
	Confusion
Semiology for generalized seizures	
Tonic	Increased muscle tone
Clonic	Rhythmic jerking
Tonic clonic	Increased muscle tone with rhythmic jerking
Atonic	Loss of muscle tone
Myoclonic	Muscle contractions

- Seizure – uncontrolled electrical impulses in the brain that manifest as focal or generalized rhythmic activity lasting 10 s to 5 min.
- Status epilepticus (SE) – a single seizure lasting more than 5 min or recurrent seizures without return to neurologic baseline in the intervening period(s).
- Generalized convulsive status epilepticus (GCSE) – status epilepticus that is clinically evident, e.g., tonic-clonic, clonic, or myoclonic movements.

- Nonconvulsive status epilepticus (NCSE) – status epilepticus without tonic-clonic, clonic, or myoclonic movements, but often with impairment in mental status with or without subtle signs (e.g., eye, facial, or finger movements) and associated with electrographic evidence of seizure activity. Similar to convulsive status epilepticus, more than 5 min or >30 min of total ictal activity in any hour of recording is consistent with NCSE. Can be focal or generalized. NCSE is common among critically ill comatose patients and accounts for 20% of all SE [9].
- Refractory status epilepticus (RSE) – can initially be GCSE or NCSE; it is defined by failure to respond to first- or second-line antiepileptic therapy. RSE occurs in a significant number of patients who present with GCSE.
- Super refractory status epilepticus (SRSE) – status epilepticus that persists or recurs more than 24 h after appropriate anesthetic therapy
- New-onset refractory status epilepticus (NORSE) – refractory status epilepticus without an obvious etiology after an initial workup.

The most common cause of SE is a prior history of epilepsy. For these patients, a number of circumstances can lower seizure threshold including recent alterations in antiepileptic medication dosing, systemic infection, or new drug exposure. Patients in the Neuro ICU can develop SE as a result of old or new cerebral insult including stroke, tumor, subdural hemorrhage, hypoxic-ischemic injury, metabolic disarray, and ethyl alcohol withdrawal (Table 12.2). The increased utilization of continuous EEG monitoring in the ICU setting has proved very useful in the evaluation of patients with fluctuating neurologic symptoms and unexplained coma. Timely identification of NCSE can focus treatment and improve outcome in neurologically ill patients.

Table 12.2 Provoked seizure etiologies

Primary neurologic disorders	Systemic disorders	Drugs that lower seizure threshold
Head trauma	Hypo/hyperglycemia	Antibiotics
CNS infections	Hyponatremia	Antidepressants
Stroke	Hypomagnesemia	Antipsychotics
Cerebrovascular diseases	Hyperthyroidism	Stimulants
Encephalopathy	Sleep deprivation	Chemotherapy drugs
Anoxic brain injury	Hyperthermia	Beta-blockers
Intracranial hemorrhage	Uremia	Narcotics
CNS structural abnormalities	Withdrawal ETOH	Antihistamines
Neurodegenerative disease	Withdrawal sedatives	Analgesics

12.2 Case Study

A 78-year-old man is transferred from another hospital to the Neuro ICU. The wife initially states that he was in his usual state of health watching TV when his eyes rolled back and he began to shake all over. Paramedics arrived at the scene, where the patient had stertorous breathing and depressed level of consciousness. He was intubated in the field and taken to the local hospital. While in the CT scan, he had a "GTC" seizure. He was treated with a benzodiazepine IV push and the seizure terminated. CT scan revealed an 8 mm acute on chronic left subdural hemorrhage with 4 mm of midline shift. He was loaded with fosphenytoin and admitted to the ICU for further management. On the way to the ICU, he begins "jerking" on the right side and the nurse administers more Ativan. On arrival to the ICU, a continuous infusion of midazolam and continuous EEG monitoring are ordered STAT.

Upon further questioning, the wife states that her husband was tripped by the dog about 2 months ago and has become increasingly unsteady but attributed it to an old knee injury. The patient's cEEG showed lateralized periodic discharges over the right temporal parietal region that evolved into frank electrographic seizures despite antiseizure therapy. He was started on a propofol infusion titrated to seizure suppression and remained seizure-free for 30 h. The infusion was slowly tapered over several hours at which point the nonconvulsive seizures recurred. He was bolused with IV midazolam and started on an infusion. Given his refractory seizures, the decision was made to go to the OR for SDH evacuation.

12.3 Initial Evaluation

12.3.1 Airway

The inability to maintain the airway is the most immediate risk to a patient with CSE. Factors that affect adequate oxygenation and ventilation include a clenched jaw, paradoxical or poorly coordinated respirations, secretions, and vomitus. Implementing precautions, including placing the patient on their side and supplying 100% oxygen via a face mask while performing continuous cardiopulmonary monitoring, are essential to minimizing the need for intubation secondary to hypoxic respiratory failure. However, despite these efforts intubation may be necessary and should be determined on a case-by-case basis. Short-acting paralytics should be used so as not to mask clinical seizure activity for a prolonged period of time.

12.3.2 Abortive Therapy

Benzodiazepines are first-line agents to control seizures [10–12]:

- Lorazepam 4 mg IV push over 2 min, if still seizing after 5 min, repeat ×1 to a max of 0.1 mg/kg IV.
- See Fig. 12.1 for status epilepticus management algorithm.

If no IV access is available, other options include:

- Rectal diazepam gel (10–20 mg, 0.2 mg/kg)
- Intranasal/buccal/IM midazolam 10 mg IV solution

12.3.3 History

Since etiology of seizures and SE varies significantly, a thorough evaluation of seizure characteristics and patient history is essential in guiding patient management:

- Seizure characteristics – Describe the seizure including onset, semiology (gaze deviation, face or extremity jerking, automatisms, altered mental status), evolution (progressing generalization), how did it cease (e.g., on its own or with medication).
- Seizure duration – Determine when the patient last seen normal or at baseline.
- History of present illness – Obtain a thorough understanding of the events leading up to the seizure including preceding illness, cognitive or behavioral changes, trauma, recent changes in medications, lifestyle, use of illicit substances or alcohol, etc.

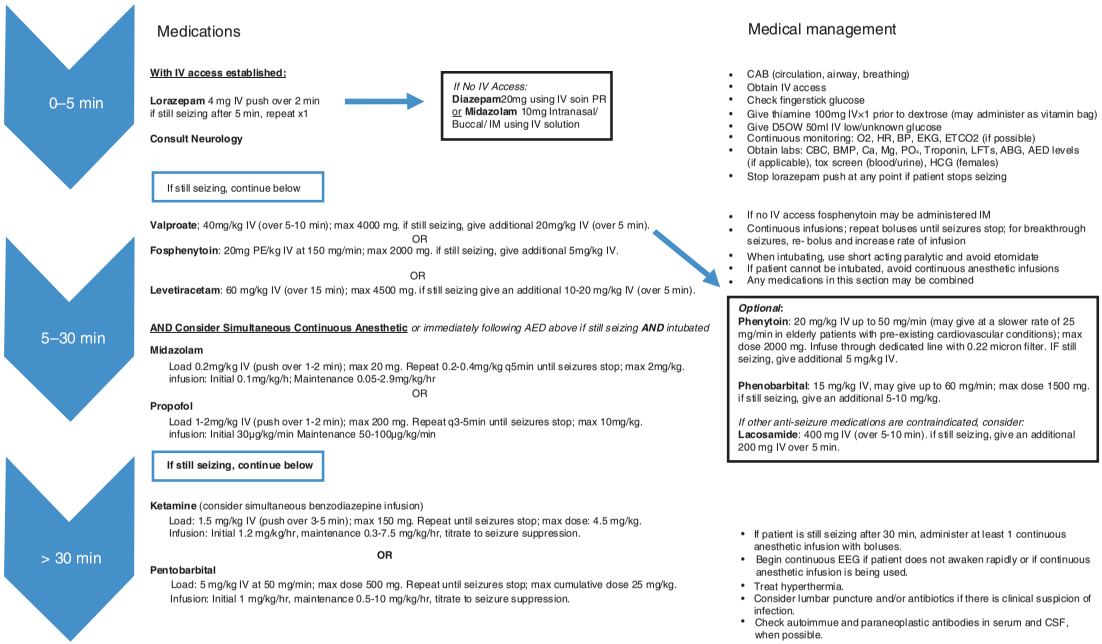

Fig. 12.1 Status epilepticus treatment algorithm

- Past medical history – This should include questions about prior seizures, history of epilepsy, and epilepsy risk factors (e.g., prior trauma, stroke, CNS infection, febrile seizures) as well as psychogenic non-epileptic seizures.
- Medication history – Special attention should be made to medications that lower seizure threshold. If the patient has a history of epilepsy, obtain information about antiseizure medication regimen recent dosing adjustments or a history of medications noncompliance.

12.3.4 Neurological Evaluation

A neurological assessment is imperative in the initial evaluation and will be fundamental in narrowing the list of differential diagnoses. A full assessment should include mental status, cranial nerves including fundoscopy, motor and sensory functioning, reflexes, and cerebellar exam.

Patients in NCSE can have pupillary abnormalities, including asymmetry and hippus. However, if the pupils are dilated, pinpoint, or unreactive, other life-threatening neurologic emergencies should be entertained, prompting an emergent neurology or neurosurgical consultation. Additionally, in NCSE the eyes may be open, but the patient is mute (eye open mutism), 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. Tone may be symmetrically or asymmetrically increased with hyperreflexia and clonus. “Awake” patients are more likely to exhibit automa-

tisms (e.g., picking, lip smacking) and behavioral changes (perseveration, agitation, emotional lability, aggressiveness).

After a self-limiting convulsive seizure, a patient's exam should return to their baseline functioning over a short period of time. Patients who do not return to their baseline level of consciousness within 30–60 min should be evaluated for nonconvulsive seizures and status epilepticus and undergo monitoring with cEEG as soon as possible. Immediately in the post-ictal phase, the patient may have a focal motor deficit (Todd's paralysis) that resolves over minutes to days.

Sometimes seizures are clear-cut and obvious in a clinical setting where the provider knows the patient and the history of the patient. However, many patients present without a diagnosis or history of seizures. The differential diagnoses for seizures can be extensive, so it is important to consider life-threatening diagnoses. There are several conditions that should be ruled out immediately or considered during the workup for a patient with seizures:

- Basilar artery thrombosis – patients may present in coma or have multiple cranial neuropathies (papillary abnormalities, diplopia, dysphagia), cerebellar signs (ataxia, nystagmus, nausea/vomiting), weakness (hemiparesis, quadriparesis), paroxysmal spasms or posturing (decerebrate). Patients with concerns for basilar thrombosis require emergent recognition of signs/symptoms and neuroimaging for possible thrombolysis.
- Ischemic stroke – patients can present with a wide range of symptoms depending on the location of the stroke and can easily mimic seizure activity or rarely be associated with ictal activity. Management of stroke requires early detection and treatment. Patients with focal deficits should be evaluated for possible TIA/stroke in case emergent treatment is warranted.
- Meningitis/encephalitis – patient may complain of headaches, but typically have flu-like symptoms; patients may

also present in a comatose state. Patients with fever and altered mental status need a lumbar puncture and antibiotics imminently; neuroinfections can cause seizures that should be treated concurrently. Lumbar puncture and antibiotics should not be delayed for other diagnostic testing if there is a strong concern for meningitis.

- Sepsis – patient may present with encephalopathy, which is often an early sign in sepsis. Again treatment of sepsis with antibiotics should be prioritized. These patients are also at increased risk for seizures, especially nonconvulsive, that would otherwise be missed without the use of cEEG.
- Hypoglycemia – patients with hypoglycemia may present in a coma, focal neurologic deficits, or seizure activity that is best treated with glucose administration. All patients with altered mental status should have a finger-stick glucose done to evaluate for the hypoglycemia as a potential etiology of their neurologic deterioration.
- Nonconvulsive status epilepticus – GCSE is generally apparent and easy to identify, but NCSE may be more insidious. Patients may be in a coma for various reasons, which can all be complicated by NCSE, especially if it is not considered or recognized as delays in diagnoses are associated with worse outcomes. If identified, NCSE should be treated aggressively.
- Venous sinus thrombosis – patients with venous sinus thrombosis may have some convulsive movements from either the thrombosis or associated hemorrhage from the venous sinus thrombosis. Treatment is typically anticoagulation as the seizures are provoked; however antiseizure medication may be appropriate if seizures persist or recur acutely.
- Other diagnoses to consider include cardiac conditions (syncope, cardiac arrhythmias), psychiatric disorders (panic attacks, conversion, malingering), and other neurological disorders (movement disorders, migraines, narcolepsy, transient global amnesia, delirium).

12.3.5 Diagnostics

Laboratory evaluation of patients presenting with seizures and SE should include metabolic studies to evaluate for hypo/hypernatremia, hypo/hyperglycemia, electrolyte disturbances, hyperammonemia, and thyroid dysfunction. Urine toxicology should be sent for cocaine and methamphetamines and ethyl alcohol, which lower seizure threshold. Drug levels of known AEDs, benzodiazepines, antidepressants, and antipsychotics can be helpful in determining seizure etiology. Complete blood count may show signs of systemic infection; however seizures can precipitate a leukocytosis, so other signs of infection should be taken into consideration. Seizures can also cause elevated lactate and CK levels due to rigorous muscle activity. Prolactin, if drawn within 30 min of seizure activity, may be helpful in distinguishing epileptic from psychogenic non-epileptic seizures, but not from syncope.

Lumbar puncture should be performed and tailored to the clinical scenario. Typically, a basic CSF panel will include gram stain and culture, cell count, protein, and glucose. See chapter *Neurological Infections* for further outline of diagnostic workup and treatment for infectious encephalitis and meningitis. Occasionally, seizures can be attributed to a paraneoplastic, autoimmune, or parainfectious encephalitides. A detailed history will help guide what can be a very extensive investigation.

Non-contrast head CT should be performed for any patient with new-onset seizures to evaluate for a neurological insult including occult trauma, hemorrhage, or tumor. CT angiography can be performed if acute ischemic stroke is considered as an alternative diagnosis. Similarly, CT venography can be considered to evaluate for cerebral venous thrombosis as potential seizure etiology. MRI can be considered once patient is clinically stabilized to evaluate for a number of conditions related to

seizures including but not limited to infection (including abscess), malignancy, hypoxic-ischemic injury, posterior reversible encephalopathy syndrome (PRES), and limbic encephalitis. MRI may demonstrate diffusion and FLAIR abnormalities due to seizure activity. These changes can be seen in the cortex as well as the deep gray nuclei (pulvinar of the thalamus) and the corpus callosum [13].

12.4 Interventions and Management

12.4.1 Continuous EEG Monitoring and Interpretation

Continuous EEG (cEEG) monitoring (>24 h duration) must be contextualized to the clinical scenario. Not all epileptiform activity is consistent with the presence of seizures, and conversely the absence of epileptiform activity does not always negate the presence of focal seizures. CEEG patterns can be caused by a wide variety of neurologic conditions, and not all cases of neurologic injury are associated with EEG abnormalities. It is critical to understand the descriptive terminology of EEG waveforms and to assess for patterns over time.

An electrographic seizure can be defined by [5, 8, 13]:

- Paroxysmal pattern that evolves in morphology, frequency, and/or spatial distribution OR
- Generalized spike-wave discharges ≥3 per second
- Clearly evolving discharges of any type that reach a frequency of >4 per second (focal or generalized)
- Paroxysmal electrographic pattern that is different from the background EEG pattern and associated with a clinical correlate

Activity observed on cEEG can be defined as epileptiform, strongly associated with seizures, or as nonepileptiform, or as features commonly seen in critically ill patients, but not associated with seizures:

- Epileptiform activity [14–19]
  - Interictal epileptiform discharges (IED) – Highly suggestive of seizure activity. IED can also be seen from withdrawal from short-acting barbiturates and benzodiazepines, metabolic derangements, and some medications.
  - Periodic discharges (PDs) – Can be lateralized (LPDs), generalized (GPDs), or bilaterally independent (BIPDs). PDs are commonly seen in brain lesions such as stroke, intracerebral hemorrhage, encephalitis, and hypoxic-ischemic encephalopathy. They are also common in patients with symptomatic seizures and are all strongly associated with seizures.
  - Rhythmic delta activity (RDA) – Can be lateralized (LRDA) or generalized (GRDA) as well as bilaterally independent (BI). Similar to PDs, RDA can be seen across the spectrum of brain injury and when lateralized is strongly association with seizures.
- Nonepileptiform activity – Can be relatively common in critically ill patient population resulting from a multitude of causes, not associated specifically with seizures, but frequently occurring after seizures.
  - Slowing – diffuse, regional, or localized. Commonly seen in post-ictal states and with focal structural lesions.
  - Frontal intermittent rhythmic delta activity (FIRDA) - Bilateral slow activity, nonspecific finding associated with encephalopathy of all causes. Can be seen in normal individuals as well. Defined by changes in amplitude or asymmetry and deviations from normal patterns.

12.4.2 Seizure Management [11, 20–22]

GCSE is a neurologic emergency warranting rapid triage and treatment. Most patients will respond to first-line medications if begun within 30 min of seizures onset, however <40% respond after 2 h of ongoing seizures [23]. Additionally, withholding antiepileptic medication because of fear of respiratory compromise has been shown to increase the risk of acute respiratory failure [10]. Figure 12.1 provides an algorithm for treatment of SE.

Benzodiazepines are the first line for treatment in initial management of seizures (see Sect. 12.3.2, above). The second-line treatment for seizures is IV AED administration. There are many options for choosing antiepileptic drugs for patients with seizures; however, not all are appropriate for use in the ICU. There are several commonly used AEDs in the ICU that are available in IV form for rapid titration and emergent administration. Please refer to section on antiepileptic drugs used in status epilepticus found in Chap. 22 *Pharmacology in the Neuro ICU* for further drug administration, level monitoring, and drug interaction information. Commonly utilized medications include valproate sodium, fosphenytoin/phenytoin, levetiracetam, phenobarbital, and lacosamide. For patients with new-onset seizures, levetiracetam is frequently used because of its relatively low-side-effect profile, limited drug interactions, and rare need for drug level monitoring when starting therapy.

Continuous infusion of AEDs is recommended to suppress seizures not controlled by first- and second-line therapies. None of the following therapies have been shown to be superior and often the choice is dictated by the patient's clinical status (e.g., arrhythmia, hypotension, fulminant liver failure, etc.). Several infusions can be utilized at this point in treatment: midazolam, propofol, ketamine, or pentobarbital. Once

seizure suppression is achieved for 24 h, it is reasonable to begin tapering continuous infusions while on cEEG to monitor for recurrent and rebound seizures, the latter of which are more common with rapid weaning. Recurrent seizures should trigger rebolusing with the infusion and/or switching to another infusion. Antiseizure medications, typically IV formulations due to potential absorption-related issues from ileus or gastroparesis in the setting of anesthetics, can facilitate weaning.

There are several additional options for the treatment of refractory SE that may be utilized if initial therapies are ineffective. Immunomodulatory treatments including high-dose corticosteroids, intravenous immunoglobulin, and plasmapheresis can be considered. These treatments may be useful in NORSE where the cause of seizures is unknown. Therapeutic hypothermia may have anticonvulsant properties; however, only low-grade evidence is available at this time. Ketogenic diet, by means of achieving the state of ketosis, may provide some benefit in seizure termination; however, while studies are promising, they are ongoing. In cases where an irritable foci can be identified, a lesionectomy can be considered. Finally, electroconvulsive therapy remains exploratory and limited to case reports.

Treatment options will vary and may become complex based on patient condition and response (or nonresponse) to therapies. However, there are five general principles to guide the management of SE:

- General supportive care – maintain airway and hemodynamic support
- Achieve cessation of seizure activity
- Prevent seizure recurrence
- Identify and correct the underlying cause, when feasible
- Management of complications resulting from seizures as well as adverse effects from AED therapy

12.4.3 Systemic Complications of Status Epilepticus

Patients suffering from seizures and status epilepticus are at risk for developing a number of systemic complications during the course of their illness. From a respiratory standpoint, hypoxemia can occur from airway obstruction, acute onset neurogenic pulmonary edema, aspiration pneumonia/pneumonitis, and respiratory failure from depressed mental status and failure to protect their airway. In the setting of prolonged ICU stays, patients are also at risk for recurrent mucous plugging, atelectasis, pleural effusions, ventilator-associated pneumonia, pulmonary emboli, and the need for tracheostomy. Cardiac injury may also occur, often manifesting as stunned myocardium (Takotsubo's cardiomyopathy), demand ischemia (Type II MI), or arrhythmias. Medications used to treat status epilepticus can cause hypotension and result in the need for hemodynamic support with pressors when volume resuscitation isn't adequate.

Excessive muscle contraction can lead to the production of lactic acidosis, and if severe, rhabdomyolysis and renal failure hyperglycemia can result from a metabolic stress response or infection in the setting of critical illness and should be appropriately treated with insulin therapies. Hyperpyrexia is also seen secondary to excess metabolic activity from seizures, and patients should be aggressively treated to achieve normothermia, especially in the early phases of acute brain injury.

12.4.4 Prognosis [24–29]

Prognosis will vary with age and etiology of the seizures. Table 12.3 shows a mortality prediction score for SE. Mortality is highly associated with anoxic brain injury, whereas sei-

Table 12.3 Mortality prediction score for status epilepticus [29]

	Features	Score
Level of consciousness	Alert, somnolent, confused	0
	Stuporous or comatose	1
Seizure type	Simple or complex partial	0
	Generalized	1
	NCSE + Coma	2
Age	<65	0
	>65	2
Previous seizures	Yes	0
	No	1
Total		0–6

Using cutoff ≥3 predicts mortality within the following statistical parameters: sensitivity 81%, specificity 65%, PPV 25%, NPV 96%, accuracy 73%

zures from benzodiazepine or alcohol withdrawal has a much lower rate of mortality. Another risk factor for increased mortality risk is no obvious cause and persistent duration of seizures; however outcomes may be marred by the nihilistic fate of the self-fulfilling prophecy when withdrawal of life-sustaining therapy is initiated too early. When compared to convulsive status epilepticus, NCSE is associated with worse outcome. Outcome in RSE, which is often nonconvulsive, is associated with significant mortality (nearly 50%) and morbidity with only a minority of patients returning to previous functional baseline. However, young patients without overt evidence of catastrophic brain injury should be treated aggressively.

Seizures can be traumatizing for anyone to witness. Families may be in a state of shock on initial encounter and may have difficulty comprehending the situation or what is being communicated to them by the healthcare team. Remember to involve the family in discussions in management and goals of care, when appropriate, on a regular basis.

Summary Points

- Seizures are considered a neurologic emergency – always manage airway and hemodynamics first; many seizures can be self-limiting and resolve spontaneously
- NCSE and CSE are common in the ICU and may only be diagnosed with EEG monitoring
- Treatment regimens can be complex and vary from patient to patient; however the general principles of management are the same.
- Prognosis varies widely based on etiology, duration of seizures, and patient's age.
- Families will require significant amounts of resources and support in order to make informed decisions related to the management of the patient.

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