Chapter 76: Status Epilepticus

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 54, Epilepsy.

KEY CONCEPTS

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1. Status epilepticus (SE) is a neurologic emergency that may be associated with significant morbidity and mortality.

2. Generalized convulsive status epilepticus (GCSE) is defined as any recurrent or continuous seizure activity lasting longer than 30 minutes in which the patient does not regain baseline mental status. Any seizure that does not stop within 5 minutes should be treated aggressively as impending SE.

3. There are two types of SE, GCSE and nonconvulsive status epilepticus (NCSE). GCSE is the most common type and is divided into four stages: (1) impending, (2) established, (3) refractory, and (4) super-refractory.

4. The pathophysiology of GCSE is unknown; however, experimental models show a dramatic decrease in γ-aminobutyric acid (GABA)–mediated inhibitory synaptic transmission and that glutamatergic excitatory synaptic transmission sustains the seizures.

5. During prolonged GCSE, $GABA_A$ receptors move from the synaptic membrane into the cytoplasm, becoming functionally inactive. Receptor loss on the synaptic surface may result in time-dependent benzodiazepine pharmacoresistance. Glutamatergic *N*-methyl-D-aspartate (NMDA) receptors also increase in number and activity, suggesting a role for ketamine.

6. Treatment is done to prevent or decrease morbidity and mortality of prolonged seizures. Pharmacologic treatment needs to be rapid and aimed at terminating both electrical and clinical seizures. The probability of poorer outcomes increases with an increased length of electroclinical seizure activity.

7. IV lorazepam is the preferred benzodiazepine for initial treatment of GCSE given its efficacy and long duration of action in the central nervous system (CNS), although IM midazolam, IV lorazepam, IV diazepam, and IV phenobarbital effectively terminate seizures lasting at least 5 minutes. Midazolam is the preferred benzodiazepine for IM and intranasal administration in patients without an established IV.

8. The hydantoins (ie, phenytoin, fosphenytoin) continue to be the long-acting antiseizure medications used most frequently, although this is changing. The comparative efficacy of these two antiseizure medications is still unknown; however, fosphenytoin is better tolerated and hence preferred. Either should be given concurrently with benzodiazepines.

9. The second antiseizure medication administered is less effective than the first “standard” antiseizure medication in both adults and pediatric patients. The third antiseizure medication may be significantly less effective.

10. If GCSE is not controlled by two antiseizure medications (a benzodiazepine and a standard antiseizure medication), it is considered refractory. In these cases, anesthetic doses of midazolam, pentobarbital, or propofol may be used and monitored with a continuous electroencephalogram (EEG).

BEYOND THE BOOK

BEYOND THE BOOK

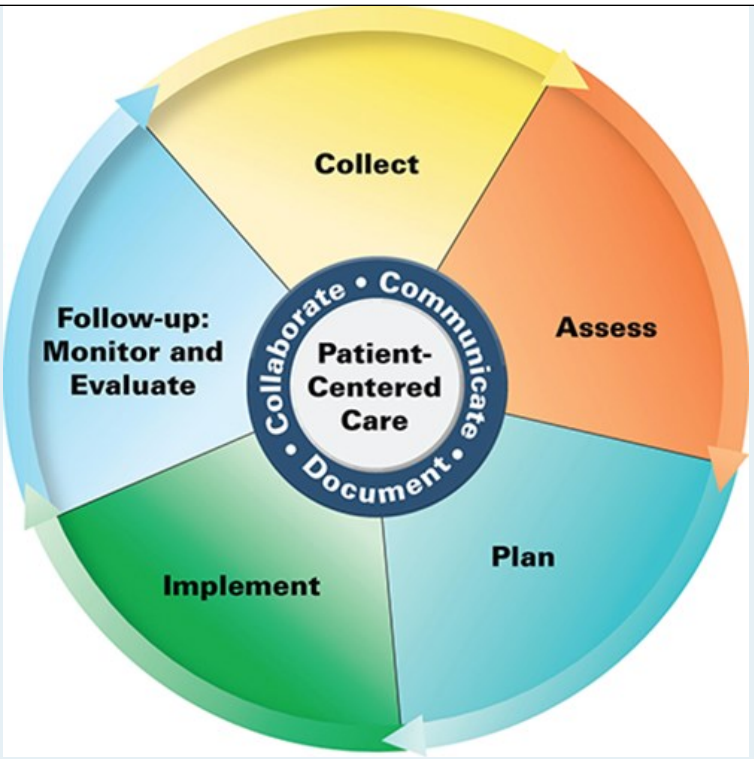
Case Question: An order is written for a 15-mg PE/kg fosphenytoin loading dose for a 60-kg patient. The dose is added to 50 mL of an appropriate fluid and is given at the maximum administration rate. There are questions about the rate settings for the infusion device (mL/min) and how long it will take to infuse the dose. Complete the following table.

Product information	Parenterally Administered Product							
	Phenytoin	Fosphenytoin	Valproate	Levetiracetam	Phenobarbital	Diazepam	Lorazepam	Midazolam
Refrigeration required yes/no								
Pharmaceutical Vehicle—Propylene glycol: yes/no								
pH of product								
Maximum infusion rate								
Compatible admixture solution(s)*								
IM administration, yes/no								
Cardiac monitoring required								
Reference range (mg/L)								

*Solution to be infused, not reconstituted

PATIENT CARE PROCESS

Patient Care Process for Status Epilepticus



Collect *(some items may be deferred to a later time due to time constraints associated with a medical emergency)*

- Patient characteristics (eg, age, weight, height)
- Time of seizure onset and duration of seizure activity (see Table 76-2)
- Past medical history (eg, known epilepsy and type or prior seizure, medication-allergies) (see Table 76-1)
- Social history (eg, ethanol use, unhealthy substance use, ketogenic diet)
- Complete a medication history of current prescription, over-the-counter (OTC) medications, herbals products, and dietary supplements, including any recently started or stopped medications (prescription or nonprescription)
- Information (eg, agent, route, dose, response) regarding antiseizure medications administered immediately prior to emergency department/hospitalization
- Objective data
  - Temperature, blood pressure, heart rate, respiratory rate, oxygen (O_2) saturation, arterial blood gases
  - Serum chemistries (eg, electrolytes, glucose, magnesium, renal/hepatic function studies); complete blood count (CBC) with differential and blood/urine cultures; urine toxicology screen; and serum antiseizure medication concentrations
  - Electroencephalogram (EEG), computed tomography (CT), magnetic resonance imaging (MRI) as needed

Assess

- If appropriate, assess medication adherence to antiseizure medications prior to admission and correct delivery of antiseizure medications during hospitalization
- Evaluate the appropriateness, effectiveness, and safety of all chronic or acute prescription and nonprescription medications. Check serum

medication concentration for an “effective” or “safe” concentration (see Table 76-4)

- Airway (arterial blood gases, respiratory rate [RR]) and cardiac (blood pressure [BP], heart rate [HR]) stability
- Temperature for the presence of fever
- Possible seizure etiologies (eg, known epilepsy, febrile, infectious, head trauma/cerebral vascular accident [CVA], substance-associated, low antiseizure medication serum concentrations) (see Table 76-3)
- Presence of seizure provoking factors (eg, ethanol, unhealthy substance use, adverse medication/herbal effect, medication interactions, low or elevated antiseizure medication serum concentration) (see Table 76-3)
- Duration of seizure activity and characteristics of the seizure (see Table 76-2)
- Available laboratory studies
- Need for adjusted dosing based on organ function (eg, liver, kidney function), serum albumin, weight

Plan*

- Management of nonepileptic causes for seizure (eg, opioid overdose, electrolytes imbalance) (see Table 76-3 and Fig. 76-1)
- Management of impending seizure activity (initial phase) including agent, dose, route, and method of administration, including the option for alternative agents and need for a second dose (see Table 76-2 and Fig. 76-1)
- Need for concurrent pharmacotherapy including thiamine and glucose, pyridoxine, antipyretic, and empiric antibiotics (see Fig. 76-1)
- First-line antiseizure medication regimens for the second phase (established stage), including agent, dose, method of administration, and frequency, including the option for a second dose if needed (see Tables 76-2 and 76-4 and Fig. 76-1)
- Anesthetic medications for the third phase (refractory GCSE stage) including agent, dosage, method of administration accompanied by a plan to titrate and withdraw therapy (see Tables 76-2 and 76-6 and Fig. 76-1)
- Monitor for effectiveness and safety of antiseizure medications including serum concentration and medication interactions during the management of GCSE (see Table 76-5)
- Pharmacotherapy in transfer to a nonintensive care unit setting or discharge home, including the transition to oral therapy and subsequent monitoring of serum antiseizure medication concentrations (see Table 76-4)
- Rescue therapies in the home environment, including need, agent, dose, method of administration, and plan should first dose fail. Need for cardiopulmonary resuscitation (CPR) training
- Patient and/or legal guardian medication education at discharge, including correct use of rescue therapies

Implement*

- Ensure all medications are ordered, that the dosage is appropriate, and discontinued as appropriate, during the patient’s transition from home to the emergency department (ED), ED to hospitalization, and home (see Tables 76-4 and 76-6)
- Ensure all medications are dispensed as prescribed (see Tables 76-4 and 76-6)
- Ensure all antiseizure medications are administered and monitored correctly (see Table 76-5)

Follow-up: Monitor and Evaluate

- Antiseizure medication effectiveness in stopping clinical and electrical seizure activity

- Presence of adverse medication reactions or medication interactions (see Table 76-5)
- Therapeutic medication monitoring performed as needed with subsequent interpretation

Collaborate with patient, caregivers, and other healthcare professionals.

INTRODUCTION

Status epilepticus (SE) is a common neurologic emergency associated with brain damage and death. The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) defines SE as a situation where there is a failure of the mechanisms responsible for seizure termination and prevention of prolonged seizures. There are two operational dimensions to this new definition. First, the length of the seizure and the time point beyond which the seizure is regarded as "continuous seizure activity"; usually 5 minutes. Second is the time of ongoing seizure activity, after which there is a risk of long-term consequences (30 minutes). Both time points are based on animal experiments and clinical research; hence, they should be considered current best estimates.[1] The traditional definition defines SE as (a) any seizure lasting longer than 30 minutes whether or not consciousness is impaired or (b) recurrent seizures without an intervening period of consciousness between seizures.[2] Clinically, this definition is limited, as the average seizure is less than 2 minutes in length and only 40% of seizures lasting 10 to 29 minutes cease without treatment.[3] Pharmacoresistance and mortality significantly increase with prolonged seizure duration. Therefore, aggressive treatment of seizures lasting 5 or more minutes is strongly recommended. It is important to note that SE can present in several forms (Table 76-1), including generalized convulsive status epilepticus (GCSE) and nonconvulsive status epilepticus (NCSE).

TABLE 76-1

International Classification of Status Epilepticus

Convulsive		Nonconvulsive	
International	**Traditional Terminology**	**International**	**Traditional Terminology**
Generalized SE • Tonic-Clonic[a,b] • Tonic[c] • Clonic[c] • Myoclonic[b] • *Erratic*[d]	Grand mal, epilepticus convulsivus	Absence[c]	Petit mal, spike-and-wave stupor, spike-and-slow-wave or 3/s spike-and-wave, epileptic fugue, epilepsiaminora continua, epileptic twilight, minor SE
Secondary generalized SE[a,b] • Tonic • Partial seizures with secondary generalization		• Partial SE[a,b] • Simple partial • Somatomotor • Dysphasic • Other types • Complex partial	• Focal motor, focal sensory, epilepsiapartialis continua, adversive SE • Elementary • Temporal lobe, psychomotor, epileptic fugue state, prolonged epileptic stupor, prolonged epileptic confusional state, continuous epileptic twilight state

SE, status epilepticus.

[a]Most common in older children.

[b]Most common in adolescents and adults.

[c]Most common in infants and young children.

[d]Most common in neonates.

Nonconvulsive status epilepticus accounts for up to 20% of all SE cases. It has variable and subtle clinical symptoms, such as cognitive impairment, automatisms, and/or behavioral changes, which make diagnosis challenging.[4] Electroencephalogram (EEG) is an important diagnostic and management tool. A benzodiazepine is the medication of choice for initial treatment, and intravenous (IV) phenytoin, valproic acid, or levetiracetam may be used as second-line.[4] In refractory cases, non-anesthetic antiseizure medication (ASMs), such as lacosamide and topiramate, are typically preferable to IV anesthetic medications, such as midazolam, propofol, and barbiturates.[4]

3 GCSE is the most common and severe form of SE. It is characterized by repeated primary or secondary generalized seizures involving both hemispheres of the brain which result in a loss of consciousness, and a persistent postictal state. GCSE can be divided into four phases: (1) stabilization, (2) initial therapy, (3) secondary therapy, and (4) third therapy (Table 76-2).[5]

TABLE 76-2

Generalized Convulsive Status Epilepticus

Phase	Time	Stage	Definition
Stabilization phase	0-5 minutes		An acute condition characterized by convulsive seizures. This may include pre-hospitalization or emergency room care
Initial-therapy phase	0-20 minutes	Impending GCSE	
Second-therapy phase	20-40 minutes	Established GCSE	An acute condition characterized by continuous seizures for at least 20 minutes, or by 20 minutes of intermittent seizures without full recovery of consciousness between events
Third-therapy phase	40-60 minutes	Refractory GCSE	An acute condition characterized by continuous seizures despite initial treatment with two ASMs
	>24 hours	Super-refractory	An acute condition characterized by seizures that continue 24 hours or longer after the administration of anesthesia, including cases in which SE recurs on reduction or withdrawal of anesthesia

ASM, antiseizure medication; GCSE, generalized convulsive status epilepticus; SE, status epilepticus.

EPIDEMIOLOGY

The worldwide incidence of GCSE varies considerably and has ranged from 5.1 to 41 per 100,000, with the incidence being highest in developing countries.[6] GCSE does not have a predilection for gender,[6] and occurs more frequently in nonwhites across all ages.[7] The incidence is highest in those less than 2 years of age[8] and older than 60 years of age.[6] Economic income may contribute to a difference in overall incidence.[6] Most GCSE occurs in individuals with no history of epilepsy; however, approximately 5% of adults and 10% to 25% of children with epilepsy will develop GCSE.

ETIOLOGY

Precipitating events for GCSE vary and generally reflect different populations and referral patterns. Most episodes in individuals with epilepsy occur because of acute antiseizure medication withdrawal, a metabolic disorder or concurrent illness, or a preexisting neurologic disease progression. Common etiologies and mortality rates are shown in Table 76-3.[7,9] Precipitating events are divided into those with or without neurologic structural lesions or those with a precipitating injury or insult. Cases with structural lesions or those with a specific neurologic insult are associated with a poor prognosis.

TABLE 76-3

Etiology and Mortality for Pediatric and Adult Cases of Status Epilepticus

Etiology	Mortality Number of Cases (%)	Mortality Number of Cases (%)
	n = 200 Cases of Pediatric SE	*n* = 512 Cases of Adult SE
Type I (No Structural Lesion)		
Infection	55 (5)	6 (35)
CNS infection	11 (0)	2 (20)
Metabolic	20 (5)	12 (36)
Low ASM levels	16 (0)	24 (7)
Alcohol	0 (0)	13 (8)
Idiopathic	6 (0)	13 (18)
Type II (Structural Lesion)		
Anoxia/hypoxia	27 (13)	14 (65)
CNS tumor	3 (50)	5 (22)
CVA	5 (0)	26 (27)
Substance overdose	5 (0)	3 (23)
Hemorrhage	5 (11)	4 (35)
Trauma	13 (0)	3 (23)
Remote causes[a]	33 (5)	7 (13)

ASM, antiseizure medication; CVA, cerebrovascular accident; SE, status epilepticus.

Percentages do not add up to 100% because some patients have multiple etiologies.

[a]More than half of the remote causes were congenital malformations and CVA in pediatric and adult patients, respectively.

Data from References 7 and 9.

There are significant differences in pediatric and adult etiologies (see Table 76-3). During their first few weeks of life, infants born to mothers with substance uses can develop medication withdrawal seizures. Other neonates can develop GCSE due to a pyridoxine deficiency, which should resolve after IV pyridoxine (100 mg). In young children, the cause is often a nonspecific illness such as fever and/or a viral illness; however, in those less than one, acute encephalopathy and metabolic disorders are major causes of GCSE. In adults, the most frequent precipitating events are cerebrovascular disease, rapid antiseizure medication withdrawal, and low antiseizure medication serum concentrations. Cerebrovascular disease is the leading cause in those who have their first seizures after age 60. Prescription, OTC, herbal, and unhealthy substance use should be considered in anyone with new-

onset GCSE.

PATHOPHYSIOLOGY

Seizures occur when excitatory neurotransmission overcomes inhibitory impulses in one or more brain regions. After a single, brief, generalized tonic-clonic seizure (less than 5 minutes), the seizure threshold is significantly elevated. And the brain's inhibitory mechanisms restore the balance of normal neurotransmission and prevent runaway excitation. In GCSE, the mechanisms that control normal brain homeostasis fail, which results in seizures occurring in close succession. In a different scenario, the magnitude of the proconvulsant stimulus is severe, and the compensatory mechanisms can be overwhelmed. In both instances, the mechanisms behind these failures are unknown, and the seizures become self-sustaining.

4 Cellurarly, it appears that an imbalance between excitatory (eg, glutamate, calcium, sodium, substance P, and neurokinin B) and inhibitory neurotransmission (eg, γ-aminobutyric acid [GABA], adenosine, potassium, neuropeptide Y, opioid peptides, and galanin) results in a seizure.[10] More specifically, $GABA_A$-mediated inhibition becomes less effective, while at the same time, glutamate's excitatory actions become enhanced. Thus, these mechanisms influence how GCSE progresses to refractory disease and impacts decisions related to sequencing antiseizure medications.

Most research has focused on gated ion channels; however, GCSE is largely caused by glutamate acting on postsynaptic *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA)/kainate receptors.[10] During GCSE, NMDA subunits are recruited to the synaptic membrane, where they form additional proconvulsant receptors. Glutamate's activation of NMDA and AMPA receptors causes gated calcium and sodium channels to open, leading to neuronal depolarization.[11] Sustained depolarization may maintain GCSE and eventually cause neuronal death through calcium-, free radical–, and kinase-mediated events.[12] Although medications acting as NMDA and AMPA receptor antagonists seem attractive, glutamate is likely not the sole mechanism for sustaining GCSE, and these other mechanisms become increasingly crucial as seizure duration increases.

5 Within minutes of repetitive seizures, receptor trafficking occurs (eg, metabotropic GABA and glutamate receptors), as the $GABA_A$ postsynaptic receptors control chloride channels to produce hyperpolarization (inhibition) of the postsynaptic cell membrane.[11] These receptors have binding sites for GABA and select antiseizure medications (eg, phenobarbital and benzodiazepines) enhance $GABA_A$-mediated chloride inhibitory currents. It was previously thought that decreased presynaptic GABA led to prolonged seizures; however, it is currently held that GABA concentrations increase during the early phases of GCSE and continue to be elevated during late GCSE. During prolonged seizures, postsynaptic $GABA_A$ receptors experience endocytosis as the receptors move from the synaptic membrane into the cytoplasm. This results in a decrease in the number of γ_2 and β_{2-3} subunits that are functionally active, decreasing response to both endogenous GABA and GABA agonists.[10] The γ_2 subunit is associated with benzodiazepine effectiveness; hence, a loss of these on the synaptic surface would result in time-dependent pharmacoresistance to a benzodiazepine. Clinically, benzodiazepine relative potencies can be reduced up to 20-fold if seizures persist for more than 30 minutes.[11] For this reason, a benzodiazepine should always be combined with another medication that acts differently. A similar phenomenon occurs with sodium channel antagonists (phenytoin); however, the magnitude of resistance is less.

As GCSE persists, complex pathophysiologic and biochemical changes lead to systemic alterations, progression of motor phenomena, and development of specific EEG findings.[12] Although these systemic complications affect the prognosis of GCSE, a prolonged seizure can destroy neurons independent of these events.[11] In fact, the systemic effects of induced seizures in animals can be blocked, but the damage to the neocortex, cerebellum, and hippocampus persists. Two distinct and predictable phases have been identified. Phase I occurs during the first 30 minutes of seizure activity, and phase II immediately follows.[12]

During phase I, each seizure markedly increases plasma epinephrine, norepinephrine, and steroid concentrations, resulting in hypertension, tachycardia, and cardiac arrhythmias. Within minutes, arterial systolic pressures can rise to above 200 mm Hg, and heart rate can increase by 83 beats per minute.[12] Mean arterial pressure does not fall below 60 mm Hg (8.0 kPa); hence, cerebral perfusion pressure is not compromised. In animals, cerebral blood flow is also increased, thereby protecting neurons from hypoxic injury.

In the presence of a hypoxic myocardium, seizure-induced increases in sympathetic and parasympathetic stimulation of the heart can result in ventricular arrhythmias.[12] Autonomic neuron stimulation can cause a release of insulin and glucagon. Concurrently, circulating catecholamines cause

an elevation of hepatic cyclic adenosine monophosphate, producing glycogenolysis. Although the patient can be hyperglycemic initially, serum glucose begins to fall.[12]

Seizure-induced muscular contractions and hypoxia cause lactic acid release, producing severe acidosis accompanied by hypotension and shock. Muscle contractions can contribute to severe rhabdomyolysis with secondary hyperkalemia and acute tubular necrosis. The airway can be obstructed, causing cyanosis or hypoxia. Additionally, an increase in salivation and tracheal and pulmonary secretions can cause aspiration pneumonia. Although transient pleocytosis can develop, it should not be attributed to SE until infectious causes have been eliminated. Between seizures, the EEG slows, and blood pressure normalizes, and although metabolic demands increase, the brain can compensate adequately.

When seizures exceed 30 minutes (phase II), the EEG ictal discharge and clonic motor activity become continuous, and the patient begins to decompensate.[12] Despite elevated levels of catecholamines, the patient can become hypotensive. During this time, cerebral blood flow autoregulation becomes dependent on mean arterial pressure and begins to fail. Excessive oxygen and glucose consumption continues; however, compensatory mechanisms are no longer able to meet demands.

During phase II, the serum glucose concentration may be normal or decreased. Profound hypoglycemia, secondary to hyperinsulinemia, can occur in those with hepatic dysfunction or reduced glycogen stores.[12] Hyperthermia and respiratory deterioration with hypoxia and ventilatory failure can develop, and there may be increased sweating and salivation. Metabolic and biochemical complications, including respiratory and metabolic acidosis, hyperkalemia, hyponatremia, and azotemia, may develop.

Morbidity and Mortality

Generalized convulsive status epilepticus is harmful to the brain. While most contend that the GCSE is responsible for the damage, it is unknown if the morbidity results from the underlying etiology or the GCSE. Regardless of the inducing stimulus, neuronal damage in animal models is evident following 30 to 60 minutes of GCSE, and most progress to develop epilepsy following a prolonged seizure. Interestingly, inhibiting the seizure-induced neuronal damage does not prevent the development of epilepsy, suggesting the seizures themselves may be harmful. It is hard to establish a relationship between GCSE and long-term outcomes because it is difficult to weigh the effects of seizure type, etiology, duration, concurrent physiologic events, and therapy or lack thereof. It has been shown that patients with a history of prolonged febrile seizures who later developed epilepsy share similar histopathologic changes (ie, hippocampal sclerosis) to those found in animal models of GCSE. In these cases, the period between the initial GCSE and the first epileptic seizure may be months to decades, suggesting a possible link between GCSE and the development of epilepsy. Importantly, studies of GCSE show that currently available antiseizure medications do not reproducibly prevent the development of epilepsy following prolonged seizures (ie, they are antiseizure medications and not antiepileptogenic).[13]

Patients who develop epilepsy following prolonged GCSE are less likely to experience remission of their seizures and may have decreased cognitive and memory function, mental impairment, or neurologic deficits when compared to those who develop epilepsy and subsequently have GCSE. Most studies have found that younger children, older patients, and those with preexisting epilepsy have a higher propensity for sequelae. Unless accompanied by an underlying neurologic abnormality, febrile SE is less likely to be associated with sequelae.

The overall worldwide case fatality rate of GCSE is 14.9%,[6] with the highest rate in those >60 years of age (24.9%), and in those with refractory GCSE (33.3%). Estimated mortality in the United States following GCSE ranges between 22,000 and 42,000 individuals per year, with rates lowest in children. The duration of seizure also impacts mortality. A 22% 1-year mortality rate has been seen for patients with refractory GCSE compared to 36% for those with super-refractory GCSE.[14] When compared with other populations, neonates have higher mortality and more neurologic sequelae.

Table 76-3 summarizes the etiology and corresponding GCSE mortality rates.[7,9] Interestingly, the mortality associated with many etiologies is significantly greater in adults than in children. Unresponsive patients may die from GCSE, but more frequently, they die from the acute illnesses that precipitated the GCSE. For example, patients with serious CNS structural changes (eg, hemorrhage and stroke) have a poorer prognosis than those with no structural lesion.

The outcome is affected by the time between the onset of GCSE and the initiation of treatment. Additionally, mortality significantly increases with increased seizure duration (eg, 2.6% for seizures 10-29 minutes, 19% for seizures lasting greater than 30 minutes, and 32% for seizures lasting greater than 60 minutes).[3,9] While mortality has decreased over the past decade, this probably reflects recognition of the need to initiate sequenced therapy

using large doses of antiseizure medication as soon as possible.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Status Epilepticus

Symptoms

- Impaired consciousness (eg, lethargy to coma)
- Disorientation once GCSE is controlled
- Pain associated with injuries (eg, tongue lacerations, shoulder dislocations, back pain, myalgias, headache, and head trauma)

Early Signs

- Generalized convulsions
- Acute injuries or CNS insults that cause extensor or flexor posturing
- Hypothermia or fever suggestive of intercurrent illnesses (eg, sepsis or meningitis)
- Incontinence
- Normal blood pressure or hypotension and respiratory compromise

Late Signs

- Clinical seizures may or may not be apparent
- Pulmonary edema with respiratory failure
- Cardiac failure (dysrhythmias, arrest, and cardiogenic shock)
- Hypotension or hypertension
- Disseminated intravascular coagulation, multisystem organ failure
- Rhabdomyolysis
- Hyperpyrexia

Initial Laboratory Tests

- Complete blood count (CBC) with differential
- Serum chemistry profile (eg, electrolytes, calcium, magnesium, glucose, serum creatinine, alanine aminotransferase [ALT], and aspartate aminotransferase [AST])
- Urine toxicology/alcohol screen
- Blood cultures
- Arterial blood gas to assess for metabolic and respiratory acidosis, oxygenation
- Serum medication concentration if previous antiseizure medication(s) are suspected or known

Other Diagnostic Tests

- Spinal tap if CNS infection suspected
- EEG should be obtained on presentation and once clinical seizures are controlled
- CT with and without contrast
- MRI
- Radiograph if indicated to diagnose fractures

Accurate diagnosis requires observation, physical examination, laboratory assessment, EEG, and neurologic imaging. The nature and duration of the seizure should be obtained, but a diagnosis of GCSE should not be made until a seizure is observed by a clinician. Most patients have an altered consciousness, ranging from obtundation to marked lethargy and somnolence with pronounced eyes-open unresponsiveness and waxy rigidity. Motor features can include muscle contractions, extensor or flexor posturing, and spasms. Over time, the clinical manifestations become less apparent. This has significant ramifications as seizures appear to terminate without treatment or with ineffective therapy.

In addition to assessing language and cognitive abilities, the physical and neurological examinations should assess motor, sensory, and reflex abnormalities, pupillary response, asymmetry, and posturing. The patient should also be examined for secondary injuries (eg, tongue lacerations, shoulder dislocations, and head and facial trauma).

Laboratory tests are essential to the diagnosis of various etiologies. Hypoglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypocalcemia, and renal failure all can cause seizures. A urine toxicology screen can help eliminate unhealthy substance use or overdose. Serum medication concentration(s) should be obtained for chronic antiseizure medications, as low concentrations can reflect partial adherence or rapid medication withdrawal. Although a baseline serum antiseizure medication concentration helps determine if a specific antiseizure medication loading dose is required, the time needed to perform the test makes this impractical. Assessment of other laboratory parameters that affect antiseizure medication dosing also can be helpful (eg, hematology and chemistries to include albumin, renal function, and hepatic function). An EEG is a valuable diagnostic tool, particularly in prolonged GCSE in whom clinically apparent seizures are not always evident. The initiation of antiseizure medication therapy should not be delayed while awaiting testing or results.

Once seizures have stopped, it is essential to determine if the patient is febrile or has a systemic or CNS infection. Many physiologic consequences of GCSE (eg, leukocytosis, pleocytosis, and hyperthermia) produce symptoms that can be confused with other conditions. If a CNS infection is suspected, a lumbar puncture should be performed, and empiric antibiotics started. If vascular, neoplastic, or infectious etiologies are suspected, computed tomography (CT) or magnetic resonance imaging (MRI) should be obtained once the seizures are controlled.

TREATMENT

Various treatments are available for the management of GCSE. These range from rescue medications to abort the impending SE, to the use of pharmacologic and nonpharmacologic therapies for GCSE and refractory/resistant SE. The field has recently begun to shift terminology away from the disease focused terms (eg, antiepileptic medication) to the more function focused terms (eg, antiseizure medication). This shift is being done since many of these medications have no impact on the underlying disease, but in fact suppress seizures.[60]

Desired Outcomes

6 The short-term desired outcomes include: (a) immediate termination of all clinical and electrical seizure activity, (b) no clinically significant adverse effects, and (c) lack of recurrent seizure activity. The long-term outcomes involve minimizing or avoiding pharmacoresistant epilepsy and/or the development of neurologic sequelae that significantly impact the quality of life.

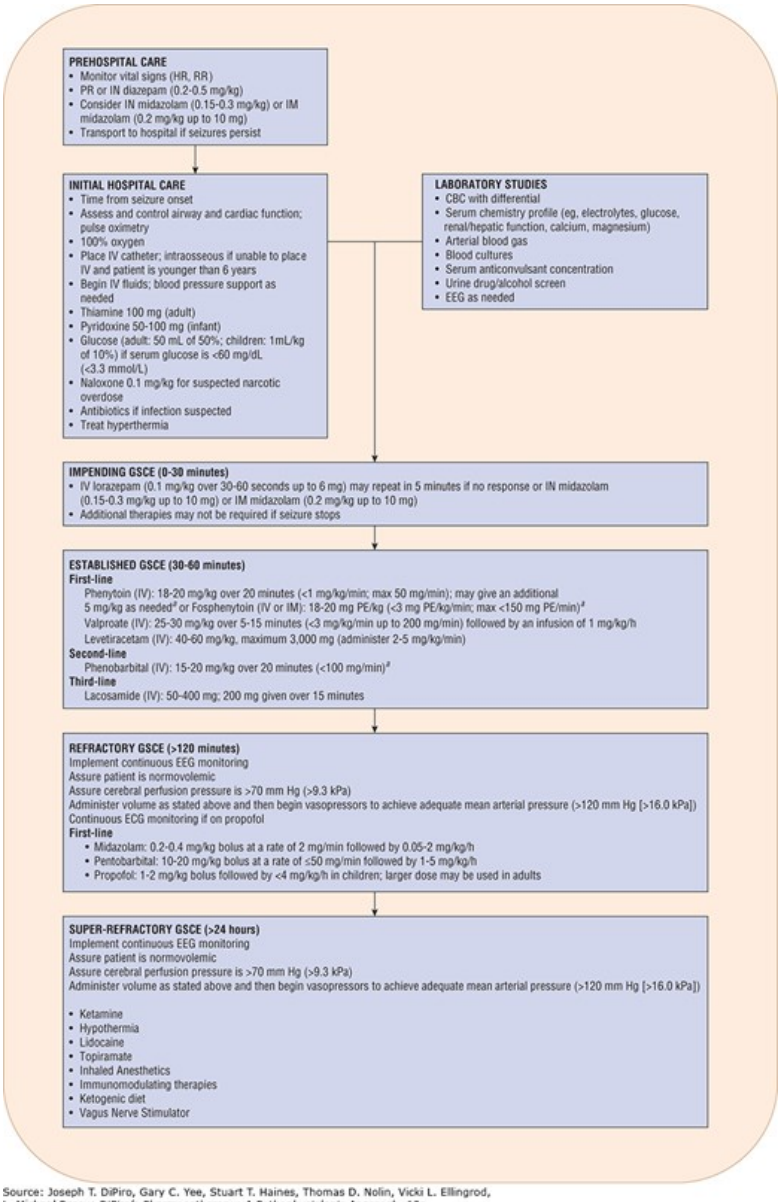
Nonpharmacologic Therapy

Stabilization Phase

Most of the treatment for GCSE consists of pharmacologic therapy in addition to supportive care. The time of seizure onset should be noted, and vital signs should be assessed. An adequate and protected airway should be established, ventilation should be maintained, and oxygen should be administered (Fig. 76-1). Intravenous access should be established, and hyperthermia, if present, should be aggressively treated (eg, rectal or IV acetaminophen and cooling blanket). Febrile GCSE is common in pediatrics, and normalization of body temperature helps minimize neurologic morbidity.

Figure 76-1

Algorithm for the treatment of GCSE. (BP, blood pressure; CBC, complete blood count; CI, continuous infusion; D12.5W, 12.5% Dextrose in water; D25W, 25% Dextrose in water; D50W, 50% Dextrose in water; EEG, electroencephalogram; GCSE, generalized convulsive status epilepticus; HR, heart rate; IN, intranasal; PE, phenytoin equivalents; PR, per rectum; RR, respiratory rate)



[a] Because variability exists in dosing, monitor serum concentration.

Laboratory studies including serum glucose and electrolyte levels (including calcium and magnesium), complete blood count, and renal and hepatic function tests should be performed. Antiseizure medication serum concentration should be obtained as needed, and a urine toxicology screen should be performed if there is a suspicion of ingestion.

Although hypoglycemia rarely causes GCSE, adults and children (ages 2 years and older) with a blood glucose less than 60 mg/dL (3.3 mmol/L) should receive 50 mL of a 50% dextrose solution and 1 mL/kg of a 25% dextrose solution, respectively.[2] Because Wernicke's encephalopathy can develop in patients with an alcohol use disorder, adults should receive IV thiamine (100 mg) before glucose administration. Serum glucose concentration should be determined to assess the need for further supplementation. Children younger than 12 to 18 months of age should receive pyridoxine (Vitamin B_6) until metabolic causes are ruled out.

If an infection is suspected, blood cultures, lumbar puncture, and a urinalysis may be needed. Antibiotic administration does not need to wait until after the lumbar puncture if the patient is medically unstable. Patients with persistent GCSE should also have frequent arterial blood gas determinations to assess for metabolic acidosis, which should be treated with sodium bicarbonate if the pH is less than 7.2. Assisted ventilation can correct respiratory acidosis.

Because electrical seizures may persist in the absence of overt clinical motor manifestations, an EEG should be performed in patients who continue to have altered consciousness after clinical control of their seizures. Patients with persistent GCSE should also have continuous EEG monitoring.

Ketogenic Diet

A small number of reports have shown that an orally or intravenously administered ketogenic diet in a 4:1 ratio of fat to combined protein and carbohydrate can be used in severe cases of super-refractory SE.[15,16] Before initiating this diet, metabolic disorders as a possible etiology should be eliminated. Close monitoring of total daily fluid, ketosis, and potential complications is essential. If metabolic acidosis develops, treatment to maintain serum bicarbonate levels greater than 18 to 20 mEq/L (mmol/L) is recommended.[15]

Vagus Nerve Stimulation

Acute placement of a vagus nerve stimulator has been used in both pediatric and adult patients with refractory SE. Its use for refractory SE is not recommended currently, as grade D evidence suggests improvement in generalized refractory SE.[17]

Pharmacologic Therapy

Initial-Therapy Phase (5-20 Minutes)

When a seizure does not stop within 5 minutes, or when doubt exists regarding the diagnosis, patients should be treated as if they have GCSE (see Fig. 76-1), and initial therapies used. The benzodiazepines are the most common class of antiseizure medications used for GCSE initial treatment. Only two[18,19] and three[18,20,21] Class 1 studies have evaluated the benzodiazepines in children and adults, respectively.

The benzodiazepines are considered effective initial therapy in most patients. Evidence-based guidelines recommend the initial use of IM midazolam, IV lorazepam, or IV diazepam (see Fig. 76-1) in adults and IV lorazepam or IV diazepam in children.[5] Intramuscular midazolam is preferred if IV access is not available; however, generally, one or two IV doses will terminate seizures within 2 to 3 minutes. All benzodiazepines are effective; therefore, preference is determined by pharmacokinetic differences, route of administration, pharmacoeconomics, adverse-effect profile, and current availability.

Diazepam is highly lipophilic with a large volume of distribution (1-2 L/kg). Although it distributes into the brain within seconds, it rapidly redistributes into fat, causing its CNS half-life to be less than 1 hour and its duration of effect to be less than 30 minutes. The rapid decrease in brain concentration, along with pharmacoresistance, can cause seizure recurrence; hence, a longer-acting antiseizure medication (eg, phenytoin, levetiracetam, or valproate) should be given immediately after diazepam. Table 76-4 outlines dosing.

TABLE 76-4

Dosing of Medications Used in the Initial and Established Treatment of GCSE

Medication (Route)	Brand Name	Initial Dose (Maximum	Maintenance Dose	Comments

		Dose)		
Diazepam (IV)	Valium plus generic			
Adult		0.25 mg/kg[a,b,c] (20 mg)	Not used	Given IV at a rate not to exceed 5 mg/min
Pediatric		0.25-0.5 mg/kg[a,c] (20 mg)	Not used	
Fosphenytoin (IV)	Cerebyx plus generic			
Adult		20-25 mg PE/kg	4-5 mg PE/kg/day	Given IV at a rate not to exceed 150 mg PE/min in adults and 3 mg PE/kg/min in pediatric patients
Pediatric		20-25 mg PE/kg	5-10 mg PE/kg/day	
Lacosamide (IV)	Vimpat			
Adult		200-400 mg	200-400 mg/day, given twice a day	Administer IV over 15 minutes
Pediatric		6-10 mg/kg (400 mg)	6-12 mg/kg/day, given twice a day	
Levetiracetam (IV)	Keppra plus generics			
Adult		2,000-3,000 mg	1,000 mg thrice a day	Given IV over 5-10 minutes
Pediatric		40-60 mg/kg (3,000 mg)	40-60 mg/kg/day, given twice or thrice a day	
Lorazepam (IV)	Ativan plus generic			
Adult		4 mg[b,c] (6 mg)	Not used	Given IV at a rate not to exceed 2 mg/min in adult and pediatric patients

Pediatric		0.1 mg/kg[a,c] (6 mg)	Not used	
Midazolam (IV, IM)	Versed plus generic			
Adult		200 mcg/kg[a,d] (10 mg)	50-500 mcg/kg/hr[e]	Given IV at a rate 0.5-1 mg/min in adults and over 2-3 minutes in pediatric patients
Pediatric		150 mcg/kg[a,d] (10 mg)	60-120 mcg/kg/hr[e]	
Phenobarbital (IV)	Generic			
Adult		10-20 mg/kg[e]	1-4 mg/kg/day[e]	Given IV at a rate not to exceed 100 mg/min in adults and 30 mg/min in pediatric patients
Pediatric		15-20 mg/kg[e]	3-5 mg/kg/day[e]	
Phenytoin (IV)	Dilantin plus generic			
Adult		20-25 mg/kg[f]	4-5 mg/kg/day[e]	Given IV at a rate not to exceed 50 mg/min[g] in adults and 3 mg/kg/min (max 50 mg/min) in pediatric patients
Pediatric		20-25 mg/kg[f]	5-10 mg/kg/day[e]	
Valproate (IV)	Depacon plus generic			
Adult		15-30 mg/kg (3,000 mg)	1-4 mg/kg/hr[e]	Administer at 3 mg/kg/min; and follow by a continuous or intermittent infusion; larger doses may be required in those on hepatic enzyme inducers, monitor serum concentrations
Pediatric		20-25 mg/kg (3,000 mg)	1-4 mg/kg/hr[e], or give every 4-6 hours	

GCSE, generalized convulsive status epilepticus; PE, phenytoin equivalents.

[a]Doses can be repeated every 10 to 15 minutes until the maximum dosage is given.

[b]Initial doses in the older patients are 2 to 5 mg.

[c]Larger doses can be required if patients chronically on a benzodiazepine (eg, clonazepam).

[d]Can be given by the intramuscular, rectal, or buccal routes.

[e]Titrate dose as needed.

[f]Administer additional loading dose based on serum concentration.

[g]The rate should not exceed 25 mg/min in older patients and those with known atherosclerotic cardiovascular disease.

Most practitioners consider IV lorazepam to be the benzodiazepine of choice for initial therapy of GCSE. A Cochrane Database Review concluded that it is as effective and safer than diazepam in children.[21] Another Cochrane Database Review that included pediatric and adult data noted no difference in death, requirements for ventilator support, or adverse effects between the two agents; however, when compared to diazepam, there was a significantly lower risk of persistent seizures with lorazepam.[22]

Lorazepam is less lipid soluble than diazepam and takes longer to achieve peak concentrations in the brain; however, its minimal redistribution into fat results in a longer CNS duration of action, providing seizure protection for up to 24 hours. It also has a higher-affinity binding to the benzodiazepine receptor compared to diazepam.

Patients chronically on a benzodiazepine (eg, clobazam and clonazepam) might develop tolerance and require large doses. Diazepam and lorazepam contain propylene glycol, which can cause dysrhythmia and hypotension if administered too rapidly (Table 76-5). They also cause vein irritation; therefore, the parenteral product should be diluted with an equal volume of compatible diluent before administration. Because of slow and erratic absorption, standard parenteral formulations should not be given IM.

TABLE 76-5

Adverse Medication Reactions and Monitoring of Patients Receiving Medications for GCSE

Medication	Adverse Medication Reaction	Monitoring Parameters	Comments
Diazepam	Hypotension and cardiac arrhythmias	Vital signs and ECG during administration	Propylene glycol causes hypotension and cardiac arrhythmias when administered too rapidly; hypotension may occur with large doses
Fosphenytoin	Hypotension and cardiac arrhythmias; paresthesia, pruritus	Vital signs and ECG during administration	Hypotension is less than that noted with phenytoin, as this product does not contain propylene glycol; pruritus generally involves the face and groin areas, is dose and rate related, and subsides 5-10 minutes after infusion
Lacosamide	Prolonged PR interval	ECG	
Levetiracetam	Somnolence, behavioral abnormalities	Mental status	
Lidocaine	Fasciculations, visual		Occur at serum concentrations between 6 and 8 mg/L (26-34 µmol/L); seizures >8 mg/L (34 µmol/L)

	disturbances, tinnitus, seizures		
Lorazepam	Apnea, hypotension, bradycardia, cardiac arrest, respiratory depression, metabolic acidosis, and renal toxicity	Vital signs and ECG during administration; HCO_3 and serum creatinine; cumulative dose of propylene glycol	Accumulation of propylene glycol during prolong continuous infusions may cause acidosis
Midazolam	Apnea, hypotension, sedation	Vital signs and ECG	
Pentobarbital	Hypotension	Vital signs and ECG during administration	Rate of infusion should be slower or dopamine should be added if hypotension occurs
Phenytoin	Hypotension and cardiac arrhythmia; nystagmus	Vital signs and ECG during administration	Propylene glycol causes hypotension and cardiac arrhythmias when administered too rapidly. Large loading doses are generally not given to older individuals with preexisting cardiac disease or in critically ill patients with marginal blood pressure. The infusion rate should be slowed if the QT interval widens or if hypotension or arrhythmias develop; horizontal nystagmus suggests serum concentration above the reference range and toxicity; if a serum phenytoin concentration validates this, the dose should be decreased
Phenobarbital	Hypotension, respiratory, and CNS depression	Vital signs and mental status; EEG if used in anesthesia doses	Contains propylene glycol; if hypotension occurs, slow the rate of administration or begin dopamine; apnea and hypopnea can be more profound in patients treated initially with benzodiazepines
Propofol	Progressive metabolic acidosis, hemodynamic instability, and bradyarrhythmias	Vital signs, ECG, osmolar gap; EEG if used in anesthesia doses	Referred to as propofol-related infusion syndrome, which can be fatal
Topiramate	Metabolic acidosis	Acid-base status (serum bicarbonate)	Extremely rare

CNS, central nervous system; ECG, electrocardiogram; EEG, electroencephalogram.

Unfortunately, there is insufficient data comparing IV lorazepam to IV midazolam in GCSE. Midazolam has an extremely short half-life, and maintenance doses must be given by continuous infusion (see Table 76-4). Because of its increased solubility, midazolam has a more reliable IM absorption than either diazepam or lorazepam. A Class 1 study showed that IM midazolam, as first-line treatment given by medical personnel in the

prehospital setting, was superior to IV lorazepam for cessation of seizures. This practice reduced intensive care unit (ICU) admission and subsequent hospitalization, with no differences in recurrent seizures or adverse effects.[18]

Intranasal (IN) midazolam and per rectum (PR) diazepam are increasingly used in out-of-hospital management and emergency department settings. However, evidenced-based guidelines indicate they and buccal midazolam are just probably effective.[5] Recent studies have focused on aborting impending SE via transmucosal benzodiazepine delivery (eg, PR, IN, and buccal) when IV and/or IM administration may be difficult or impossible (eg, home setting, extended care, and paramedic). Rectal absorption of diazepam is rapid but varies significantly (50%-100%) due to first-pass metabolism and can be challenging to administer at home. Buccal and sublingual routes bypass gastric and hepatic first-pass metabolism, but bioavailability can be incomplete as the medication is often swallowed. Buccal administration is easily accomplished, and the volume of fluid is small enough (eg, 2-5 mL) that aspiration is unlikely. While successful sublingual administration is unlikely due to muscular contractions of the jaw and clenching of teeth, non-IV midazolam is as effective as PR diazepam for termination of early SE in children.[23]

Intranasally administered midazolam readily crosses the nasal mucosa and the blood-brain barrier to produce a rapid rise in both serum and cerebrospinal fluid concentrations.[2] In fact, serum concentrations are comparable to those noted following IV injection. When compared to PR diazepam, all studies have concluded that IN midazolam results in higher serum concentrations, faster onset of action, more effective seizure control, and fewer adverse effects.[24] A commercially available, FDA-approved product for IN administration of midazolam became available in 2019, and a diazepam nasal spray product was approved in early 2020.[25-27]

Benzodiazepines are the first-line treatment for seizure emergencies; however, they are frequently underdosed, particularly in the out of hospital setting. A study including 1,170 benzodiazepine doses found that only 14.3% of midazolam and 23.9% of lorazepam doses met guideline recommendations.[28] Now that several benzodiazepine options are available for out-of-hospital treatment of seizure emergencies, it is critical to ensure that adequate doses are being prescribed and administered.

Guidelines also recommend IV phenobarbital as an alternative first-line agent in adults.[5] It is an effective and well-tolerated initial therapy in adults if benzodiazepines are not an option. Although evidence-based studies establish IV phenobarbital use, its slower administration rate than benzodiazepines relegates it to alternative initial therapy. Phenobarbital has biphasic distribution into body organs, and during phase I, it distributes into highly vascular organs but not the brain. Except for fat, phenobarbital distributes throughout the body during phase II; hence, lean body mass should be used in calculating doses in obese patients. Although the highest brain concentrations occur 12 to 60 minutes after an IV dose, seizures are controlled within minutes of the loading dose.[20]

The loading and maintenance dose for phenobarbital are given in Table 76-4. When necessary, larger loading doses (30 mg/kg) have been used in neonates without adverse effects. Phenobarbital exhibits first-order linear pharmacokinetics, and there is no maximum dose beyond which further doses are likely to be ineffective. For this reason, if the initial loading dose does not stop the seizures within 20 to 30 minutes, an option would be to give an additional dose (10-20 mg/kg) or move to anesthetic agents.[29] Once GCSE is controlled, start the maintenance dose within 12 to 24 hours. Although injectable phenobarbital contains propylene glycol, it can be given more rapidly than phenytoin (see Table 76-4). While it can be safely administered IM, its rate of absorption is too slow to be effective.[2]

Although rare, brief cardiorespiratory depression can necessitate assisted ventilation or require intubation (see Table 76-5). This is especially true if a benzodiazepine is used concomitantly with a barbiturate. The rate of respiratory depression in patients with GCSE who received benzodiazepines is lower than that reported in a similar population treated with placebo.[5] Importantly, there was no difference in cardiorespiratory adverse events in adults who are given either a benzodiazepine or phenobarbital.[20] Hypotension secondary to a reduction in vasomotor tone can occur following large doses of either a benzodiazepine or barbiturate.[2]

Second-Therapy Phase: Established GSCE (20-40 Minutes)

8 9 Second-phase antiseizure medications (eg, hydantoin, valproate, phenobarbital, levetiracetam, or lacosamide) may not be needed if seizures stop after administering initial therapies. The choice of which long-acting, second-line agent to give is controversial as there is no evidence to base a preferred option. When given, an agent should be administered immediately after a benzodiazepine. Dosing can be found in Table 76-4.

A hydantoin is one of three second-line agents that can be used when GCSE is unresponsive to benzodiazepine treatment or continues to occur after successful benzodiazepine treatment.[5] However, data supports a higher rate of seizure cessation and fewer adverse events with levetiracetam versus phenytoin.[30] When used by itself, phenytoin is inferior to lorazepam, phenobarbital, or diazepam plus phenytoin at stopping GCSE within 20 minutes of infusion.[20,31] While the most recent guidelines advocate for a hydantoin,[5] which are frequently used in practice, questions remain regarding if a hydantoin should be administered alone, in larger doses, or at all when seizures recur following benzodiazepine administration.

Phenytoin has a long half-life (20-36 hours) and causes less respiratory depression and less sedation than benzodiazepines or phenobarbital. However, it cannot be delivered rapidly enough to be considered a first-line single agent.[2] Injectable phenytoin should be diluted to greater than or equal to 5 mg/mL in normal saline; otherwise, microcrystals will precipitate if it is mixed in a glucose-containing solution. The vehicle (40% propylene glycol) can cause administration-related hypotension and cardiac arrhythmias (see Table 76-5). For this reason, the maximum rate of infusion is limited (see Table 76-4).

Table 76-4 includes suggested IV loading doses. A loading dose reduction is recommended for older patients, and a larger loading dose is required in obese individuals. If the patient has been on phenytoin prior to admission and the serum concentration is known, consider using this information in determining a loading dose. Although some advocate administering an additional 5 mg/kg dose in those with unresponsive GCSE, there is no evidence supporting this practice. Importantly this can cause concentrations to exceed the reference range and produce toxicity. In addition, because phenytoin has poor lipid solubility and enters the brain slowly, it can take up to 60 minutes before the pharmacodynamic effect is apparent. This delay is significant when considering administration of a second loading dose, as therapeutic serum concentrations, 10 to 20 mg/L (40-79 µmol/L), generally do not persist more than 24 hours; hence, maintenance doses (see Table 76-4) should be started within 12 to 24 hours of the loading dose.

Phenytoin has an alkaline pH, which may cause pain and burning during infusion. Phlebitis can occur during chronic infusion and tissue necrosis is likely on infiltration. Intramuscular administration of phenytoin is not recommended because absorption is delayed, erratic, and can crystallize in tissue. Although oral loading doses have been used in patients not actively seizing, it may take 4 to 12 hours before adequate serum concentrations are obtained. Thus, this practice is not recommended.

Fosphenytoin is considered by many to be the hydantoin of choice[5] as it is a water-soluble phosphate ester that has no known pharmacologic activity, and after IV or IM dosing is converted rapidly (7-15 minutes) and completely (100%) to phenytoin by blood and tissue phosphatases. The conversion delay was a concern initially; however, this time is offset by high protein binding, saturable binding at high concentrations, and the rapid rate of infusion. Since it does not contain propylene glycol, it is compatible with most common IV fluids. It should be dosed using phenytoin equivalents (PE), thereby obviating the need for interconversion between phenytoin and fosphenytoin. The loading dose and rates of administration of fosphenytoin can be found in Table 76-4. Because of delays in achieving adequate phenytoin serum concentrations, a loading dose should not be given IM unless IV access is impossible.

Fosphenytoin serum concentrations have no value, and therefore, serum phenytoin concentrations should be used for therapeutic medication monitoring with the desired serum concentration range being the same as phenytoin. However, fosphenytoin cross-reacts with some phenytoin immunoassays causing an overestimation of phenytoin concentration; hence, levels should not be obtained for at least 2 hours after IV, and 4 hours after IM administration.

Alternatively, the current guidelines also recommend a single dose of IV valproate or IV levetiracetam as acceptable first-line agents, if a benzodiazepine fails to control seizures after 20 minutes, or if seizures recur following a benzodiazepine and/or a hydantoin use.[5] Intravenous valproate and continuous infusion diazepam are comparable in GCSE.[32,33] One meta-analysis noted that valproate controlled refractory SE sooner than diazepam. However, there was no difference within 30 minutes of administration.[34] There was also no difference in control of GCSE between valproate and phenytoin.[27] A second meta-analysis noted that there is sufficient evidence to use valproate as first-line therapy in those with SE refractory to benzodiazepines.[35] Three randomized controlled trials have investigated the efficacy of levetiracetam[36-38] or valproate[36] versus fosphenytoin or phenytoin. One of these found that levetiracetam was not superior to phenytoin,[38] one concluded levetiracetam may be a reasonable alternative to phenytoin,[37] and one found that levetiracetam, fosphenytoin, and valproate all had similar safety and efficacy as a second-line GCSE agents.[36]

Several loading and continuous-infusion doses for valproate (see Table 76-4) have been used in adult and pediatric patients. Current guidelines

recommend 40 mg/kg up to 3,000 mg as a single dose.[5] Although the manufacturer originally recommended IV valproate be given no faster than 20 mg/min, much faster rates have been studied (40 mg/min; 2-10 mg/kg/min) and are used for load dose administration. One study suggested the need to consider the effects of enzyme-inducing antiseizure medications when dosing and recommended that the continuous-infusion rate be determined by the presence of concurrent antiseizure medications (no inducers present, 1 mg/kg/hr; one or more inducers [eg, phenytoin and phenobarbital], 2 mg/kg/hr; and inducers and pentobarbital coma, 4 mg/kg/hr).[39] In general, IV valproate is well tolerated with no respiratory depression. Hemodynamic instability is extremely rare; however, vital signs should be monitored closely during the loading dose for hypotension.

Evidence for the use of IV levetiracetam is limited; however, evidence exists to support it as first-line therapy in those refractory to benzodiazepines.[40] Historically, it was used in cases of super-refractory SE, but it is being used earlier due to medication shortages that have made traditional medications unavailable. It is as effective as IV lorazepam in aborting seizures and preventing recurrence,[41-43] and compared to phenytoin is equally effective at terminating seizures and preventing recurrence at 24 hours.[43] Levetiracetam is not hepatically metabolized and is minimally protein bound, making medication interactions unlikely. Doses for IV levetiracetam are noted in Table 76-4 and are infused over about 5 minutes. Although guidelines recommend a maximum single dose of 4,500 mg,[5] most clinicians use 3,000 mg/day.

Despite being recommended as an alternative first-line agent for initial therapy, recent guidelines recommend phenobarbital as an alternative agent when a hydantoin, valproic acid, or levetiracetam is not available or has failed. Before moving to third-therapy phase, all agents noted in phase II should be administered as single doses, and not multiple mini-boluses, given at maximally tolerated doses.

Third-Therapy Phase: Refractory GCSE (40-60 Minutes)

10 When adequate doses of a benzodiazepine and a single dose of a second antiseizure medication (hydantoin, valproate, levetiracetam and/or barbiturate) fail, the condition is termed *refractory*.[5] After initial control, seizures can recur in 6% to 19% of patients. Approximately 10% to 15% of patients will develop refractory GCSE, and about 30% whose seizures are “clinically” controlled will have persistent electrical manifestations after antiseizure medication administration. When a patient develops refractory GCSE, an intense search should be performed for an acute or progressive cause.

While the goal is to stop electrical epileptiform activity, there is no consensus regarding the agent of choice, sequencing of therapy, or treatment of refractory GCSE.[44] Historically, one would recommend a repeat dose of a second-therapy phase; however, practitioners are increasingly using an anesthetic agent and not another traditional antiseizure medication due to the low probability that an additional traditional antiseizure medication will interrupt the established GCSE. There is a clear consensus that if a repeat dose of a traditional antiseizure medication fails, anesthetizing the patient to suppress cerebral ictal discharges should occur.[5] An anesthetic dose of midazolam, pentobarbital, or propofol may be indicated. Doses for these agents can be found in Table 76-5. Although it is likely that the patient is already being mechanically ventilated, intubation and respiratory support are mandatory during the use of anesthetic agents, along with continuous EEG monitoring.

While HLA-B*1502 has been associated with severe skin reactions in patients receiving phenytoin, this is applicable to chronic and not acute, single dose therapy. Recently, CYP2C variants that included CYP2C9*3, which reduce medication clearance, were identified as important genetic factors associated with phenytoin-related severe cutaneous adverse reactions.[45] Medication resistance factors have also been identified in surgically removed human epileptogenic tissue, as multimedication resistance proteins (P-glycoprotein) are localized to endothelial cells in brain capillaries and associated astroglia. Since multimedication resistance factors are localized to abnormal tissues, they appear to have little or no effect on systemic pharmacokinetic parameters of a medication. Still, they may affect local medication distribution within the target epileptogenic areas. If a role in refractory human epilepsy is confirmed, medication s that inhibit P-glycoprotein (eg, verapamil) may prove useful. However, the role of multimedication -resistant proteins in the treatment of seizure emergencies is not clear.

Benzodiazepines

During prolonged seizures, the number of γ_2 and $\beta_{2\text{-}3}$ subunits on the $GABA_A$ receptors decrease as the receptors move from the synaptic membrane into the cytoplasm. This move makes them functionally inactive, which may decrease the effectiveness of both endogenous GABA and GABA agonists resulting in time-dependent pharmacoresistance. Following GCSE that persists for more than 30 minutes, the relative potencies of benzodiazepines can be reduced up to 20-fold. For this reason, some believe that anesthetic doses of midazolam should be the first-line agent in refractory GCSE. If a

benzodiazepine is used, it should always be combined with another medication that acts at a different site. Table 76-6 shows the loading and maintenance doses of midazolam.[32] Most patients respond to these doses within an hour. Although studies used seizure termination on EEG as the endpoint for success, EEG burst suppression is rarely achieved with the recommended doses of midazolam. Tachyphylaxis rapidly develops within 24 to 48 hours; hence, the dose is often increased to prevent seizure relapse.[2]

TABLE 76-6

Dosing of Medications Used to Treat Refractory or Super-Refractory GCSE

Medication (Brand Name)	Initial Dose (Maximum Dose)	Maintenance Dose	Comments
Ketamine (generics)			
Adult	1-4 mg	1-5 mg/kg/hr	
Pediatric	0.5-2 mg/kg	1-10 mg/kg/hr	
Lacosamide (Vimpat)			
Adult	200-400 mg	200 mg bid	Administer IV over 15 minutes, monitor serum concentrations
Pediatric	6-10 mg/kg (400 mg)	6-12 mg/kg/day, given twice a day	
Lidocaine (generics)			
Adult	50-100 mg	1.5-3.5 mg/kg/hr	Administer IV in ≤2 minutes
Pediatric	1 mg/kg (maximum 3-5 mg/kg in the first hour)	1.2-3 mg/kg/hr	
Midazolam (Versed plus generic)			
Adult	200 mcg/kg[a]	50-500 mcg/kg/hr[b]	Initial dose may be given IM; administer IV over 0.5-1 mg/min; continuous-infusion rate should be increased every 15 minutes in those who do not respond and should be guided by EEG response; development of tachyphylaxis can require frequent increases in dose; decrease dose by 1 mcg/kg/min every 2 hours once GCSE is controlled

Pediatric	150 mcg/kg[a]	60-120 mcg/kg/hr[b]	
Pentobarbital (generics)			
Adult	10-20 mg/kg	1-5 mg/kg/hr[b]	Over 1-2 hours, the rate of infusion should be slowed or dopamine should be added if hypotension occurs; gradually titrate dose upward until there is evidence of burst suppression on EEG (ie, isoelectric EEG) or prohibitive adverse effects occur. Twelve hours after a burst suppression is obtained, the rate should be titrated downward every 2-4 hours
Pediatric	15-20 mg/kg	1-5 mg/kg/hr[b]	
Propofol (Diprivan plus generic)			
Adult	2 mg/kg	5-10 mg/kg/hr[b]	Over 10 seconds in adults and 20-30 seconds in pediatric patients
Pediatric	3 mg/kg	2-4 mg/kg/hr[c]	
Topiramate (Topamax plus generic)			
Adult	300-500 mg	400-1,600 mg/day	Given orally in divided dose every 12 hours. Doses as large as 25 mg/kg/day for 2-5 days have been used in children. Monitor serum bicarbonate levels and serum concentrations
Pediatric	5-15 mg/kg (400 mg)	5-10 mg/kg/day, given thrice a day	

EEG, electroencephalogram; GCSE, generalized convulsive status epilepticus; IM, intramuscular; IV, intravenous.

[a]Doses can be repeated twice at 10-15 minute intervals until the maximum dosage is given.

[b]Titrate dose as needed.

[c]Generally recommended not to exceed a dose of 4 mg/kg/hr and a duration of 48 hours.

There is no specific protocol for tapering midazolam, but some suggest a seizure-free period of 24 to 48 hours before decreasing by 1 to 2 mcg/kg/min every 15 minutes.[2] Maintaining the patient's phenytoin and phenobarbital serum concentration(s) above 20 mg/L (79 µmol/L) and 40 mg/L (172 µmol/L), respectively, enhances successful discontinuation.

Because of midazolam's short half-life, patients can return to consciousness more rapidly compared to those receiving larger doses of more sedating antiseizure medications (eg, phenytoin and phenobarbital). Generally, continuous-infusion midazolam has been well tolerated, with few cases of hypotension and respiratory depression. If hypotension and poikilothermia occur, they can require supportive therapies. When adverse effects do

occur, patients recover quickly; however, the use of large doses has caused a "midazolam infusion syndrome" in adults, which is characterized by delayed arousal (ie, hours to days) following midazolam discontinuation. This has tempered its use in adults; however, its use has continued as an important agent in pediatrics. The availability of a pharmacological antidote for benzodiazepines, flumazenil, enhances the safe use of midazolam.

Pentobarbital

Use of a short-acting barbiturate is another anesthesia option (ie, pentobarbital or thiopental). These agents are preferred because they allow a more rapid reversal of coma. Although barbiturates are used frequently, there are no controlled trials to support this practice. In refractory GCSE, overall response rates are significantly greater in those treated with pentobarbital compared to midazolam or propofol.[46] The recurrence of seizures is also less frequent with pentobarbital and propofol. The reported mortality rates are similar for the three medications, but significant hypotension was more common with pentobarbital.

Several sources note that the initial loading dose of pentobarbital is 5 mg/kg; however, this dose is inadequate to achieve the serum concentrations (40 mg/L; 172 µmoL/L) necessary to induce an isoelectric EEG (see Table 76-6). Although the duration of barbiturate coma in most studies has been 2 to 3 days, it has been used safely for 53 days in an 18-year-old patient.[47] To avoid complications (eg, pneumonia and pulmonary edema), pentobarbital should be discontinued as soon as possible. The risk of seizure recurrence is minimized if other antiseizure medications are therapeutic before pentobarbital is withdrawn. Because pentobarbital is a potent hepatic enzyme inducer, higher maintenance doses of most concurrent antiseizure medications will be needed. Adverse medication reactions should be carefully monitored as de-induction occurs and antiseizure medication concentrations increase, which can occur up to a month after pentobarbital's discontinuation.

Propofol

Propofol is also a viable first-line alternative in phase III. It is extremely lipid soluble and has a large volume of distribution, a very rapid onset of action, and an extremely short half-life that promotes easy titration and rapid awakening on medication discontinuation. Although several studies have compared propofol and barbiturates, most studies were underpowered; however, its efficacy appears to be comparable to midazolam for refractory GCSE.[46,48] Propofol is given as a loading dose followed by a continuous infusion. The loading dose can be repeated every 3 to 5 minutes until the desired clinical response is obtained; however, the dose should be reduced once EEG burst suppression is achieved.

Adverse medication reactions can be found in Table 76-5. Prolonged infusions greater than 4 mg/kg/hr are associated with propofol-related infusion syndrome (PRIS), which may be more common in children and limits its use in this population.[49,50] Signs and symptoms of PRIS include progressive metabolic acidosis, hemodynamic instability, and bradyarrhythmias that are refractory to aggressive pharmacological treatments. It may occur with or without the presence of hepatomegaly, rhabdomyolysis, or lipemia. A retrospective case series of 41 patients with refractory GCSE noted that 10% had sudden unexplained cardiorespiratory arrests, and 35% had non-life-threatening features of PRIS.[50] Propofol may be proconvulsant in some patients as involuntary myoclonic movements have been reported.

Vital signs should be carefully monitored, and a continuous electrocardiogram (ECG) should be assessed for dysrhythmias. Guidelines proposing laboratory monitoring do not exist, but it would seem advisable to assess serum lactic acid, serum triglycerides, serum creatinine, creatine kinase, and hepatic enzymes in patients receiving doses larger than 4 mg/kg/hr and/or those receiving therapy for more than 48 hours.

The role and position of other antiseizure medications in refractory GCSE remains unclear, and shortages often complicate the selection of a second-phase antiseizure medication. The literature supports the use of lacosamide and topiramate's efficacy in refractory GCSE, although these data come from case reports or case series. Two reviews have noted there is insufficient evidence to support the routine use of lacosamide in benzodiazepine-resistant GCSE.[40,51,52] Topiramate has been given orally in adults and in children with GCSE and should be implemented at full therapeutic doses, divided three times a day (see Table 76-6).[2,53] To administer nasogastrically, the tablets should be crushed, mixed with water, and administered via syringe. The response tends to be delayed hours to days. Once seizures are controlled, the dose should be tapered to a standard age/weight–appropriate maintenance dosage. Aggressive implementation of large topiramate doses may cause hyperchloremic, non-anion gap metabolic acidosis due to inhibition of type II and IV carbonic anhydrase enzymes. This is not dose related, as it has been noted following small doses, as well as overdoses. If metabolic acidosis occurs, treat with citrates to maintain serum bicarbonate of at least 20 mEq/L (mmol/L).[2]

Super-Refractory GCSE (>24 Hours)

Persistent GCSE or recurring seizures after anesthetic medications have failed are challenging. Therefore, agents with a broad range of pharmacologic mechanisms may be tried, such as ketamine, a noncompetitive antagonist of NMDA receptors. During prolonged seizures, the number and activity of GABA receptors gradually decrease; thus, the commonly used first-line and second-line antiseizure medications slowly fail. Simultaneously, the number and activity of glutamatergic NMDA receptors increase, often causing refractory status epilepticus (RSE). A summary of the findings regarding ketamine use in RSE was recently published.[2,54] Additionally, others have proposed an expert consensus-based treatment protocol for its use.[55] Overall, ketamine appears to be a reasonable agent to consider in refractory GCSE that has failed general anesthesia, especially in those with cardiac instability. Ketamine doses can be found in Table 76-6. An advantage of ketamine is its ability to maintain arterial blood pressure, pulse rate, and cardiac output. Adverse events noted include hallucinations upon awakening, increased salivation, and increased intraocular and intracranial pressure.

Currently, weak evidence supports the use of lidocaine in super-refractory GCSE, although clinically it has been used when other agents fail.[56] When administered intravenously (see Table 76-6) it has a rapid onset of action. The therapeutic reference range for GCSE has not been established. However, the reference serum concentration range for the antiarrhythmic effects of lidocaine is 2 to 6 mg/L (8.5-26 µmol/L). Serum lidocaine concentrations and ECG should be monitored to avoid medication accumulation and toxicity (see Table 76-5).

Inhaled anesthetics are currently not used until other approaches fail. A few studies have used inhaled anesthetics (particularly isoflurane) for the treatment of refractory SE.[15,57] Halothane, isoflurane, and other inhaled anesthetics can produce EEG suppression. These agents are challenging to deliver outside the operating room and require an anesthesiologist; however, they offer no proven advantages over traditional antiseizure medications (eg, barbiturate coma or continuous-infusion benzodiazepine), and can increase intracranial pressure. If used, dosing is titrated to obtain EEG burst suppression, and although required concentrations are variable, isoflurane generally stops seizure at concentrations of 0.5% to 3%. It is important to note that these concentrations are not ordinarily associated with hemodynamic effects; however, isoflurane can induce hypotension. Therefore, close hemodynamic monitoring is necessary, and the administration of isotonic fluids and vasopressors as needed.

Data that suggest the development of super-refractory GCSE may be due to antibodies directed against the voltage-gated potassium channels and the NMDA receptor. However, the use of immunomodulating therapies (eg, corticosteroids and IV immune globulin) is based solely upon animal data.[15] Additionally, mounting evidence suggests that inflammation plays a role in epileptogenesis, particularly the activation of select inflammatory signaling pathways (eg, interleukin-1 receptor/toll-like receptor [IL-1R/TLR]). Steroids may also decrease blood-brain barrier opening and reverse GABAergic inhibition and affect NMDA and voltage-gated potassium channels. Although little evidence supports the use of steroids, in the absence of contraindications, a trial of large doses of steroids that IVIG follows should be considered. Typically, patients are given methylprednisolone 15 mg/kg/day every 6 hours, up to 1 g/day, for 3 days. Patients who respond should continue long-term steroids, IV immunoglobulins, and other immunomodulatory agents such as cyclophosphamide or rituximab.[58]

Controlled mild hypothermia reduces excitatory transmission, epileptic discharges, reduces brain edema, cerebral metabolic rate, oxygen utilization, and ATP consumption. Few studies have assessed the efficacy or safety of hypothermia in refractory GCSE and a meta-analysis suggested that only level D evidence supports the use of hypothermia in refractory SE.[59] Despite an absence of medical evidence, there has been a resurgence in the use of hypothermia, especially its use early on in super-refractory GCSE. When used, a core body temperature of about 32°C to 34°C is targeted for at least 24 to 48 hours. It may or may not be given in combination with barbiturate anesthetics,[15] but is often used concurrently with ketamine. Cardiovascular and coagulation parameters, biochemistry and acid-base balance, and serum lactate should all be monitored. Hypothermia may significantly reduce the clearance of several medication s, including anesthetics and antiseizure medications, resulting in a need for monitoring of serum concentrations.[2]

EVALUATION OF THERAPEUTIC OUTCOMES

Initial success for GCSE is defined as termination of all clinical and electrical seizure activity, but ultimate success is measured by the patient's subsequent quality of life. The morbidity and mortality associated with GCSE are primarily affected by the underlying etiology; however, morbidity and mortality can be minimized by the rapid implementation of a rational therapeutic plan. The EEG is a vital tool that not only allows practitioners to determine when abnormal electrical activity has been aborted but also can assist in determining which antiseizure medication was effective. Because many antiseizure medications affect the cardiorespiratory system, vital signs (eg, heart rate, respiratory rate, and blood pressure) must be monitored during medication loading and infusion. Finally, the infusion site must be assessed for any evidence of infiltration before and during the administration of phenytoin. Information regarding the patient's past medical and medication history and imaging studies (eg, MRI) can also help

determine if there is a defined etiology for the original episode of GCSE. This information can then be used to guide future medication therapy and help determine if the patient is at risk for a poor outcome.

CONCLUSION

GCSE is a medical emergency that requires all healthcare professionals to be knowledgeable about the phases of the disorder, the therapies that align with each phase, and secondary complications that need to be addressed. This requires clinicians to have a working knowledge of the Patient Care Process used for status epilepticus and understand what evidence-based information exists to select therapies. Additionally, knowing and identifying any provoking factors and/or various etiologies important in prevention and treatment is an integral part of care. Finally, it is also essential that outpatient therapies be aggressively used to abort impending SE.

ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate
ASM	antiseizure medication
CNS	central nervous system
CT	computed tomography
ECG	electrocardiogram
EEG	electroencephalogram, electroencephalography
GABA	γ-aminobutyric acid
GCSE	generalized convulsive status epilepticus
ICU	intensive care unit
IL-1R/TLR	interleukin-1 receptor/toll-like receptor
ILAE	International League Against Epilepsy
IM	intramuscular
IN	intranasal
IV	intravenous
MRI	magnetic resonance imaging
NCSE	nonconvulsive status epilepticus
NMDA	*N*-methyl-D-aspartate
PE	phenytoin equivalents
PRIS	propofol-related infusion syndrome
RSE	refractory status epilepticus
SE	status epilepticus

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SELF-ASSESSMENT QUESTIONS

1. An 8-year-old has fallen to the ground and began twitching and jerking both arms and legs. The jerking lasted for about 2 to 3 minutes, after which he would wake up, but have no memory of the event and began to seize again. When the emergency medical technicians (EMTs) arrive at the home the child is still seizing. Which medication should the EMTs administer?

   A. IM diazepam

   B. IM phenytoin

   C. IV lorazepam

   D. IN phenobarbital

2. A 32-year-old arrives in the emergency department due to a generalized convulsive seizure. They were given a single 0.1 mg/kg dose of lorazepam in the ED but continues to seize. The duration of seizures is now 15 minutes. Which would you recommend?

   A. Administer an IV loading dose of phenobarbital

   B. Administer an IM dose of diazepam instead of lorazepam

   C. Administer a second IV dose of the lorazepam

   D. Do not give additional antiseizure medications until an EEG is performed

3. Which is a risk factor for poor outcome in a patient with GCSE?

   A. Seizures persisting for more than 60 minutes

   B. Adults <60 years of age

   C. Patients without any CNS structural abnormalities

   D. Febrile seizure

4. Which is *true* regarding IV fosphenytoin and IV phenytoin?

A. Phenytoin causes pruritus, whereas fosphenytoin does not.

B. Fosphenytoin does not cause arrhythmias, whereas phenytoin does.

C. A phenytoin serum concentration should be drawn 1 hour after IV loading dose of phenytoin; whereas a phenytoin serum concentration should be drawn 2 hours after an IV dose of fosphenytoin.

D. The rate of administration is the same for both drugs.

5. Which is *true* regarding diazepam and lorazepam?

A. Lorazepam has a more rapid onset than diazepam.

B. Lorazepam has a longer duration of action than diazepam.

C. Diazepam is not metabolized while lorazepam is metabolized.

D. Diazepam can be given IM, while lorazepam can only be given IV.

6. Which is *true* regarding the administration of propofol?

A. Prolonged infusions greater than 4 mg/kg/hr have been associated with propofol-related infusion syndrome in pediatric patients.

B. The long half-life enables the drug to be given intermittently in patients with refractory GCSE.

C. It should be used in phase II (established GCSE).

D. It may cause tachyarrhythmias.

7. A 57-year-old (85 kg) patient with a history of complex partial seizures (2 per month) presents to the ED because of a “long” seizure at home that was at least partly witnessed by his partner. They were given a single dose of lorazepam and is now seizure free. Theychronically have received Carbatrol 600 mg BID. All chemistries, including liver function test and CBC, are normal. What would you recommend as part of this patient’s workup?

A. STAT EEG

B. STAT MRI

C. Carbamazepine serum concentration

D. Urine drug screen

8. Tachyphylaxis is most commonly associated with which medication?

A. Midazolam

B. Ketamine

C. Propofol

D. Phenobarbital

9. Which should *not* be administered IM in GCSE?

A. Midazolam

B. Phenobarbital

C. Diazepam

D. Fosphenytoin

10. Phenytoin, phenobarbital, diazepam, and lorazepam all contain propylene glycol. Which is *not* a sign of propylene glycol toxicity?

A. Dysrhythmia

B. Hypotension

C. Metabolic acidosis

D. Hepatic failure

11. Which is *true* regarding IN midazolam?

A. It should not be used in infants.

B. The entire dose should be administered in the same nostril.

C. The syringe used to administer the IN midazolam should be overfilled by 0.1 mL.

D. Effectiveness is the same whether or not an atomizer is used.

12. A 2-year-old child is transported to the emergency department following a generalized tonic-clonic seizure. The parent states that the child does not have epilepsy, but does take Flonase, Singular, Theo-Dur, and albuterol prn. They are afebrile. As part of the initial workup, which test would be most helpful in evaluating the seizure etiology?

A. Blood electrolytes

B. Liver function test

C. STAT EEG

D. Serum theophylline concentration

13. 75 mg of fosphenytoin is equivalent to how many milligrams of phenytoin?

A. 50 mg PE

B. 75 mg PE

C. 100 mg PE

D. 125 mg PE

14. An adult patient is admitted to the ICU for persistent GCSE. To date, the patient has received appropriate doses of 0.1 mg/kg lorazepam and 20 mg/kg PE fosphenytoin (1,500 mg PE), but continues to seize. Which IV medication would be best to recommend?

A. IV lorazepam

B. IV levetiracetam

C. CI propofol

D. Hypothermia

15. An EMT contacts you regarding the storage of antiseizure medications used during transport. Which must be refrigerated?

A. Midazolam

B. Fosphenytoin

C. Valproate

D. Phenobarbital

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** The Evidence-based guidelines recommend the initial use of IM midazolam, IV lorazepam, or IV diazepam in adults and the use of IV lorazepam or IV diazepam in children. IM midazolam is preferred if IV access is not available (see Fig. 76-1 and section "Initial Therapy Phase").

2. **C.** Since seizures have persisted for <20 minutes, the patient is still in the initial phase of SE. At this time, the guidelines recommend that the patient received a second dose of lorazepam (see Fig. 76-1 and section "Initial Therapy Phase").

3. **A.** Mortality significantly increases with increased seizure duration (eg, 2.6% for seizures 10 to 29 minutes, 19% for seizures lasting greater than 30 minutes, and 32% for seizures lasting greater than 60 minutes) (see section "Morbidity and Mortality").

4. **C.** A phenytoin serum concentration should be drawn 1 hour after the end of an IV loading phenytoin; whereas a phenytoin serum concentration should be drawn 2 hours after the end of an IV dose of fosphenytoin (see section "Second-Therapy Phase: Established GCSE").

5. **B.** Lorazepam is less lipid soluble than diazepam and takes longer to achieve peak concentrations in the brain; however, its minimal redistribution into fat results in a longer duration of action in the CNS, which can provide seizure protection for up to 24 hours. It also has a higher-affinity binding to the benzodiazepine receptor than diazepam (see section "Initial-Therapy Phase").

6. **A.** Prolonged infusions greater than 4 mg/kg/hr have been associated with propofol-related infusion syndrome (PRIS). Signs and symptoms of PRIS include progressive metabolic acidosis, hemodynamic instability, and bradyarrhythmias that are refractory to aggressive pharmacological treatments and occur primarily in pediatric patients. It may occur with or without the presence of hepatomegaly, rhabdomyolysis, or lipemia. It is more common in children, and this limits the use of this agent in the pediatric population (see Table 76-5 and section "Third-Therapy Phase: Refractory GCSE").

7. **C.** Because seizures stopped after a single dose of lorazepam, no additional initial antiseizure medication is warranted. Given the patient has been already diagnosed with epilepsy, there is no need for an EEG, MRI, or urine toxicology screen. One of the most frequent precipitating events for SE in adults is low antiseizure medication concentrations. A serum carbamazepine concentration will allow assessment of patient adherence to chronic therapy and influence on current presentation, requirement for a change in dosage, and need for patient education (see Table 76-3 and Patient Care Process for Status Epilepticus).

8. **A.** During prolonged seizures, the number of γ_2 and $\beta_{2\text{-}3}$ subunits on the GABAA receptors decrease as the receptors move from the synaptic membrane into the cytoplasm where they are functionally inactive. These modifications may decrease the effectiveness of both endogenous GABA and GABA agonists and result in time-dependent pharmacoresistance. Following GCSE that persist for more than 30 minutes, the relative potencies of benzodiazepines can be reduced up to 20-fold. Tachyphylaxis to midazolam rapidly develops within 24 to 48 hours; hence, the dose is often increased to prevent seizure relapse (see section "Third-Therapy Phase: Refractory GCSE" and its subsection "Benzodiazepine").

9. **C.** Because of slow and erratic absorption, diazepam should not be given IM. In patients without an established IV site, IM midazolam is the preferred benzodiazepine for intramuscular administration (see Table 76-4 and section "Initial Therapy Phase").

10. **D.** Continuous infusion of medications that contain propylene glycol has been known to cause hyperosmolality, increased anion gap and osmolar gap metabolic acidosis (due to lactic acidosis), central nervous system depression, cardiac arrhythmias, hypotension, respiratory arrest, hemolysis, and acute renal failure. This most frequently occurs in patients with renal dysfunction, who were receiving prolonged infusions of medications that contain propylene glycol (see Table 76-5).

11. **C.** It is imperative to account for medication that will remain in the dead space within the atomizer tip by overfilling the syringe with 0.1 mL of

medication (see section "Initial-Therapy Phase").

12. **D.** Many medications are known to cause seizures if used in excess. Theophylline is such a medication. Whenever a patient without a history of epilepsy presents with a seizure, it is imperative that the clinician rule out medications as an etiology (see Patient Care Process box).

13. **B.** The dose, concentration, and infusion rates for fosphenytoin are expressed as phenytoin equivalents (PE); fosphenytoin should *always* be prescribed and dispensed in PE; fosphenytoin 1.5 mg is equivalent to phenytoin 1 mg and is referred to as 1 mg PE (see Fig. 76-1 and Table 76-4).

14. **C.** When adequate doses of a benzodiazepine and a single dose of a second antiseizure medication(hydantoin, valproate, levetiracetam, and/or barbiturate) have failed, the condition is termed *refractory*. At this time, the goal is to stop electrical epileptiform activity as soon as possible, which could be best accomplished by anesthetizing the patient. Anesthetic dose of midazolam, pentobarbital, or propofol would be indicated (see Fig. 76-1 and section "Third-Therapy Phase: Refractory GCSE").

15. **B.** Store intact vials refrigerated at 2°C to 8°C (36°F-46°F). Do not store at room temperature for more than 48 hours. After opening, discard any unused solution in vials (see the Beyond the Book activity).