Pharmacological Management of Seizures and Status Epilepticus in Critically Ill Patients

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Abstract
Seizures are serious complications seen in critically ill patients and can lead to significant morbidity and mortality if the cause is not identified and treated quickly. Uncontrolled seizures can lead to status epilepticus (SE), which is considered a medical emergency. The first-line treatment of seizures is an intravenous (IV) benzodiazepine followed by anticonvulsant therapy. Refractory SE can evolve into a nonconvulsive state requiring IV anesthetics or induction of pharmacological coma. To prevent seizures and further complications in critically ill patients with acute neurological disease or injury, short-term seizure prophylaxis should be considered in certain patients.

Keywords
seizures, status epilepticus, intensive care unit, critically ill, prophylaxis

Introduction
Seizures are a common occurrence in critically ill patients and are associated with significant morbidity and mortality. Patients may be admitted to the intensive care unit (ICU) for seizure management or may develop seizures while in the ICU as a result of their underlying acute illness. Status epilepticus (SE) is a neurologic emergency that can lead to permanent brain damage or death if untreated. It has traditionally been defined as any seizure lasting more than 30 minutes with or without a loss of consciousness. It can also be defined as recurrent seizures without recovery of consciousness between episodes. However, these definitions do not translate well in the ICU setting where the onset of seizures may be insidious and unclear due to the variety of severe illnesses seen. A more practical definition would be continuous seizures lasting more than 5 minutes or two or more seizures without complete recovery of consciousness. Refractory status epilepticus (RSE) can be defined as seizure activity that does not respond to first- or second-line anticonvulsant therapy.

Identification of seizures and SE in the ICU patient poses a challenge due to variability in presentation as seizure activity can range from nonconvulsive to convulsive. Nonconvulsive status epilepticus (NCSE) is characterized by a persistent state of impaired consciousness, which is a common nonspecific finding in many critically ill patients. For ICU patients with NCSE, electroencephalography (EEG) is essential for a prompt diagnosis. Generalized convulsive status epilepticus (GCSE) is characterized by full body motor seizures and involves global areas of the cerebral cortex. Certain risk factors for seizures or SE may warrant prophylactic anticonvulsant therapy in ICU patients, especially those with significant central nervous system (CNS) injury.

Prevention and control of seizure activity, specifically SE, is extremely important; therefore, this article will focus on the treatment of SE and the use of seizure prophylaxis in critically ill patients.

Epidemiology of SE
There are an estimated 150 000 cases of SE in the United States each year, with approximately 55 000 associated deaths and an estimated annual direct cost for inpatient admissions of $4 billion. In general, SE affects African Americans, children, and the elderly more frequently. It is important to ascertain the underlying cause of SE, as this will guide empiric treatment, possibly limiting the duration of SE and improving

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outcomes. The causes of SE can be categorized as acute or chronic. Acute processes that cause SE include metabolic disturbances; CNS disorders, infections, or injuries; hypoxia; drug toxicity (eg, theophylline, isoniazid, cyclosporine, cocaine); or acute illness. Chronic causes include preexisting epilepsy, chronic alcohol abuse (withdrawal seizures), CNS tumors, and stroke. Many of these conditions are readily identified in critically ill patients. In epileptics, the common causes of SE are anticonvulsant withdrawal or subtherapeutic anticonvulsant levels, which are readily treated through readmittance and optimization of their maintenance regimens. Patients with SE due to chronic processes generally recover well after starting anticonvulsant drug therapy.

Pathophysiology of SE

Isolated seizures are typically self-resolving and pose little danger to the patient. However, when the brain is unable to control this excess cortical electrical activity, SE can ensue. The exact reason for this failure is unknown and probably involves multiple mechanisms, but the most popular theory relates to the imbalance of excitatory and inhibitory neurotransmitters. The primary excitatory amino acid in the CNS is glutamate which stimulates postsynaptic N-methyl-D-aspartate (NMDA) receptors, causing an influx of calcium into the cells and depolarization of the neuron. Sustained depolarization may eventually cause irreversible neuronal injury and death. The primary inhibitory neurotransmitter is γ-aminobutyric acid (GABA) that antagonizes the excitatory response through the stimulation of GABA$_A$ receptors, enhancing chloride inhibitory currents, leading to hyperpolarization and inhibition of the postsynaptic cell membrane. This inhibition may diminish with time perhaps due to a mechanistic shift in the functional properties of the GABA$_A$ receptors or a downregulation of the number of these receptors, which inevitably causes a decrease in response to the GABA-receptor agonists used to treat SE. In this situation, NMDA receptor antagonists may offer some benefit in controlling the excitotoxicity before serious and irreversible neurological damage occurs. Immediate treatment for seizures is essential as seizures lasting more than 30 minutes can cause injury and neuronal loss in the hippocampus, cortex, and thalamus resulting from excessive electrical activity and alterations in cerebral metabolic demand. The clinical impact of the GABA$_A$-receptor changes on treatment response and worsening of neuronal injury with prolongation of seizure activity highlight the importance of rapidly controlling SE.

Several systemic changes occur in 2 phases during the course of SE. Phase I (early phase) describes the initial 30 minutes of seizure activity where seizures produce a sharp increase in autonomic activity with elevated levels of plasma catecholamines (epinephrine, norepinephrine) and steroid concentrations, resulting in hypertension, tachycardia, hyperglycemia, fever, sweating, and salivation. Cerebral blood flow is also increased to preserve the oxygen supply to the brain during this period of high metabolic demand. Increases in sympathetic and parasympathetic stimulation along with muscle hypoxia can lead to ventricular arrhythmias, severe acidosis, and rhabdomyolysis, which could then lead to hypotension, shock, and acute tubular necrosis.

After approximately 30 minutes of continuous seizure activity, phase II (late phase) begins with loss of cerebral autoregulation, decreased cerebral blood flow, increased intracranial pressure (ICP), and systemic hypotension. Cerebral metabolic demand is still high; however, the body is no longer able to compensate. The systemic changes that may occur include hypoglycemia, hyperthermia, respiratory failure, hypoxia, respiratory and metabolic acidosis, hyperkalemia, hyponatremia, and uremia. This physiologic compromise, especially hypotension and hypoxia, may exacerbate neurologic damage already sustained from the excitotoxicity of unblunted seizures. Motor activity may not be clinically evident after a prolonged period of seizures, but the uncontrolled electrical activity in the brain may continue. It may appear that the SE has resolved clinically, but EEG monitoring may reveal continued seizure activity. This is referred to as subclinical seizures or nonconvulsive status and requires rapid recognition and treatment.

Clinical Presentation and Diagnosis of Seizures

When a critically ill patient presents with seizures, a thorough evaluation is needed to determine the type and duration of the seizure activity. This will help guide therapy and identify which laboratory and diagnostic tests to order. Once seizures are controlled, a full neurologic exam should be conducted to evaluate level of consciousness (coma, lethargy, or somnolence), motor function and reflexes (rhythmic contractions, rigidity, spasms, or posturing), and pupillary response. The value of this exam is extremely limited in patients receiving neuromuscular blocking agents and may have to be delayed until after the paralytic is removed. A physical exam to identify secondary injuries (eg, shoulder dislocations, lacerations) from seizure activity should also be conducted and appropriate treatment ordered. Often, the seizure is a sign of an underlying problem or an acute injury (eg, intracranial bleeding) and should not be ignored.

Seizures in ICU patients can be very difficult to identify since they may not present with the traditional convulsive tonic-clonic movements but instead present nonspecifically with altered mental status changes, somnolence, agitation, confusion, or obtundation. Hypertension, tachycardia, fever, and diaphoresis are also presenting symptoms and are very commonly seen in a critically ill patient, complicating the seizure diagnosis. A loss of bowel or bladder function may not be noticed if urethral catheters or rectal bags are present and since many are already on mechanical ventilation, respiratory compromise may not be readily identified. When seizure activity is sustained for more than approximately 30 to 60 minutes, muscle contractions may no longer be visible. Twitching of the face, hands, or feet may be seen in nonparalyzed, comatose patients with prolonged seizures.
Proper laboratory tests may lead to the identification of treatable causes of seizures or SE including hypoglycemia, hypo- or hypernatremia, hypomagnesemia, hypocalcemia, and renal and liver failure, conditions which are frequently seen in the critically ill patient. Frequent laboratory monitoring in the ICU may allow clinicians to examine trends and prevent a majority of metabolically induced seizures. An initial drug screen can help identify drugs of abuse that may induce seizures such as cocaine, amphetamines, heroin, and phencyclidine (PCP). Leukocytosis in a febrile patient is suggestive of an active infection that should be evaluated and treated appropriately including collecting and analyzing blood, cerebrospinal fluid (CSF), sputum or tracheal aspirate, and urine after the seizures are controlled to identify a potential infectious source. Computed tomography (CT) or magnetic resonance imaging (MRI) are performed to rule out CNS abscesses, acute intracranial hemorrhage, or tumors, all of which may be a source for seizure activity. Therapeutic drug monitoring should be performed if medication-related seizures or subtherapeutic anticonvulsant levels are suspected. Antibiotics can be a common source of drug-induced seizures in the ICU especially in patients requiring high doses for deep-seated infections (eg, meningitis) or those with renal or hepatic insufficiency that can lead to drug accumulation. Table 1 lists common drugs that may induce seizures in the ICU setting. Certain drug interactions have also been known to result in seizures. Meropenem can significantly decrease the serum levels of valproic acid within 24 hours, placing patients at risk of breakthrough seizures from subtherapeutic concentrations. Knowing the source of the seizure will help guide the initial anticonvulsant therapy and increase the probability of halting seizure activity, although the cause of many seizures remains unknown in up to a third of patients.

Diagnosing seizures or SE in ICU patients is very challenging due to the acuity of illnesses seen. Many patients are already obtunded or comatose or are experiencing variations in vital signs that may not solely be attributed to seizure activity. EEG can be very helpful in these cases where seizures are suspected and other causes of decline in neurological status have been ruled out. EEG is also warranted in patients where no physical signs of seizure activity can be assessed such as those on paralytics or those in NCSE. However, it is essential that seizure treatment never be delayed while awaiting EEG results.

### Treatment of Seizures and SE

The goals of treatment for seizures and SE include the cessation of any seizure activity, both clinical and subclinical, and seizure prevention. Ideally, this is achieved through directed pharmacotherapy with minimization of any side effects, drug interactions, or adverse reactions. Seizure complications should also be treated.

After securing a proper airway in nonintubated patients, the initial approach to seizures and SE in critically ill patients is the administration of parenteral benzodiazepines followed by the initiation of an anticonvulsant drug (Table 2). Since many ICU patients may be hemodynamically unstable, fluid therapy and/or vasopressors may be necessary especially when using agents that cause hypotension. Medications are typically given intravenously (IV) in critically ill patients for immediate onset of action, but certain medications can be given intramuscularly (IM), rectally, bucally, or via an endotracheal tube if necessary. Once the seizures are controlled, clinicians must identify...
### Table 2. Medications Used to Treat Seizures and Status Epilepticus in Adult ICU Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading Dose</th>
<th>Administration Rate and Repeat Dosing</th>
<th>Therapeutic Range</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.15 mg/kg</td>
<td>5 mg/min (IVP); repeat: every 5 minutes</td>
<td>NA</td>
<td>Hypotension</td>
<td>Fast onset but rapid redistribution into body fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory depression</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg</td>
<td>2 mg/min (IVP); repeat: 10-15 minutes</td>
<td>NA</td>
<td>Hypotension</td>
<td>Preferred benzodiazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory depression</td>
<td>Dilute 1:1 with saline before administering</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg</td>
<td>2 mg/min (IVP); 0.05-2 mg/kg per hour (CI)</td>
<td>NA</td>
<td>Sedation</td>
<td>Tachyphylaxis occurs after prolonged use Must adjust renally</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory depression</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>15-20 mg/kg</td>
<td>Up to 50 mg/min IV</td>
<td>10-20 µg/mL</td>
<td>Arrhythmias</td>
<td>Only compatible in saline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypotension Phlebitis Purple glove syndrome</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>15-20 mg PE/kg (IV or IM)</td>
<td>Up to 150 mg PE/min IV</td>
<td>10-20 µg/mL</td>
<td>Paresthesias</td>
<td>Compatible in saline, dextrose, and lactated Ringer’s solutions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>20 mg/kg IV</td>
<td>50-100 mg/min IV</td>
<td>15-40 µg/mL</td>
<td>Hypotension Sedation Respiratory depression</td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>15-20 mg/kg</td>
<td>(up to 40 mg/kg)</td>
<td>3-6 mg/kg per min IV</td>
<td>50-150 µg/mL</td>
<td>Thrombocytopenia Hyperammonemia Pancreatitis</td>
</tr>
<tr>
<td>Propofol</td>
<td>1-2 mg/kg</td>
<td>2-15 mg/kg per hour (CI)</td>
<td>NA typically titrated to EEG</td>
<td>Hypotension Respiratory depression Cardiac failure (PRIS)</td>
<td>Must adjust daily caloric intake</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>10-15 mg/kg</td>
<td>Up to 50 mg/min IV; 0.5-4 mg/kg per hour (CI)</td>
<td>10-20 µg/mL (typically titrated to EEG)</td>
<td>Hypotension Respiratory depression Cardiac depression</td>
<td>Usually requires mechanical ventilation</td>
</tr>
<tr>
<td>Thiopental</td>
<td>5 mg/kg</td>
<td>5 mg/kg per hour (CI) titrated to EEG</td>
<td>NA</td>
<td>Hypotension Respiratory depression Cardiac depression</td>
<td>Metabolized to pentobarbital</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>NA (doses of 1000-3000 mg given IV over 10-30 minutes have been reported)</td>
<td>500-1500 mg IV over 30 minutes; dosed every 12 hours (adjust for renal dysfunction)</td>
<td>NA</td>
<td>Psychosis Somnolence Dizziness</td>
<td>May be considered second- or third-line agent Minimal drug interactions Not hepatically metabolized</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>NA</td>
<td>200 mg IV over 30 minutes; dosed every 12 hours</td>
<td>NA</td>
<td>Dizziness</td>
<td>May be considered second- or third-line agent Minimal drug interactions</td>
</tr>
<tr>
<td>Topiramate</td>
<td>NA</td>
<td>300-1600 mg/day orally (divided twice daily)</td>
<td>NA</td>
<td>Metabolic acidosis</td>
<td>Usually reserved for refractory status epilepticus</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.9-3 mg/kg</td>
<td>0.3-7.5 mg/kg per hour IV</td>
<td>NA</td>
<td>Increased blood pressure, heart rate, cardiac output, and intracranial pressure Cerebellar and cognitive dysfunction seen with high or prolonged doses</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, continuous infusion; EEG, electroencephalogram; ICU, intensive care unit; IM, intramuscular; IV, intravenous; IVP, intravenous push; N/A, not applicable; PE, phenytoin equivalents; PRIS, propofol related infusion syndrome.
and treat the underlying cause of the seizures, such as toxins, hypoglycemia, or trauma. Nondrug interventions include administration of oxygen or intubation for mechanical ventilation in hypoxic patients or body cooling for febrile patients that are unresponsive to antipyretic therapy. Neurologists or epileptologists should be consulted as appropriate. Table 3 reviews a proposed algorithm for the treatment of SE in the ICU.

**Benzodiazepines**

Initial drug therapy begins with the administration of an IV benzodiazepine since they are most effective in quickly aborting seizure activity and are easily administered. Treiman et al performed a blinded, randomized, prospective study of four IV regimens for the primary treatment of SE—lorazepam (0.1 mg/kg), diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), phenytoin (18 mg/kg) alone, and phenobarbital (15 mg/kg) alone. Lorazepam was found to be more successful than phenytoin alone in aborting overt SE within 20 minutes of therapy (64.9% vs 43.6%, P = .002) although no regimen was found to be more efficacious in the intent-to-treat analysis, which included both overt and subtle SE. Clinically, IV bolus doses of diazepam, lorazepam, and midazolam have all been used to treat seizures and SE because of their rapid effects at enhancing postsynaptic inhibitory GABA_A receptor activity in the CNS through interaction with a benzodiazepine-specific receptor site. This promotes an influx of chloride into the neurons resulting in hyperpolarization of the membrane and inhibition of nerve impulse transmission. Lorazepam is now considered the first-line agent by most clinicians although other parenteral benzodiazepines are also effective. When treating patients on chronic benzodiazepine therapy, higher doses may be required to overcome the effects of tolerance. Diazepam and lorazepam both contain a propylene glycol diluent, which can cause hypotension if administered rapidly and peripheral venous irritation if not diluted (1:1 ratio) with normal saline prior to administration. In ICU patients that have a central line in place, the risks of phlebitis may be minimal.

Diazepam is extremely lipophilic and penetrates quickly into the CNS but also rapidly redistributes out into the body fat and muscle, resulting in a fast decline in CNS concentrations and early recurrence of seizures. To halt seizures, doses of 0.15 mg/kg at a rate of 5 mg/min are recommended and can be repeated every 5 minutes. Respiratory depression is the most common side effect and should be closely monitored in critically ill patients who are not mechanically ventilated. If IV access is not available, another benzodiazepine should be initiated as IM administration of diazepam is not recommended due to erratic absorption. Lorazepam is less lipophilic and has a longer redistribution half-life as compared to diazepam, resulting in prolonged duration of action and a decrease in the need for repeated doses. Lorazepam is given as a single IV dose of 0.1 mg/kg at a rate of 2 mg/min and can be repeated every 10 to 15 minutes up to a maximum cumulative dose of 8 mg, although some clinicians may elect to exceed this if the patient is already mechanically ventilated. Midazolam can also be used to treat seizures and SE. It is a water-soluble agent that becomes more lipophilic at physiologic pH and readily diffuses into the CNS. In patients without IV access, it can be administered IM,23 buccally,24 or nasally.25 Compared to diazepam and lorazepam, it has fewer cardiovascular and respiratory side effects, making it a desirable choice in unstable ICU patients. Due to its short half-life, midazolam must be redosed frequently or administered as a continuous infusion in order to prevent seizure recurrence. Midazolam can be dosed at 0.2 mg/kg either IV or IM as a single dose,22 or buccally24 or intranasally25 at 0.3 mg/kg. Nasal administration of midazolam in SE can be hindered by rapid breathing and increased nasal secretions and may not be optimal in ICU patients. A continuous infusion may be initiated in a mechanically ventilated patient after an appropriate bolus dose at a rate ranging from 0.75 to 10 μg/kg per minute.

**Anticonvulsant Drugs**

Once the first dose of benzodiazepine is given, an anticonvulsant should be started to prevent seizures from recurring. If the underlying cause of the seizures has been corrected (eg, hypoglycemia) and seizure activity has ceased, an anticonvulsant may not be necessary. Parenteral anticonvulsants that have been used in critically ill patients for seizures include phenytoin, fosphenytoin, phenobarbital, valproate sodium, levetiracetam, and, most recently, lacosamide. Anticonvulsants like phenytoin, fosphenytoin, and phenobarbital are generally not given as first-line therapy since they are infused relatively slowly in order to avoid adverse effects, delaying their onset of action. The newer agents such as levetiracetam and lacosamide seem to be better tolerated when given as IV infusions in this setting but need further study to confirm their place in the primary treatment of SE. Once the loading dose of the anticonvulsant is administered (if appropriate), maintenance doses must be initiated to ensure that therapeutic levels are maintained. Chronic and idiosyncratic side effects, the patient’s renal and hepatic function, as well as potential drug interactions should guide the clinician in the selection of appropriate agent.

Phenytoin has traditionally been the most widely used anticonvulsant in SE. Its main mechanism of action is through the blockage of voltage-gated sodium channels. It is administered IV as a loading dose (for patients previously not on phenytoin) of 15 to 20 mg/kg at a rate not to exceed 50 mg/min to avoid hypotension and arrhythmias. The loading dose must be modified in patients on maintenance phenytoin therapy who have subtherapeutic levels in order to avoid toxic serum concentrations. Table 4 has several equations that clinicians can use to dose and monitor phenytoin therapy, including one to calculate a mini loading dose in patients with subtherapeutic serum phenytoin levels. Continuous monitoring of electrocardiogram (ECG), heart rate, and blood pressure is recommended during the administration of the loading dose, and maintenance therapy should be started approximately 12 hours after the loading dose. Phenytoin can be challenging to use in the ICU because

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it should not be infused concomitantly with other medications because of stability issues (it is soluble in propylene glycol and compatible only with 0.9% sodium chloride solutions). It should not be given via the IM route since extravasation of phenytoin can cause local skin discoloration, edema, pain, and sometimes severe tissue necrosis, a complication commonly known as purple glove syndrome.31

With the recent release of its generic formulation, fosphenytoin has become the drug of choice in most ICUs. Fosphenytoin is a parenteral, water-soluble, phosphoester prodrug that is rapidly converted in vivo to phenytoin. It is compatible with most IV solutions used in the ICU and is well tolerated as an IM injection if IV access is limited or unavailable, even with the large volumes associated with loading doses (20 to 30 mL).32 It is dosed in milligrams of phenytoin equivalents (PE), and it can be administered up to 150 mg PE/min, which is 3 times faster than IV phenytoin. The IV loading dose for phenytoin-naive patients is 15 to 20 mg PE/kg. Clinicians should still monitor blood pressure, ECG, and heart rate during the infusion although it is better tolerated than phenytoin. Maintenance doses of IV fosphenytoin or oral phenytoin are started 12 hours after the loading dose (conversion from fosphenytoin to oral phenytoin should be 1:1). Perioral and perineal paresthesias are common with fosphenytoin, usually resolve within a few

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### Table 3. Algorithm for Treatment of Status Epilepticus in Adult ICU Patients (Adapted From Brophy and Tesoro103)

<table>
<thead>
<tr>
<th>Time in Minutes</th>
<th>Monitoring Parameters/Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Recheck vital signs; reassess airway; obtain 12-lead ECG; check blood glucose; check recent laboratory tests and examine trends: metabolic panel complete blood count with differential liver function tests arterial blood gas if febrile, obtain pan-cultures serum anticonvulsant levels serum drug screen</td>
<td>Stabilize airway (intubate if necessary) and administer oxygen if indicated; consider securing additional IV access and optimize intravenous fluids; consider vasopressor therapy if hemodynamically unstable; give antipyretic therapy if febrile; discontinue enteral tube feeding; discontinue insulin infusion if hypoglycemic</td>
</tr>
<tr>
<td>0-10</td>
<td>Continue to monitor vital signs; physical and neurological exam; review medications for possible drug-induced seizures</td>
<td>Lorazepam 0.1 mg/kg IVP at 2 mg/min (may repeat in 10-15 minutes if no response) or midazolam 0.2 mg/kg IV or diazepam 0.15 mg/kg IV at 5 mg/min (may repeat in 5 minutes if no response)—monitor for respiratory depression and intubate if necessary; anticonvulsants may not be necessary if underlying cause is corrected and seizures have resolved</td>
</tr>
<tr>
<td>10-30</td>
<td>Continue to monitor vital signs; review new laboratory results and correct any underlying abnormalities; CT scan (if seizures controlled)</td>
<td>Phenytoin 15-20 mg/kg IV at a maximum rate of 50 mg/min (or fosphenytoin 15-20 mg PE/kg IV at a maximum rate of 150 mg/min); in patients allergic to phenytoin, give valproate sodium 20 mg/kg IV at a maximum rate of 6 mg/kg per minute</td>
</tr>
<tr>
<td>30-60</td>
<td>Continue to monitor vital signs; consult neurologist/epileptologist (patients may be considered in refractory status epilepticus during this time period and may require advancing to the next step); obtain EEG</td>
<td>If seizures continue: additional phenytoin bolus 5-10 mg/kg IV at a maximum rate of 50 mg/min (or fosphenytoin 5-10 mg PE/kg IV at a maximum rate of 150 mg PE/min) or start phenobarbital at 20 mg/kg IV at a maximum rate of 100 mg/min or start valproate sodium 20 mg/kg IV at a maximum rate of 6 mg/kg per minute; may also consider adding levetiracetam 500-1500 mg IV q12h (adjust for renal dysfunction) or lacasamide 200 mg IV q12h (adjust for patients with end-stage renal disease)</td>
</tr>
<tr>
<td>Greater than 60—refractory status epilepticus</td>
<td>Continue to monitor vital signs; obtain EEG; consider MRI when patient is stable</td>
<td>Midazolam 2 mg/kg bolus followed by 0.05-2 mg/kg per hour CI or propofol 1 mg/kg bolus followed by 2-15 mg/kg per hour CI or pentobarbital 10-15 mg/kg bolus over 1-2 hours followed by 0.5-4 mg/kg per hour or thiopental 5 mg/kg IV bolus followed by 5 mg/kg per hour CI; consider intubation and/or pressor support if not already done; optimize anticonvulsant levels: repeat boluses of phenobarbital 10 mg/kg or valproate sodium 20 mg/kg at 6 mg/kg per minute maximum; if still in SE, consider adding parenteral levetiracetam 500 mg IV q12h, or lacasamide 200 mg IV q12h, or enteral topiramate 500 mg q12h; if SE still persists, consider parenteral ketamine</td>
</tr>
</tbody>
</table>

Abbreviations: CI, continuous infusion; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalography; ICU, intensive care unit; IV, intravenous; IVP, intravenous push; MRI, magnetic resonance imaging; PE, phenytoin equivalents
Table 4. Equations for Phenytoin Dosing and Monitoring

To calculate a loading dose for patients with subtherapeutic serum phenytoin concentrations:

\[
Dose = (C_{desired} - C_{measured}) \times V_d \times \text{patient weight in kilograms}
\]

To adjust total phenytoin concentrations in patients with renal disease\(^{29}\):

\[
C_{adjusted} = C_{observed}[0.1 \times \text{albumin} + 0.1]
\]

To adjust total phenytoin concentrations in patients with hypoalbuminemia\(^{29}\):

\[
C_{adjusted} = C_{observed}[0.2 \times \text{albumin} + 0.1]
\]

To adjust total phenytoin levels in elderly and critically ill patients with hypoalbuminemia\(^{29}\):

\[
C_{adjusted} = C_{observed}[0.25 \times \text{albumin} + 0.1]
\]

Abbreviation: \(V_d\) = volume of distribution (0.5-1 L/kg).

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minutes, and should not necessitate stopping the infusion. If necessary, serum phenytoin levels should be obtained 2 hours after an IV load or 4 hours after an IM load.

If phenytoin or fosphenytoin fails to prevent seizure recurrence, additional boluses may be administered or phenobarbital can be initiated. An IV load of 15 to 20 mg/kg can be infused at a maximum rate of 100 mg/min. Phenobarbital can produce significant sedation, hypotension, and respiratory depression and patients may require mechanical ventilation. Its long half-life makes it a popular agent for both acute treatment and chronic maintenance therapy, but it should not be confused with pentobarbital, another barbiturate with a shorter half-life that is commonly used for inducing coma and may be used to treat refractory SE. Emerging evidence suggests that phenobarbital may not be effective in SE due to the progressive resistance of the GABA\(_A\) receptor, a site where benzodiazepines, phenytoin, and barbiturates act.\(^{33}\) Many of the newer agents (eg, levetiracetam, lacosamide) have non-GABA\(_A\) mechanisms of action that may make them attractive alternatives if phenobarbital is not tolerated or contraindicated.

Although valproate sodium is not Food and Drug Administration (FDA) approved for SE, it has been reported to be successful in the treatment of various types of SE including generalized tonic-clonic, myoclonic, and NCSE.\(^{34,35}\) It may serve as an alternative agent for patients with allergies or intolerance to phenytoin or phenobarbital. Its mechanism of action is not clear but may be related to increasing the CNS concentration of GABA\(_A\). It has reportedly good efficacy with cessation of both physical and EEG seizure activity but with less cardiopulmonary toxicity than traditional agents.\(^{36}\) Valproate sodium is administered IV as a 15 to 20 mg/kg load and infused at a maximum rate of 6 mg/kg per minute. Higher doses of 30 to 40 mg/kg have been used successfully to achieve serum levels of 100 to 150 \(\mu\)g/mL in less responsive cases of SE.\(^{37}\) One study showed comparable efficacy to IV phenytoin in relatively young SE patients who had already received up to 20 mg of IV diazepam. Overall, IV valproate at 20 mg/kg was successful in treating 88% of patients with SE compared to 84% of patients given IV phenytoin at 20 mg/kg.\(^{38}\) Another recent study in older patients also revealed similar success rates between IV valproate (87.8%) and IV phenytoin (88%) although this study did not administer benzodiazepines initially.\(^{39}\) Therapy with valproate sodium is associated with significant thrombocytopenia, hyperammonemnic encephalopathy, and pancreatitis; therefore, close monitoring of the complete blood count (CBC), ammonia levels, and amylase and lipase concentrations after initiation of therapy is warranted. The use of oral levocarnitine to prevent valproic acid–induced hepatotoxicity and encephalopathy may be a viable option in select patients (eg, pediatric patients),\(^{40}\) but further study is warranted in the setting of SE in adults.

Although not FDA approved for SE, levetiracetam is a newer anticonvulsant that is structurally dissimilar from other agents and has no direct affinity for GABA, glycine, or NMDA receptors in the brain. Its exact mechanism against seizures is unknown although it does bind to the synaptic vesicle protein 2A (SV2A), which is involved in neurotransmitter release.\(^{41}\) It has ideal characteristics in that it does not display the cardiopulmonary, hepatic, and sedative side effects seen with the other agents nor does it have potentially harmful drug interactions due to its low protein binding and lack of hepatic metabolism. It may serve as an alternative agent to those patients who are intolerant of phenytoin, phenobarbital, or valproate sodium. IV levetiracetam has been studied in ICU patients with SE and reported to be safe.\(^{42,43}\) It must be adjusted in patients with renal impairment or failure as 66% of the parent drug is excreted through the kidneys unchanged. However, dosing levetiracetam in ICU patients who are undergoing continuous renal replacement therapy is challenging since it is not known how much of the drug is removed via each of the different modalities, and the recommended dosing for intermittent hemodialysis may not be appropriate, leading to suboptimal therapy. Loading doses of 1500 to 2000 mg have been given in SE\(^{27}\) although this practice is not universally accepted, and the most common maintenance dose reported is 500 mg every 12 hours.

Therapy can be titrated up to a maximum daily dose of 3000 mg as clinically indicated since there is no standardized therapeutic level monitoring currently in practice. Its place in therapy has not been established although many have used it in combination with one of the traditional anticonvulsants,\(^{19}\) especially in patients with severe hepatic disease or cardiovascular compromise. Early administration seems to confer more success in halting seizure activity.\(^{44}\) Maintenance doses of the anticonvulsant drugs must be started after appropriate loading doses have been given to sustain their effects once the seizures have been controlled. When appropriate, serum concentrations should approach the higher end of the therapeutic range. Care must be taken when interpreting total serum phenytoin concentrations in patients with conditions that may decrease its high protein binding and give a false picture of subtherapeutic levels. Such conditions are commonly seen in ICU patients and include uremia, liver failure, burns, malnutrition, pregnancy, or elderly age. Use of appropriate equations (see Table 4) to adjust total levels or

\[C = \frac{Dose}{V_d \times \text{patient weight in kilograms}}\]

\[C_{adjusted} = C_{observed}[0.2 \times \text{albumin} + 0.1]\]
measuring free concentrations of phenytoin in these patients are required to appropriately maintain therapeutic levels and adjust therapy. Many of the older anticonvulsants affect liver enzymes as cytochrome P450 (CYP) enzyme inducers (phenytoin, phenobarbital—CYP2C9, CYP2C19, CYP3A4) or inhibitors (valproate sodium—CYP2C9), and appropriate adjustments should be made to other drugs that are hepatically metabolized via these enzyme pathways. Routine monitoring of liver function is also reasonable in the ICU as transaminitis can occur suddenly in the acutely ill, which may require dose adjustments, drug discontinuation, or substitution with an alternative agent. Certain anticonvulsants require special consideration when delivered via an enteral feeding tube, a common route for nutrition in ICU patients. Concomitant administration of phenytoin suspension with enteral tube feeds can result in decreased absorption and subsequent decrease in serum levels in critically ill patients.45 It is recommended that enteral nutrition be held for at least 1 to 2 hours before and after doses of phenytoin suspension and that the feeding tube be flushed with at least 30 mL of water before and after the dose to minimize any interactions between the suspension and the tube feeds. Appropriate readjustment of the tube feeding rate should be performed in order to prevent suboptimal nutrition. Carbamazepine suspension should also be separated from other drugs and liquids when given via feeding tubes and diluted with an equal amount of water to optimize its absorption.46

Pharmacogenetics has recently come into play in the determination of suitable candidates for certain anticonvulsants and may help ICU clinicians avoid significant drug-related problems. Patients with the HLA-B*1502 allele, who take carbamazepine are at a higher risk of developing severe cutaneous reactions such as toxic epidermal necrolysis or Stevens-Johnson syndrome.47 This variant allele is seen frequently in Asian populations including those of Han Chinese, Filipino, Malaysian, South Asian Indian, or Thai descent,48 and genotypic testing is highly recommended before initiating carbamazepine in these patients. This mutation has not been identified in patients of European, Hispanic, or Native American descent. The use of phenytoin or fosphenytoin as alternatives to carbamazepine is not recommended at this time in patients who test positive for the HLA-B*1502 allele until a full investigation by the Food and Drug Administration is complete. Valproate sodium or some of the newer anticonvulsant agents may be suitable in this case. Other applications of pharmacogenetic principles include the identification of patients with mutant alleles that affect CYP2C9/CYP2C19 function. Genetic polymorphisms of this enzyme system can result in decreased metabolic function resulting in potentially toxic phenytoin concentrations following the administration of normal therapeutic doses.49

**Refractory Status Epilepticus**

Seizures unresponsive to first-line therapy (benzodiazepines) and second-line therapy (anticonvulsants) or those that persist beyond 60 minutes in duration are considered RSE.50 Up to 30% of patients with SE will progress to RSE with an associated mortality rate of 50%,51 especially in critically ill patients with multiple comorbid disease states typically found in an ICU. Unfortunately, patients in RSE are unlikely to return to their baseline state, even with subsequent control of their seizures; one meta-analysis reported only 29% of patients returned to their premorbid state.52 As RSE progresses, clinical signs may become subtle or even unnoticeable, and eventually only an EEG will be able to detect ongoing seizure activity that places the patient at risk for significant brain damage or even death.

The optimal therapy for RSE has not been clearly determined and clinicians must aggressively investigate and treat any possible etiology including acute infection, tumors, drugs, metabolic disorders, hepatic failure, or fever.53 Continuous EEG monitoring is necessary to confirm successful resolution of seizures, but treatment must not be delayed if continuous EEG monitoring is not immediately available or while awaiting results. Any currently administered anticonvulsants should be maintained, and their serum concentrations maximized to prevent withdrawal or breakthrough seizures. Slightly supratherapeutic target concentrations are preferred by some clinicians unless severe toxicities occur. The administration of various continuous IV infusions of benzodiazepines, anesthetic agents, or barbiturates has all been instituted in the treatment of RSE. The goal of “burst suppression” on the EEG is common but controversial and not accepted universally.54 Overall, the purpose is to suppress all clinical and electroencephalographic evidence of seizures.55 Patients are normally intubated and mechanically ventilated for these treatments, and collaboration with a neurologist, neurointensivist, or epileptologist is highly recommended.

**Midazolam**

Midazolam can be initially loaded at 0.2 mg/kg and repeated up to a maximum of 2 mg/kg after which a continuous infusion of 0.05 to 2 mg/kg per hour is recommended.56-58 The dose should be decreased after extended use because the active metabolite can accumulate over time,59 especially in patients with renal impairment. Breakthrough seizures have been reported and usually respond to a bolus and a 20% rate increase. However, tachyphylaxis can still occur and the patient should be switched to an alternative agent if seizure activity cannot be controlled.

**Propofol**

The exact anticonvulsant properties of the anesthetic propofol are unknown but may be related to its ability to block sodium channels and modulate GABA-mediated neurotransmission.60 Loading doses of 1 mg/kg are repeated every 3 to 5 minutes until clinical response is observed, after which a continuous infusion of 2 to 4 mg/kg per hour can be initiated. Propofol is associated with significant hypotension, especially with large doses such as those associated with loading. Long-term (greater than 48
hours), high-dose (greater than 5 mg/kg per hour) propofol infusions are associated with rhabdomyolysis, acidosis, and cardiac arrhythmias (propofol-related infusion syndrome or PRIS). A recent study of ICU patients admitted with refractory SE reported rates of cardiorespiratory arrest and death at 10% and 6%, respectively, associated with the prolonged use of high doses of propofol. The patients who died in this series had no prior cardiovascular disease history but still suffered cardiac arrest despite intensive monitoring. Risk factors that have been associated with increased mortality in patients suspected of PRIS include age ≤18 years, male gender, history of vasopressor use, or presence of cardiac abnormalities, metabolic acidosis, hypotension, renal failure, rhabdomyolysis, or hyperlipidemia. Propofol should be tapered slowly to avoid withdrawal seizures as it has a very short serum half-life. High-dose propofol therapy also provides a considerable amount of lipid-based calories (1 kcal/mL), so other sources of nutrition may have to be appropriately adjusted to prevent overfeeding. Abnormal movements and myoclonus that may mimic seizure activity have also been associated with propofol use and should be evaluated before more aggressive therapy is initiated.

**Pentobarbital**

Barbiturate therapy has been reported to be highly successful in treating RSE, but it has considerable cardiovascular toxicities, and risks must be weighed against potential benefit in the critically ill patient. Significant hypotension, myocardial and respiratory depression, ileus, and infection (especially gram-positive organisms) have all been reported as major complications from barbiturates. Patients must be mechanically ventilated, and the use of IV vasopressor therapy, invasive hemodynamic monitoring, and total parenteral nutrition may be necessary. However, barbiturates have beneficial effects on elevated ICP and cerebral metabolism that may benefit patients with head trauma or severe cerebral edema.

Pentobarbital is initially loaded IV at 10 to 15 mg/kg over 1 to 2 hours, followed by a continuous infusion of 0.5 to 4 mg/kg per hour. After 12 to 24 hours of seizure control as seen on continuous EEG monitoring, treatment may be tapered off. Tapering methods may vary but one example would be to decrease the continuous infusion rate by 0.5 to 1 mg/kg per hour every 4 to 6 hours as tolerated. Any evidence of seizure activity would prompt a return to the previous rate and a reassessment of the anticonvulsant regimen (ie, increasing doses, adding new agents), followed by slower attempt at tapering. A meta-analysis of RSE therapies reported a lower incidence of treatment failure with pentobarbital (3%) compared to midazolam (21%) or propofol (20%), although the incidence of hypotension requiring vasopressors was higher in patients treated with pentobarbital. This relative efficacy must be considered together with its complications to determine the most ideal agent in the ICU patient. Patients who are refractory to or intolerant of midazolam and/or propofol therapies could be considered for barbiturate therapy. Appropriate adjustments must be made in concomitant medications that are hepatically metabolized, especially other anticonvulsants, since pentobarbital is a potent inducer of liver enzymes.

**Thiopental**

Thiopental is a short-acting barbiturate that is metabolized into pentobarbital. One study described the use of high-dose thiopental in mechanically ventilated patients with RSE in an ICU. Ten patients received an initial IV bolus of 5 mg/kg followed by boluses of 1 to 2 mg/kg every 3 to 5 minutes until burst suppression was seen on EEG, after which a continuous infusion of 5 mg/kg per hour was initiated and titrated to keep the patient in burst suppression. All patients received IV dexamethasone and foscarnet prior to thiopental although many patients were on 2 or 3 anticonvulsants in the ICU. Clinical seizure control and burst suppression were achieved in all patients, but the authors did note a pattern of Staphylococcus aureus cultured from the tracheal aspirates of 6 patients without evidence of pneumonia on chest X-ray, suggesting that barbiturates may have immunosuppressive properties, predisposing them to possible infectious risk.

**Levetiracetam**

Both IV and oral levetiracetam formulations have been used in RSE patients as adjunct therapy with some success, although it is unclear if levetiracetam would be effective as monotherapy. Doses of up to 2500 mg given over 5 minutes in patients with SE appear to be well tolerated. There appears to be more benefit in patients with refractory focal seizures, who are given levetiracetam than other seizure types.

**Other Agents**

Ketamine acts as an antagonist at the phenycyclidine site of the NMDA receptor and has been reported to be successful in treating SE that is refractory to other agents. It is theorized that with uncontrolled seizures, NMDA receptors are upregulated over time while the GABA_A receptors become downregulated and therefore more refractory to agonists, making treatment of refractory SE with ketamine a potential option. It is also different from any of the traditional RSE treatments in that it increases blood pressure, heart rate, and cardiac output; but caution must be used in head injury patients or those with intracranial mass lesions since it may raise ICP. Sheth and Gidal treated a 13-year-old girl with seizures refractory to lorazepam, phenytoin, barbiturates, propofol, and valproate sodium with IV ketamine loaded at 2 mg/kg followed by a continuous infusion reaching a maximum rate of 7.5 mg/kg per hour. Her seizures responded well initially, but higher doses were required over 14 days before weaning off. The patient was reported to have significant deficits in short-term memory and global cognition and there are concerns about NMDA antagonist toxicity after prolonged or high-dose ketamine therapy, reportedly manifesting as cerebellar dysfunction and extensive cognitive dysfunction.
Seizure Prophylaxis

Certain ICU patients may be at high risk for seizures due to neurological trauma or intracranial surgery or the presence of a cortical lesion (eg, brain tumor) and may receive anticonvulsant drug therapy to prevent seizures for a limited period of time. The side effects of anticonvulsants can be significant in ICU patients and may include severe rash (eg, Stevens-Johnson syndrome), fever, hematological side effects, and neurobehavioral abnormalities. Controversy still exists as to which populations should receive seizure prophylaxis, which anticonvulsant is the ideal agent, and the duration of prophylaxis.

Anticonvulsants appear to protect traumatic brain injury patients from early-onset seizures (within 7 days) but not from late onset seizures (>7 days posttrauma).26 Risk factors that may increase the risk of posttraumatic seizures include a Glasgow Coma Scale <10, presence of a cortical contusion, depressed skull fracture, epidural, subdural, or intraparenchymal hemorrhage, penetrating head injury, or seizure within 24 hours of injury.28 In aneurysmal subarachnoid hemorrhage (SAH), a 3-day course of phenytoin was as effective in preventing seizures compared to prophylaxis until discharge.80 In general, anticonvulsant use has been implicated in poorer patient outcome (based on Glasgow Outcomes Score) and associated with in-hospital complications such as fever.51 Prolonged exposure to phenytoin specifically has been associated with poor neurological (based on modified Rankin scale) and cognitive outcomes82 and should be limited to high-risk patients. Risk factors for long-term seizure activity in aneurysmal SAH patients that may warrant extended prophylaxis include prior seizures, history of hypertension, intraparenchymal hematoma, infarction, or middle cerebral artery aneurysm.83 Patients with intracranial aneurysms that are treated with endovascular coiling may have a lower seizure risk than those who undergo craniotomy for surgical clipping.84 Patients with intracerebral hemorrhage who have seizures typically present with a higher National Institute of Health Stroke Scale (NIHSS) score, midline shift,85 or lobar hemorrhage.86 Prolonged treatment (>7 days) with prophylactic anticonvulsants appears to be related to poor outcomes in this patient population as well.87,88 Patients with newly diagnosed brain tumors and no history of seizures do not benefit from anticonvulsant prophylaxis and may even incur serious side effects from such regimens.89,90 Phenytoin has been implicated in serious dermatological adverse effects in cancer patients undergoing radiation treatment.91 Older generation anticonvulsants have also been associated with significant interactions with chemotherapeutic agents as well.92 Patients undergoing supratentorial neurosurgery for tumor resection are typically given a course of postoperative anticonvulsants of which the newer generation agents (ie, levetiracetam, lamotrigine) may be of some benefit due to their overall tolerability and lack of serious adverse events and drug interactions.93 Recommendations for the use of seizure prophylaxis in patients with neurological injuries are listed in Table 5.

Cognition may already be compromised in many ICU patients, and the addition of anticonvulsant therapy may exacerbate this condition over time. Many of the newer agents like levetiracetam lack any major detrimental effects on neurocognitive status and may be of benefit when used as prophylaxis.103 Still, it may be reasonable to delay the implementation of anticonvulsant therapy in certain patients until the first seizure occurs; however, the difficulty in identifying these seizures in the critically ill and the potential risk of subclinical seizure types to go untreated makes this decision very difficult and complex and may underscore the need for EEG monitoring in patients with impaired neurological function.
If no seizure activity occurs during the prophylaxis period, the anticonvulsant should be discontinued. Often, patients are started on antiseizure medications in the ICU and then are inappropriately continued on them after discharged for an indeterminate length of time. This could lead to an increase in drug interactions and serious adverse drug events that could further complicate the patient’s clinical status as well as place an undue burden on them with associated costs related to drug procurement and monitoring. To avoid unnecessary medications and further complications, it is critical to monitor for seizure activity and discontinue prophylaxis when appropriate.

Conclusion

Seizures in the critically ill patient present many challenges to clinicians. Detection and diagnosis of seizures may be difficult due to the various comorbidities seen in the ICU, but prompt identification and treatment can produce optimal results. Status epilepticus may be initially seen with physical convulsions but may progress if untreated to a nonconvulsive state that can be difficult to control and lead to substantial morbidity. Parenteral benzodiazepines remain first-line treatment for SE followed by the anticonvulsants, of which there are newer options that may be better tolerated in ICU patients. Refractory SE requires more aggressive treatment with continuous anesthetic agents or coma induction, which is associated with significant toxicities. A risk to benefit assessment should always be made with regard to seizure prophylaxis in critically ill patients to optimize recovery and prevent further complications.

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