Status Epilepticus

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Status Epilepticus

Status epilepticus (SE) is a condition resulting either from initiation of mechanisms that lead to abnormally prolonged seizures (longer than five minutes), or the failure of the mechanisms responsible for seizure termination. Common causes of SE in children are febrile seizures and metabolic etiologies, such as inborn errors of metabolism and hypoglycemia. Ultimately, the goal of therapy is to terminate both the clinical and electrical seizure activity safely and rapidly. The authors present an approach to the diagnostic evaluation and therapeutic management of neonates and children in SE.

— Ann Dietrich, MD, FAAP, FACEP, Editor

Definition

Historically, SE has been defined as seizures that are continuous for 30 minutes or longer, or repetitive seizures between which the patient does not regain consciousness.[1,2] However, this definition is evolving. Many authorities now consider SE to include seizures lasting for longer than five minutes or multiple seizures with no return to baseline in between.

The International League Against Epilepsy revised its definition of SE in 2015 to incorporate both of these time points (five minutes and 30 minutes). It now defines SE as a condition resulting either from initiation of mechanisms that lead to abnormally prolonged seizures (longer than five minutes), or the failure of the mechanisms responsible for seizure termination. It is a condition that can have long-term consequences if it lasts longer than 30 minutes, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.[3,4] All seizure types can result in SE.

Epidemiology

Each year, about 150,000 children and adolescents in the United States will seek medical attention for evaluation of a newly occurring seizure disorder of some type, and about 1% of children and adolescents will experience at least one afebrile seizure by 14 years of age.[5]

The estimated incidence of childhood SE is between 17 and 23 episodes per 100,000 children per year.[6,7] Incidence rates and causes of SE vary substantially by age, with the highest incidence in the first year of life. Febrile SE is the most common etiology[8]; approximately 60% of children are neurologically healthy prior to the first episode of SE.

Ten percent to 20% of children with epilepsy will have at least one episode of SE in their lifetime,[9] with SE occurring as the first seizure in 12%. Patients with partial seizures that tend to occur in clusters (three or more within 24 hours, with return to baseline between seizures) have a higher incidence of SE compared to those who do not cluster (47% vs. 13%).[10] Risk factors for SE in children with symptomatic epilepsy include focal background electroencephalography (EEG) abnormalities, focal seizures with secondary generalization, occurrence of SE as the first seizure, and generalized abnormalities on neuroimaging.[11]

EXECUTIVE SUMMARY

- Historically, status epilepticus (SE) has been defined as seizures that are continuous for 30 minutes or longer, or repetitive seizures between which the patient does not regain consciousness. However, this definition is evolving, with many authorities now considering SE to include seizures that last for longer than five minutes or multiple seizures with no return to baseline in between.
- Neurologic sequelae from SE usually are caused by the underlying condition rather than the seizures themselves and are associated with younger age, progressive encephalopathy, duration (longer than 24 hours), prior epilepsy, and specific EEG findings.
- Psychogenic nonepileptic seizures (PNES) usually present with a prolonged episode of generalized, atypical-appearing motor activity and a prompt return of consciousness. A diagnosis of PNES is seen more frequently in teenage patients with underlying psychiatric disorders, such as affective and anxiety disorders, and it is less common in younger children. PNES is best distinguished from true seizures by capturing the event on a video EEG monitor.
- The first-line treatment for SE is benzodiazepines, including diazepam, lorazepam, and midazolam. If intravenous (IV) access is not readily available, rectal diazepam, intramuscular midazolam, intranasal midazolam, and buccal midazolam can be considered.
- If seizures continue for 10 minutes after administration of at least two doses of a benzodiazepine, a second-line treatment with a long-acting antiseizure medication is indicated. Phenytoin/fosphenytoin, levetiracetam, and valproic acid are the recommended options in this setting. Levetiracetam is a preferred choice over phenytoin because of its ease of use, more rapid administration, and equivalent efficacy.
- For symptomatic hypoglycemia, one should give an initial bolus of 2 mL/kg of dextrose 10% (0.2 g dextrose/kg of body weight).
- In children with acute, symptomatic hyponatremia, an initial hypertonic (3%) saline dose of 3 to 5 mL/kg IV should be administered over 10 to 15 minutes.
- Neonates are a distinct subset of the population, and neonatal seizures warrant special consideration. Seizures in the neonatal period most frequently occur within the first week of life. Approximately 85% of neonatal seizures occur as a consequence of a specific identifiable etiology.

Morbidity

Neurologic sequelae from SE usually are caused by the underlying condition rather than the seizures themselves and are associated with younger age, progressive encephalopathy, duration (longer than 24 hours), prior epilepsy, and specific EEG findings. These EEG findings include a suppression of basic activity as well as periodic burst and suppression patterns. A systematic review found that while rates of neurologic sequelae are increased in younger patients with a longer duration of seizures, these factors also are linked to and difficult to separate from the underlying cause. These sequelae include focal motor deficits, cognitive deficits, behavioral disorders, and chronic epilepsy.[12-14]

Mortality

Like morbidity, mortality results from the underlying condition or from respiratory, cardiovascular, or metabolic complications.[15] The underlying etiology is the main predictor of mortality. The reported mortality rates of SE in children vary between 3% and 9%.[6,16,17]

Etiology

Causes of seizures and epilepsy can be broadly categorized as structural, metabolic, genetic, immune, infectious, and idiopathic. (*See Table 1.*) All seizure types can result in SE. Therefore, it is important to note the various etiologies of seizure and epilepsy syndromes, because SE may be an acute symptom of medical disease process.[8,18] Also, while some causes of seizures can affect children of any age (trauma, central nervous system [CNS] or systemic infections, neoplastic and degenerative diseases), others have a predilection for certain age groups. For example, in the neonatal period, perinatal hypoxic-ischemic injury, intracranial hemorrhage, metabolic disturbances, and CNS or systemic infections are more common causes of seizures (*see section on neonatal SE*). In older infants and young children, febrile seizures are a common cause of SE. Many of the genetic syndromes also tend to present during this period. In adolescents and young adults, toxic insults and traumatic injuries from increased risk-taking behaviors are seen more commonly.

Research is emerging about new-onset refractory SE (NORSE). This occurs in patients with no previous diagnosis of an epileptic or neurologic disorder. A subset of NORSE, febrile infection-related epilepsy syndrome (FIRES) occurs between 24 hours and two weeks after a febrile infection and results in refractory SE. FIRES usually occurs in children 3-15 years of age. The pathogeneses of NORSE and FIRES are largely unknown, because there often is no active structural, metabolic, or toxic cause. The prognosis for both conditions generally is poor.

Pathophysiology

Seizure activity involves hypersynchrony of neuronal discharges with cerebral manifestations, including increased blood flow, increased oxygen and glucose consumption, and increased carbon dioxide and lactic acid production. Systemic alterations (from a massive sympathetic discharge) also occur, such as tachycardia, hypertension, and hyperglycemia. This combination gives rise to the failure of adequate ventilation, leading to hypoxia, hypercarbia, and respiratory acidosis. Prolonged skeletal muscle activity (with convulsive seizures) results in lactic acidosis, rhabdomyolysis, hyperkalemia, hyperthermia, and hypoglycemia.

SE occurs because of the failure of the normal mechanisms that limit the spread and recurrence of isolated seizures.[19,20] This failure occurs because excitation is excessive and/or inhibition is ineffective. The following section describes some of the mechanisms believed to be involved in this process.

Glutamate is the major excitatory amino acid neurotransmitter in the brain. It is thought that excessive activation of excitatory amino acid receptors by glutamate has a role to play in SE. Other excitatory

Table 1. Etiology of Seizures

Metabolic Hepatic failure, hypercarbia, hyperosmolality, hypocalcemia, hypoglycemia,* hyponatremia, hypoxia, hypomagnesemia, uremia, inborn errors of metabolism,* pyridoxine deficiency*	**Toxicologic** Anticonvulsant, camphor, carbon monoxide, cocaine, heavy metals (lead), tricyclic antidepressants, isoniazid, lithium
Infectious Brain abscess, encephalitis, fever,* meningitis, parasites (central nervous system), syphilis	**Traumatic Injuries** Cerebral contusion, diffuse axonal injury, intracranial hemorrhage, perinatal hypoxic-ischemic injury
Congenital Anomalies/ Genetic Syndromes Dravet syndrome, Angelman syndrome, generalized epilepsy with febrile seizures plus, Lennox-Gastaut syndrome	**Obstetric Complication** Eclampsia
Oncologic Primary brain tumor, metastatic disease	**Endocrine** Addison's disease, hyperthyroidism, hypothyroidism
Idiopathic/Cryptogenic*	
* More common pediatric etiologies	

neurotransmitters that contribute to SE include aspartate and acetylcholine.[21]

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, and antagonists to its effects or alterations in its metabolism in the substantia nigra may contribute to SE.[22] This was demonstrated in an animal model where the rate of GABA synthesis in the substantia nigra declined significantly during induced SE.[23] Other inhibitory mechanisms include the calcium ion-dependent potassium ion current and blockage of N-methyl-D-aspartate channels by magnesium.

Classification

SE, like seizures, is classified by clinical presentation into four major types based on whether the seizure is focal or generalized and whether it is convulsive or nonconvulsive. (*See Table 2.*)

Clinical Features/Systemic Complications

Clinical features will vary based on the type of SE, either convulsive or nonconvulsive.

Convulsive SE usually presents with continuous muscle contractions that could be tonic-clonic, tonic, or clonic movements. It usually is associated with alteration in consciousness. These prolonged, generalized muscle contractions may lead to elevated body temperature and rhabdomyolysis. Rhabdomyolysis can cause hyperkalemia, increased release of muscle enzymes, and myoglobinuria, which can precipitate acute renal failure.

Another systemic change associated with prolonged seizures/SE is hypoxemia, which may lead to respiratory acidosis.[24] Further metabolic disturbances include an alteration in brain glucose levels, lactic acidosis, and depletion of brain adenosine triphosphate. Severe hypoxemia and acidosis result in impaired myocardial function, reduced cardiac output, and hypotension, further disrupting cellular function.

Other systemic effects noted include changes in blood pressure, heart rate, and central venous pressures. At the start of SE, there is an increase in these parameters from the massive release of catecholamine and sympathetic discharge. This increase is accompanied by a large increase in cerebral blood flow, thought to compensate for the brain's increased metabolic needs.[25] However, with the persistence of SE, blood pressure declines, resulting in hypotension. There also is a decline in cerebral blood flow, with the inability to meet the increased demands for substrates and oxygen.

Intracranial pressure is increased during SE. This further interferes with the supply of substrates and oxygen and results in cerebral edema. Factors that contribute to increased intracranial pressure include metabolic acidosis, hypoxemia, and hypercarbia with compensatory cerebral vasodilatation and increased cerebral blood flow.[26]

Nonconvulsive SE with or without alteration in awareness will have similar features without the generalized muscle contractions and its effects.

Differential Diagnosis

Seizures resulting in SE often are due to an underlying cause, such as toxins, neoplasms, and infections. However, an additional consideration in the differential diagnosis is psychogenic nonepileptic seizures (PNES). Patients with PNES usually present with a prolonged episode of generalized, atypical-appearing motor activity and a prompt return of consciousness. PNES is seen more frequently in teenage patients with underlying psychiatric disorders, such as affective and anxiety disorders, and it is less common in younger children.[27,28] A family history of seizures or a friend or acquaintance with seizures usually is present in patients with PNES.

Important distinguishing features of PNES from SE are fluctuating course, asynchronous movements, pelvic thrusting, side-to-side head or body movements, ictal eye closure, ictal crying, memory recall, and absence of postictal confusion.[29] In addition, patients with PNES typically are unresponsive to standard anticonvulsant medications. PNES is best distinguished from true seizures by capturing the event on a video EEG monitor.

Additional considerations in the differential diagnosis for seizures and SE are medication-induced dystonic reactions, conversion disorder, syncope, and arrhythmias.

Management

There are three principal goals in the management of a patient in SE. The initial steps are summarized in Table 3. The first priority is to address airway, breathing, and circulation. The second priority is to stop any ongoing seizure activity (both clinical and EEG seizure activity). Finally, it is important to consider reversible causes and initiate the indicated treatment, as well as diagnose the underlying etiology of the seizure episode. This requires astute history gathering and may require ancillary testing.

Perform a brief physical examination to assess respiratory and circulatory status. Establish an adequate airway immediately (e.g., reposition, suction, or use adjunctive

Table 2. Classifications of Status Epilepticus

- Focal SE *without* impairment of consciousness or awareness (simple partial SE): Continuous or repeated focal motor or sensory seizures without impaired consciousness
- Focal SE *with* impairment of consciousness or awareness (complex partial SE): Continuous or repeated episodes of focal motor, sensory, or cognitive symptoms with impaired consciousness (non-convulsive SE)
- Generalized convulsive SE including tonic-clonic, tonic, and clonic movements: Always associated with loss of consciousness
- Absence SE: Generalized seizure activity, characterized clinically by altered awareness, but not necessarily unconsciousness

SE: status epilepticus
Adapted from: Wilfong A. Clinical features and complications of status epilepticus in children. UptoDate. Updated Dec. 19, 2019. Available at: https://www.uptodate.com/contents/clinical-features-and-complications-of-status-epilepticus-in-children.

airway equipment, such as an oropharyngeal airway or nasal pharyngeal airway, as needed). If there is respiratory compromise, institute supportive therapy (e.g., administration of oxygen, positive pressure ventilation, or mechanical ventilation) as needed. Secure parenteral access (intravenous [IV] catheter or intraosseous [IO]) as soon as possible to obtain blood samples and administer medications. Monitor ongoing vital signs. A rapid neurologic examination should be performed to provide a preliminary classification of the type of SE. A brief history obtained from a parent or caregiver may help determine the cause or precipitants of the seizure.

The second priority is to stop any ongoing seizure activity (both clinical and EEG seizure activity). The first-line treatment for SE is benzodiazepines because they can rapidly control seizures.[30] Diazepam, lorazepam, and midazolam are the three benzodiazepines most commonly used to treat SE. Historically, lorazepam has been the first drug of choice because of its long half-life and safety profile.[30] It is important to note that benzodiazepines can be given via intramuscular (IM), rectal (PR), intranasal (IN), and IO routes if IV access is not readily available. However, there is evidence that IV-administered agents abort seizure activity more rapidly.[31-33] If IV access is not readily available, PR diazepam, IM midazolam, IN midazolam, and buccal midazolam can be considered.

Lorazepam is administered at a dose of 0.1 mg/kg IV, up to a maximum of 4 mg; its effect is assessed over five to 10 minutes.[34] Diazepam is administered at a dose of 0.2 mg/kg IV up to a maximum dose of 8 mg.[35] If seizures continue after five minutes, give additional doses of lorazepam or diazepam. It is important to remember that the risk of respiratory depression increases with administration of repeated doses of benzodiazepines.[36,37] Be prepared to establish a definitive airway in those situations.

If seizures continue for 10 minutes after administration of at least two doses of a benzodiazepine, a second-line treatment with a long-acting antiseizure medication is indicated. Phenytoin/fosphenytoin, levetiracetam, and valproic acid (VPA) are the recommended options in this setting.[38] Levetiracetam is a preferred choice over phenytoin because of its ease of use, more rapid administration, and equivalent efficacy.[39,40] The recommended dose is 40 mg/kg IV. The recommended loading dose of fosphenytoin is 20 mg phenytoin equivalents (PE)/kg IV. If seizures persist, an additional 5 to 10 mg PE/kg IV of fosphenytoin can be given 10 minutes after the loading dose. The dose for phenytoin and fosphenytoin is the same. VPA is an alternative and should be considered as an initial therapy in children who did not respond to levetiracetam or fosphenytoin in previous episodes of SE, in children with a hypersensitivity to phenytoin or fosphenytoin, in cases of toxin-induced SE, or in children on chronic VPA therapy who are known to have had recent nonadherence and in whom VPA levels are suspected to be low.[41] The recommended IV loading dose of VPA is 20-40 mg/kg. An additional 20 mg/kg can be administered after 15-20 minutes, if needed.

If convulsive SE persists for 30 minutes after first- and second-line treatments are instituted, it is considered refractory SE and a third-line treatment is recommended. The drugs most commonly used in refractory SE are midazolam, pentobarbital, and propofol, usually administered as a continuous infusion.[42-44] Midazolam is given as continuous infusion of 0.05 to 2 mg/kg/hour; for breakthrough seizures, additional 0.1 to 0.2 mg/kg boluses can be given and the continuous infusion rate increased by 0.05 to 0.1 mg/kg/hour every three to four hours. Pentobarbital is given as an initial bolus infusion of 5 to 15 mg/kg IV followed by a continuous infusion of 0.5 to 5.0 mg/kg per hour. Propofol may terminate seizures rapidly, but it is rarely used in children because of its Federal Drug Administration black box warning regarding propofol infusion syndrome. The duration of the continuous infusion is dependent on achieving a suppression-burst pattern on continuous EEG for 24 to 48 hours (usually in the intensive care unit setting).

The third priority in the management of a patient with SE is identifying reversible causes (i.e., electrolyte imbalances or toxic insults) and initiating prompt, specific treatment to stop the seizures.

Treatment of Reversible Causes

Hypoglycemia

For symptomatic hypoglycemia, one should give an initial bolus of 2 mL/kg of dextrose 10% (0.2 g dextrose/kg of body weight). If glucose fails to increase after 15 to 20 minutes, repeat the bolus. Higher concentrations of dextrose are not recommended as an initial bolus because they frequently result in hyperglycemia with a subsequent insulin surge, triggering further hypoglycemia. After the initial bolus, start a dextrose infusion to prevent recurrent hypoglycemia. Neonates should be started on D10 containing isotonic maintenance fluids. Because older children have lower glucose requirements, they should be started on D5 containing isotonic fluids at maintenance rate.

Hyponatremia

Cerebral edema is a potential complication of symptomatic hyponatremia with seizures. The risk of morbidity from delayed therapy is greater than the risk of complications from too rapid correction and osmotic demyelination. Therefore, aggressive initial correction is recommended.

In children with acute, symptomatic hyponatremia, an initial hypertonic (3%) saline dose of 3 to 5 mL/kg IV should be administered over 10 to 15 minutes.[45] If

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Table 3. Initial Management of Status Epilepticus in Children

Timeline	Assessment	Supportive care	Seizure therapy
0 to 5 minutes	Obtain initial vital signs, including temperature	Open airway Suction secretions Administer 100% O_2	**Benzodiazepine:** **Lorazepam** 0.1 mg/kg IV or IO, maximum 4 mg **OR** **Diazepam** 0.2 mg/kg IV or IO, maximum 8 mg **IV or IO access not achieved within 3 minutes:** **Buccal midazolam** 0.2 mg/kg, maximum 10 mg **OR** **IM midazolam** 0.1 to 0.1 mg/kg, maximum 10 mg **OR** **Rectal diazepam** (Diastat gel or injection solution given rectally) 0.5 mg/kg, maximum 20 mg
	Identify airway obstruction and hypoxemia	Place continuous cardiorespiratory monitors and pulse oximetry	
	Identify impaired oxygenation or ventilation	Perform bag-valve-mask ventilation, as needed Prepare for RSI*	
	Obtain rapid bedside blood glucose and other studies, as indicated[Δ]	Establish IV or IO access	
	Evaluate for signs of sepsis/meningitis	Treat hypoglycemia (IV dextrose 0.25 to 0.5 g/kg)	
	Evaluate for signs of head trauma	Treat fever (acetaminophen 15 mg/kg rectally)	
5 to 10 minutes	Reevaluate vital signs, airway, breathing, and circulation	Maintain monitoring, ventilatory support, and vascular access	**Benzodiazepine: second dose**
	Evaluate for signs of trauma, sepsis, meningitis, or encephalitis	Give antibiotics if signs of sepsis or meningitis[◊]	
10 to 15 minutes	Reevaluate vital signs, airway, breathing, and circulation	Maintain monitoring, ventilatory support, and vascular access	**Levetiracetam** 40 mg/kg IV or IO **OR** **Fosphenytoin**[¶] 20 mg PE per kg IV or IO[§] **OR** **Valproate** 20 to 40 mg/kg IV or IO **OR** **Phenobarbital** 20 mg/kg IV or IO, maximum 1 g, (expect respiratory depression with apnea)[¥]
		Place second IV	
		RSI potentially indicated*	
15 to 30 minutes	Reevaluate vital signs, airway, breathing, and circulation	Maintain monitoring, ventilatory support, and vascular access	**Fosphenytoin**[¶] (if not already given) 20 mg PE per kg IV or IO[◊] **OR** **Valproate** 20 to 40 mg/kg IV or IO **OR** **Phenobarbital** (if not already given) 20 mg/kg IV or IO, maximum 1 g (10 mg/kg if phenobarbital already given)[¥] **OR** **Levetiracetam** (if not already given) 40 mg/kg IV or IO **AND** **Pyridoxine** 100 mg IV or IO in infants < 1 year of age **Pyridoxine** 70 mg IV or IO, maximum 5 g, if INH poisoning suspected **Obtain pediatric neurology consultation**[‡]
	Obtain continuous EEG monitoring, if available		

IV: intravenous; IO: intraosseous; IM: intramuscular; O_2: oxygen; RSI: rapid sequence endotracheal intubation; PE: phenytoin equivalents; EEG: electroencephalogram; INH: isoniazid.

* Rapid sequence intubation should be performed if airway, ventilation, or oxygenation cannot be maintained and if the seizure becomes prolonged.
¶ Phenytoin and fosphenytoin may be less effective for the treatment of seizures due to toxins or drugs and may intensify seizures caused by cocaine, other local anesthetics, theophylline, or lindane. In such cases, levetiracetam, valproate, or phenobarbital should be used.
Δ For ancillary studies to obtain in chilren with status epilepticus, refer to UpToDate topics on status epilepticus in children.
◊ Empiric antibiotic regimens vary depending on patient susceptibility and likely pathogen.
§ Do not exceed 3 mg/kg per minute (maximum rate: 150 mg per minute). Fosphenytoin may be ineffective for toxin-induced seizures and may intensify seizures caused by cocaine and other local anesthetics, theophylline, or lindane. If fosphenytoin not available, may use phenytoin 20 mg/kg IV, do not exceed 1 mg/kg per minute (maximum rate: 50 mg per minute) with ECG monitoring.
¥ Do not exceed 1 mg/kg per minute.
‡ In patients with ongoing seizure activity despite two initial doses of benzodiazepine and a second-therapy antiseizure drug, preparation for a continuous infusion of midazolam, propofol, or pentobarbital should occur simultaneously with administration of a third-therapy antiseizure drug.

Table 4. Laboratory Studies for Children With Status Epilepticus

Population	Studies
All patients	Serum electrolytes; serum calcium, phosphate, magnesium; brain imaging (CT or MRI)
Epilepsy patients maintained on anticonvulsants	Anticonvulsant level
Febrile patients	CBC with differential; blood culture; urinalysis, urine cultures; CSF culture
Poisoned patient	Urine screen for amphetamines, cocaine, PCP; aspirin level; venous or arterial pH and pCO_2; ECG when seizures stop
Infants younger than 6 months of age	Blood gas; plasma ammonia; plasma amino acids; PT, PTT; serum AST, ALT, LDH, alkaline phosphatase; blood lactate and pyruvate; urinalysis; urine for reducing substances

CT: computed tomography; MRI: magnetic resonance imaging; EEG: electroencephalogram; CBC: complete blood count; CSF: cerebrospinal fluid; PCP: phencyclidine; pCO_2, partial pressure of carbon dioxide; ECG: electrocardiogram; PT: prothrombin time; PTT: partial thromboplastin time; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.

(Continued from page 28)
the seizures persist, recheck serum sodium levels and repeat the infusion. Once the seizure has been abated, if hyponatremia persists, the child's clinical status and serum sodium level can guide further IV fluid replacement.[46] The targeted goal is to raise the serum sodium not more rapidly than 8 to 9 mEq/L over the initial 24 hours.[47-50] Patients with persistent SE secondary to hyponatremia likely will be refractory to antiepileptic medications if the underlying hyponatremia has not been addressed.

Hypocalcemia

IV calcium is indicated to treat symptomatic hypocalcemia. The recommended regimen is 100 to 200 mg/kg/dose of calcium gluconate, administered intravenously over five to 10 minutes. This should be given slowly because of the risk of serious cardiac dysfunction, including systolic arrest.[51] Although calcium chloride also can be used for correction, it is more likely to cause tissue necrosis if extravasated.

Hypomagnesemia

Hypocalcemia is difficult to correct in the setting of concurrent hypomagnesemia. If administering magnesium in the form of magnesium sulfate, the appropriate dose is 25 to 50 mg/kg/dose IV every four to six hours for two to three doses with a maximum dose of 2,000 mg/dose. Continue magnesium repletion as long as the serum magnesium concentration is less than 0.8 mEq/L (1 mg/dL).

Toxic Insults

In the management of toxic insults, benzodiazepines are a temporizing measure at best. Definitive therapy would include the antidote for a given poisoning. Examples include seizures resulting from methanol or ethylene glycol toxicity, for which one should administer fomepizole, which acts to inhibit the enzyme alcohol dehydrogenase. Pyridoxine should be administered in suspected isoniazid toxicity. It is highly recommended that providers contact the local poison control center in these situations for additional recommendations.

The third priority in the management of SE includes diagnosing the underlying etiology of the seizure episode. A parent or caregiver may provide a history to help determine the cause or precipitants of the seizures. It is prudent to obtain information about the seizure episode, any preceding events (e.g., history of trauma, fever, headache or vomiting, toxin exposure or ingestion), underlying seizure disorder, current medications, and any history of missed medication. Inquire about surgical history (e.g., ventriculo-peritoneal shunt placement), family history, and travel history. A thorough physical examination must be performed, checking for evidence of an infectious or traumatic etiology. Examine the skin for rashes or other congenital skin lesions, dysmorphic features, or stigmata of underlying hepatic, renal, or endocrinologic disorders.

Laboratory Studies

Table 4 highlights priorities for laboratory testing in children with SE. Blood and urine should be obtained for the following: a rapid "finger-stick" glucose, serum electrolytes (including calcium, phosphate, and magnesium levels), venous or arterial pH and pCO_2, urinalysis and a complete blood count, urine and blood toxicology, and serum anticonvulsant drug levels. Of note, patients with an infection may have an elevated white blood cell count (WBC). However, an elevated WBC also may be due to demargination, in which case it will return to reference ranges in 12-24 hours. Although institutional panels for limited and extended toxicology screens may vary, substances such as ethanol, cocaine, amphetamines, methamphetamines, lysergic acid diethylamide (LSD), and phencyclidine (PCP) have been reported to cause SE and should be explored if clinically indicated. Blood cultures should be obtained if there is evidence of systemic infection. Similarly, cerebrospinal fluid studies via a lumbar puncture (LP) should be obtained if there is concern for a CNS infection. Children with known epilepsy have a decreased seizure threshold during infections because of the increased metabolic stress. When patients present in SE, they may have a localizing source of their infection, in which case the clinician must use their best judgment to determine if an LP is indicated. A renal function panel, creatine phosphokinase, and urinalysis can be obtained to monitor for complications of SE, such as rhabdomyolysis.

Neuroimaging. Consider computed tomography (CT)/magnetic resonance imaging (MRI). CT may be performed in the emergency department setting, but MRI has superior yield for determining the underlying etiology. Consider neuroimaging when SE is the first presentation of epilepsy; if there are signs or symptoms of elevated intracranial pressure; if the patient presents with a focal seizure or has a persistent focal neurologic deficit; in the setting of head trauma; in unexplained persistent seizure activity, as well as in children whose recovery from SE does not follow the expected course.[36,52] Expert consultation with neurology is helpful in instances of refractory SE.

Other Therapies. Observational data suggest that other antiseizure drugs, including lacosamide and topiramate, may play a role in the management of SE, particularly in the refractory setting. Other emerging

therapies include ketamine and the ketogenic diet.[53-56] Immunomodulatory therapy including IV corticosteroids and IV immunoglobulin has been used to treat NORSE and FIRES.

Neonatal Seizures

Neonates are a distinct subset of the population, and neonatal seizures warrant special consideration. Seizures in the neonatal period most frequently occur within the first week of life. Newborns at higher risk for seizures are those who are born at a younger gestational age and lower birth weight. The estimated incidence of seizures in this age group is from 1.5 to 5.5 per 1,000.[57-65] The etiology, classification, diagnosis, and management of neonatal seizures varies from that of older children.

Etiology

Approximately 85% of neonatal seizures occur as a consequence of a specific identifiable etiology. These are broadly classified as neonatal encephalopathy and hypoxic-ischemic encephalopathy; structural brain injuries, including ischemic and hemorrhagic stroke; metabolic disturbances (most often glucose and electrolyte abnormalities); CNS or systemic infections; drug withdrawal or intoxication; and inborn errors of metabolism.

Neonatal encephalopathy subsequent to hypoxia-ischemia is the most common cause of neonatal seizures.[66,67] In a prospective multicenter study of 426 consecutive neonates with seizures, hypoxic ischemic encephalopathy was the most common etiology (38%), followed by ischemic stroke (18%), and intracranial hemorrhage (11%).

Metabolic disturbances resulting in neonatal seizures are potentially treatable and include hypocalcemia, hypomagnesemia, and hypoglycemia. Typically, reversal of these abnormalities is sufficient to treat the acute symptomatic seizures, and anticonvulsant medications usually are not necessary.

Bacterial and viral infections of the CNS also can cause seizures and result in SE.[68] For example, prenatal infections — toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus infection (TORCH) — are potential risk factors for seizures. Any neonate with suspected seizures should be considered to have a systemic and/or CNS infection until proven otherwise and should have an immediate evaluation for infection.

Drug withdrawal and intoxication are additional causes of neonatal seizures. Neonates exposed to substances in utero may experience a withdrawal syndrome in the first days of life that can include seizures.

Inborn errors of metabolism also can manifest as seizures, especially in the neonatal period. They should be suspected when seizures begin several days postpartum following a normal pregnancy and delivery, absent postpartum complications.[69] Other clues include a family history of consanguinity or early sibling death; physical signs, such as organomegaly, cardiomyopathy, or hematologic abnormalities; and seizures refractory to conventional treatment.

Classification

Seizures in the neonatal period are unique when compared with those of older infants and children. Neonatal seizures are classified according to their motor manifestations into focal clonic, multifocal clonic, generalized tonic, myoclonic, spasms, and motor automatisms.[70-77]

Subtle seizures are common and are associated with abnormal eye movements, lip smacking, and swimming or pedaling movements.[78]

Even the most discerning clinician may find it difficult to identify seizure activity in a newborn. This is because neonates, particularly preterm infants, often display normal physical activity that, when occurring suddenly, may resemble seizures. This includes sucking, gagging, coughing, and stretching. Further, many neonatal seizures are subclinical or nonconvulsive. Jitteriness, for example, may resemble a seizure, but is distinguished clinically from clonic seizures by the lack of associated ocular movements and a tremor that is suppressed by flexing the limb. Often, a bedside EEG is required to distinguish these normal events from seizures.[72,79,80] The history and physical exam can identify risk factors and provide clinical clues to guide judicious use of testing. They also can help clarify the underlying etiology as either acute symptomatic seizures or neonatal onset of epilepsy.

Maternal History. Specific conditions during pregnancy can predispose infants to illnesses that may manifest as seizure activity. For example, infants born to women who experienced gestational diabetes are at risk for neonatal hypoglycemia. Maternal infections, such as sexually transmitted infections, or even more vague histories of fever and rash may expose infants to in utero transmission of the infection. Maternal use of prescription or illegal substances can lead to seizure activity in the newborn as a result of drug intoxication or withdrawal.

Family History. In addition to confirming if there is a family history of epilepsy, there are additional familial historical clues that can help guide the diagnosis. A family history of consanguinity or early sibling death from unknown causes warrants consideration of inborn errors of metabolism. These errors often lead to electrolyte disturbances, which subsequently can cause seizures.

Physical Exam. Aspects of the physical examination may direct further testing and provide clues to the underlying etiology. One should pay attention to the infant's head size and fontanelle. Macro- and microcephaly can indicate a structural abnormality, while a bulging fontanelle may suggest meningitis or increased intracranial pressure. Rashes may indicate a TORCH infection. The motor exam can detect asymmetry in spontaneous movements or abnormal tone that may suggest a structural brain lesion or neonatal encephalopathy.

Laboratory Investigation. Infection and sepsis are among the most common causes of neonatal seizure, and often the clinical manifestations can be otherwise subtle. As such, a proper sepsis evaluation should ensue, and the clinician should obtain cerebrospinal fluid and blood and urine cultures in addition to the rest of the septic workup. Additional blood tests that can be helpful are serum electrolytes, magnesium levels, measures of transaminase levels, ammonia, lactate, and an arterial blood gas. Similarly, a urinalysis and toxicology screen may help guide management. Although the results may not be available in the acute setting, serum pyruvate and amino acids, TORCH titers, urine-reducing substances, and urine organic acids can assist with longitudinal diagnosis and management.

Other Testing. Similar to older children, MRI is the neuroimaging modality of choice for neonates presenting with seizures. MRI can detect intracranial hemorrhage, ischemic stroke, brain malformations, and evidence of hypoxic ischemic damage. If vascular pathology is suspected, one can order MRI venography or angiography. If MRI is not readily available, a cranial ultrasound can be used to identify intracranial hemorrhage or hydrocephalus. CT generally should be avoided in young children, especially neonates, since MRI

provides superior resolution and does not involve exposure to ionizing radiation.[81,82] The gold standard for neonatal seizure diagnosis is multi-channel video EEG monitoring.[81]

Management

The management goal of neonatal seizures is to stabilize the infant, quickly identify and treat any reversible causes, and administer antiepileptic drugs (AEDs) when necessary. While AEDs may be effective at treating neonatal epilepsy, intractable SE may ensue if there is another underlying cause that has not been properly addressed. This can lead to irreversible brain damage.

Reversible Causes. Infections, particularly those involving the CNS, should be treated promptly with broad-spectrum antibiotics, with doses sufficient to treat meningitis. Herpes simplex virus should be considered in any neonate with seizures and acyclovir administered.

Metabolic Disturbances. Electrolyte abnormalities are common, yet reversible, causes of neonatal seizures.

Hypoglycemia. Correct immediately with 2 mL/kg of D10 administered intravenously. Neonates may require additional boluses; however, once the hypoglycemia has been corrected, maintenance fluids should contain an IV infusion of dextrose, specifically D10.

Hypocalcemia. Treat with 10% calcium gluconate via IV (100 mg/kg or 1 mL/kg) infused over five to 10 minutes. It is important to monitor the heart rate for bradycardia and the infusion site for infiltration during administration. The clinician can repeat the dose in 10 minutes if no response occurs. It is important to note that calcium chloride can be used as an alternative; however, it is associated with tissue necrosis and extravasation when administered through a peripheral IV line.

Hypomagnesemia. In neonates, 50 to 100 mg/kg/dose of magnesium sulfate can be injected intramuscularly or given intravenously over 10 to 15 minutes. It is important to monitor the patient carefully during administration, as apnea from respiratory muscle paralysis can result from transient hypermagnesemia. Cardiac arrest subsequently can ensue; therefore, it also is important to have calcium gluconate immediately available. The dose of magnesium can be repeated every 12 hours as needed until the serum magnesium levels have returned to normal.

Pyridoxine Dependent Seizures (PDS). Although it occurs rarely, pyridoxine deficiency has been shown to cause intractable, recurrent seizures in neonates. These seizures often are resistant to most antiepileptic medications. However, they do respond to the administration of pyridoxine. If given intravenously in the acute setting, pyridoxine should be administered with close cardiopulmonary monitoring, as it is associated with neonatal apnea. Monitoring the patient with continuous EEG during administration also is recommended. Trial doses of 100 mg IV have been recommended, and can be repeated every five to 15 minutes up to a maximum of 500 mg. In rare cases of PDS, infants who did not respond to pyridoxine have had successful abortion of their seizures with leucovorin.[83]

Antiepileptic Drugs. Phenobarbital is the first-line AED used in the management of neonatal seizures.[66,84-87] The initial dose is 20 mg/kg IV given over 15-20 minutes. If necessary, an additional 10-20 mg/kg IV can be administered in 10 mg/kg aliquots until seizure cessation. It is important to note that sedation, respiratory arrest, and hypotension are potential complications of phenobarbital administration.

Acute treatment also can be initiated with a short-acting benzodiazepine. Other antiseizure drugs that can be given intravenously include levetiracetam, fosphenytoin, and lidocaine. (*See Figure 1.*)

Disposition

Patients in SE usually will need to be admitted to the hospital, often to an intensive care unit. Continuous EEG monitoring should be instituted during the inpatient stay to monitor for seizure activity.

Summary

SE is a condition resulting either from initiation of mechanisms that lead to abnormally prolonged seizures (longer than five minutes), or the failure of the mechanisms responsible for seizure termination. Common causes of SE in children are febrile seizures and metabolic etiologies, such as hyponatremia and hypoglycemia. Ultimately, the goal of therapy is to terminate both the clinical and electrical seizure activity safely and rapidly. This can be accomplished by meeting the three principal treatment priorities: addressing airway, breathing, and circulation; stopping any ongoing seizure activity; and considering reversible causes and initiating the indicated treatment, as well as diagnosing the underlying etiology of the seizure episode.

The mainstay in any emergency is to first assess and maintain adequate airway, breathing, and circulation. Next, providers should obtain parenteral access and administer an appropriate dose of benzodiazepine, or in the case of a neonatal seizure, a dose of phenobarbital. One should simultaneously obtain a history to identify any antecedent illness or intoxication, while assessing for any findings suggestive of sepsis or head trauma. The blood glucose level should be obtained rapidly, and other blood samples sent as indicated. If the seizure persists, the patient can be given a second dose of benzodiazepine, being sure to correct any metabolic derangement and administer antibiotics, if warranted. Providers should be prepared to provide additional respiratory and ventilatory support after the administration of multiple doses of benzodiazepines, as respiratory depression commonly ensues. Second- and third-line treatments for SE include the administration of fosphenytoin, levetiracetam, VPA, or continuous infusions of midazolam, pentobarbital, or propofol.

Once the patient is hemodynamically stable and the clinical seizure activity has been terminated, expert consultation with neurology should be considered, and can guide the decision to obtain additional studies, such as neuroimaging and EEG.

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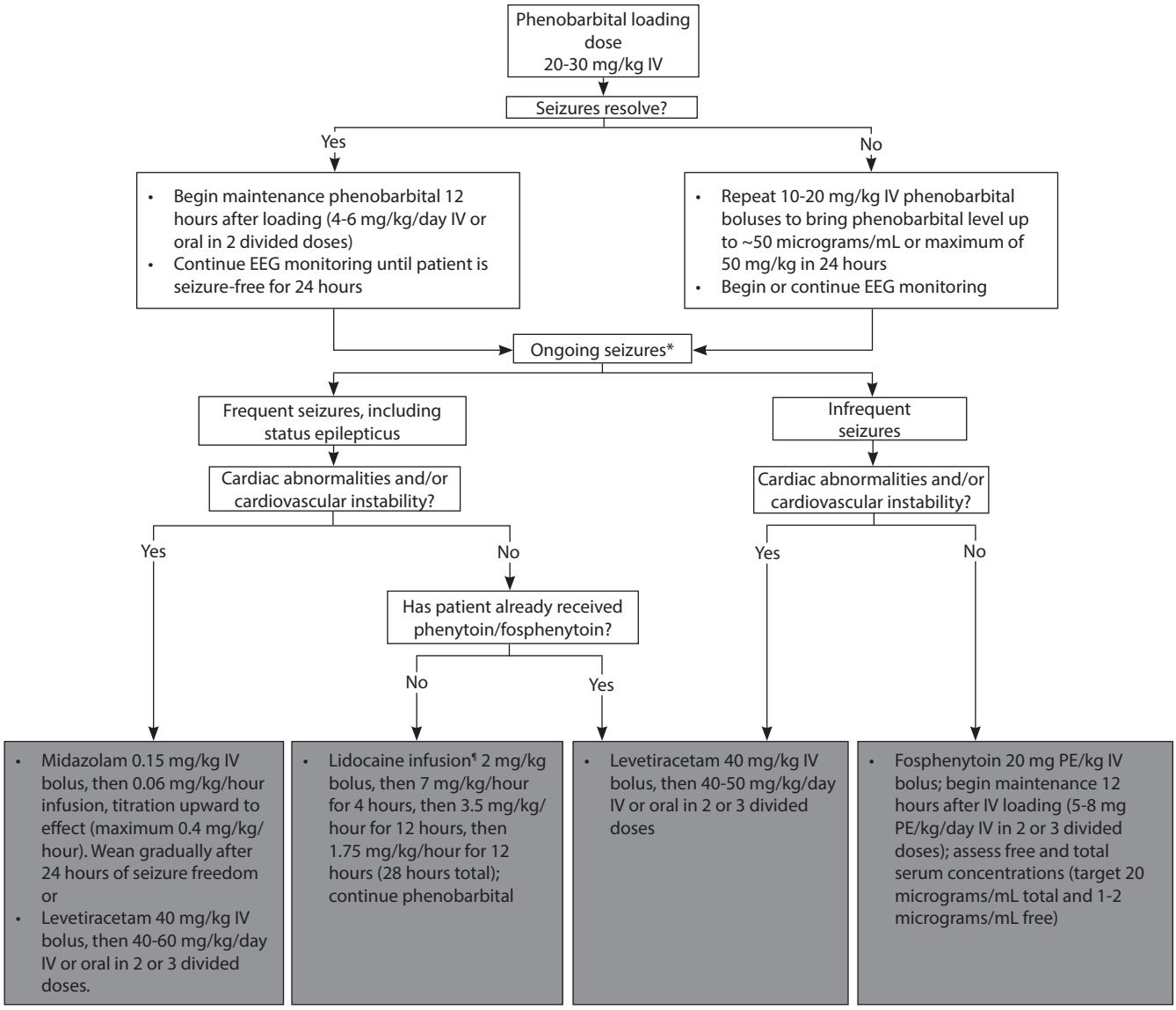
Figure 1. Antiseizure Drug Therapy for Neonatal Seizures



EEG: electroencephalography; IV: intravenous; PE: phenytoin equivalents
* There are limited data on comparative efficacy and best dosing strategies for second-line therapies.
¶ Low body weight (< 2.5 kg) and newborns undergoing hypothermia treatment are at risk for accumulation of lidocaine. Adjust dose for low body weight or if using concurrent therapeutic hypothermia[1]. Refer to accompanying text and separate table of lidocaine dosing for neonatal seizures.
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CME/CE Questions

1. Which of the following is a physiologic cerebral manifestation noted during the initial stage of status epilepticus?
   a. Decreased blood flow
   b. Increased glucose consumption
   c. Decreased carbon dioxide production
   d. Increased oxygen production

2. A 6-year-old presents to the emergency department after having convulsive seizure activity for 20 minutes prior to arrival. What is the first priority in treatment?
   a. Perform neuroimaging.
   b. Obtain a "finger-stick" glucose.
   c. Determine if the patient has missed any doses of antiepileptics.
   d. Establish an adequate airway.

3. What is the best choice for initial management of status epilepticus?
   a. Diazepam 0.05 mg/kg rectally
   b. Lorazepam 0.1 mg/kg intravenously
   c. Levetiracetam 40 mg/kg intramuscularly
   d. Fosphenytoin 20 mg (PE)/kg intravenously

4. A 12-day-old infant presents in status epilepticus. His serum electrolytes as well as computed tomography scan are normal. The seizure activity does not stop after administering multiple doses of antiepileptic medications. Which of the following treatments is the next best step?
   a. Administer IV pyridoxine.
   b. Obtain cerebrospinal fluid studies via lumbar puncture.
   c. Administer hypertonic saline.
   d. Obtain urine toxicology tests.

5. Which of the following are indications for performing emergent neuroimaging in a patient who presents with status epilepticus?
   a. The patient experiences respiratory failure after the administration of benzodiazepines.
   b. The patient has persistent systolic hypertension and tachycardia.
   c. Status epilepticus is the patient's first presentation of epilepsy.
   d. All of the above

6. Neurologic sequelae from status epilepticus are usually caused by the underlying condition rather than the seizures and are associated with all the following except:
   a. Younger age
   b. Nonspecific electroencephalography findings
   c. A long duration of seizure activity
   d. Prior diagnosis of epilepsy

7. A 10-year-old child presents in status epilepticus. The convulsant seizure activity continues for 10 minutes despite the appropriate administration of two doses of lorazepam. The next best step in this patient's management is to:
   a. Administer a bolus infusion of pentobarbital 10 mg/kg IV.
   b. Administer a loading dose of phenobarbitol of 40 mg (PE)/kg IV.
   c. Administer midazolam as continuous infusion of 0.05 to 2 mg/kg/hour.
   d. Administer a bolus infusion of levetiracetam 40 mg/kg IV.

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