Anticonvulsant Medications in the Pediatric Emergency Room and Intensive Care Unit

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Abstract: Seizures are common in pediatric emergency care units, either as the main medical issue or in association with an additional neurological problem. Rapid treatment prolonged and repetitive seizures or status epilepticus is important. Multiple anti-convulsant medications are useful in this setting, and each has various indications and potential adverse effects that must be considered in regard to individual patients. This review discusses new data regarding anticonvulsants that are useful in these settings, including fosphenytoin, valproic acid, levetiracetam, and topiramate. A status epilepticus treatment algorithm is suggested, incorporating changes from traditional algorithms based on these new data. Treatment issues specific to complex medical patients, including patients with brain tumors, renal dysfunction, hepatic dysfunction, transplant, congenital heart disease, and anticoagulation, are also discussed.

Key Words: anticonvulsant medication, intensive care unit, seizure, status epilepticus

TARGET AUDIENCE

This continuing medical education activity is intended for physicians, nurse practitioners and nurses who manage children and adolescents in an emergency department, office practice, or any setting where patients with seizures seek care. Specialists including pediatricians, emergency physicians, family practitioners, neurologists and pediatric emergency physicians will find this information especially useful.

LEARNING OBJECTIVES

After completion of this article, the reader should be able to:

1. Distinguish the clinical characteristics and risks of status epilepticus.
2. Describe the management of children with SE and be familiar with its treatment in children with various chronic diseases.
3. Compare and contrast the properties of newly licensed IV anticonvulsant agents, including fosphenytion, valproic acid, levetiracetam, and topiramate.

Antiseizure medications are commonly used for seizure prophylaxis in children with underlying epilepsy and to treat acute symptomatic seizures, acute repetitive seizures, and status epilepticus (SE). An epileptic seizure has been defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[1] The diagnosis of epilepsy requires at least 1 unprovoked seizure and an enduring predisposition to generate epileptic seizures.[1] Seizures and epilepsy types are initially divided into those with generalized onset and those with partial (focal or localization-related) onset.[2–4] Generalized seizures initially involve the entire cortex, and consciousness is generally lost. Partial seizures begin in 1 portion of the brain with symptoms related to that region's function and may remain restricted to that location without affected alertness (simple partial seizure), spread to involve adjacent regions such that consciousness is affected (complex partial seizures) or may spread widely to involve the entire cortex (secondary generalization). Seizures may occur in an individual with an underlying tendency to have seizures (epilepsy) or may be secondary to an ongoing process that primarily or secondarily affects the central nervous system (acute symptomatic seizures). Especially in the pediatric emergency medicine or critical care setting, the initial evaluation of a patient with a seizure must focus on identifying and treating any underlying condition that may be causing seizures, in addition to terminating any ongoing seizures. Seizures may be isolated events that terminate spontaneously within several minutes, may occur as a group of isolated seizures that occur in close succession but with some recovery between seizures (repetitive seizures), or may be continuous or very frequent seizures without recovery between seizures (SE).[5] Status epilepticus is associated with high morbidity and mortality and requires prompt recognition and management. There have been recent advances including new definitions of SE, new anticonvulsant medications, and new indications for urgent electroencephalography (EEG).

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The authors discuss the unlabeled use and dosing of anticonvulsant medications including phenytoin, fosphenytoin, phenobarbital, levetiracetam, topiramate, valproic acid, and pyridoxine that are not approved by the Food and Drug Administration.

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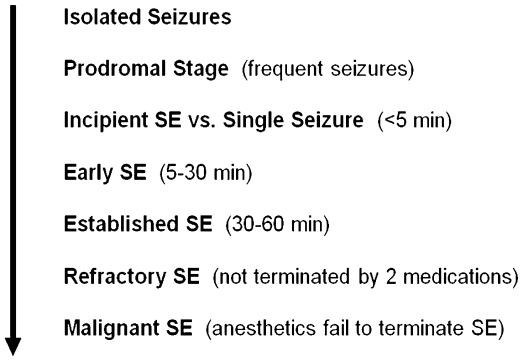

FIGURE 1. Continuum of seizures to status epilepticus.

These issues are discussed, and a strategy for SE management incorporating these new data is presented. In addition, commonly used antiseizure medications are discussed with regard to side effects, drug interactions, and issues related to the care of the medically complex child.

STATUS EPILEPTICUS

New Definitions

At the beginning of any seizure, it is unknown whether it will terminate spontaneously after a few minutes, as occurs with most seizures,[6] or whether it will persist and become SE (Fig. 1). As the seizure persists, care must be escalated. There is increasing recognition that SE is associated with high morbidity and mortality[7] and, as a seizure persists, standard medications are less effective in terminating the seizure.[8–10] This has led to shortening of the minimum seizure duration to diagnose SE from 30 minutes to 5 minutes.[11] To better describe this period, it is divided into incipient SE (less than 5 minutes and may still be an isolated seizure), early SE (5–30 minutes), and established SE (30–60 minutes).[12] In some children with SE, seizures persist despite treatment with adequate doses of 2 or 3 anticonvulsant medications and this constitutes refractory SE (RSE). The exact definition of RSE is still unclear, with different studies defining RSE with varying durations (no time criteria, 30 minutes, 1 hour, 2 hours) and lack of response to different numbers (2 or 3) and types of medications.

When benzodiazepines do not terminate SE, many children develop RSE.[8,9,13] Studies in children have indicated that SE lasted more than 1 hour in 26% to 45%,[14,15] longer than 2 hours in 17% to 25%,[15,16] and longer than 4 hours in 10%.[15] In a recent prospective population-based study of children with SE that led to emergency department presentation, the incidence of SE lasting longer than 60 minutes was higher than the incidence of SE lasting less than 60 minutes across all ages and etiologies.[17] Refractory SE is associated with high morbidity and mortality.[9,18,19] In a subgroup of patients, RSE may last for weeks to months, despite treatment with multiple anticonvulsant and coma-inducing medications. This lengthy course was reported in 20% of adults with RSE[20] and has been referred to as malignant RSE,[20] de-novo cryptogenic refractory multifocal febrile SE,[21] or new-onset RSE.[22] Malignant RSE is associated with an encephalitic etiology, younger age, previous good health, and high morbidity and mortality.[20–22] Similar cases have been described in children.[23] It remains unclear whether this represents a specific disease entity or a just a particularly severe variant of RSE because of certain etiologies.

Convulsive and Nonconvulsive SE

Status epilepticus is not a single entity, but can be divided into subtypes. Status epilepticus may be convulsive, in which clear seizure activity is visible. The most commonly recognized type is tonic-clonic convulsive SE, which may be primarily or secondarily generalized. Convulsive SE may also be focal (partial or localization related) SE, including focal motor or sensory seizures with retained awareness, or focal seizures in which consciousness is altered producing an epileptic encephalopathy that may be referred to as an epileptic twilight or epileptic confusional state, that is sometimes associated with minor motor manifestations. Absence SE, also called spike wave stupor, can also mimic complex partial SE clinically, although the EEG patterns are quite different. Status epilepticus that is purely tonic, clonic, or myoclonic more often occurs in children with pre-existing encephalopathy. Myoclonic SE, in which myoclonic seizures have an EEG correlate and may be treated with anticonvulsant medications, must be differentiated from non-epileptic myoclonus, in which there is no EEG correlate, and the abnormal movement is generally symptomatic of a severe underlying encephalopathy.

Status epilepticus may also be non-convulsive (NCSE). Nonconvulsive status epilepticus denotes nearly continuous electrographic seizures without convulsive activity, manifesting as altered mental status or coma.[24] Because there are no clinical manifestations, EEG is required for diagnosis and management, and this may lead to a delay in diagnosis. In 1 study, 16% of patients were in NCSE for more than 24 hours before the diagnosis was established.[25] Studies have revealed NCSE in 23% to 34% of children who underwent long-term EEG monitoring in pediatric intensive care unit (PICU) or emergency departments.[26–29] Nonconvulsive status epilepticus occurs after convulsive SE in 20% to 26% of children,[27,30] after convulsive seizures in 60% of children, and with no proceeding convulsions in 10% to 20% of children.[27,30] There is a high incidence of NCSE across a wide range of ages and etiologies.[26–30] Many children with NCSE are not identified by a standard 30-minute EEG recording, but most are detected within 24 hours by long-term EEG monitoring, although rare outliers require several days of long-term EEG monitoring.[28,30] Detecting NCSE is important so that appropriate treatment can be initiated. Studies have suggested that continuous electrographic discharges, even without clinical seizures, can be harmful, as evidenced by elevated serum neuron-specific enolase, a putative marker of neuronal injury.[31] A study in adults indicated that duration of NCSE and time to detection predict outcome in patients with NCSE. Mortality was 36% when NCSE was diagnosed within 30 minutes of onset and 75% when diagnosis was delayed for over 24 hours. When NCSE lasted less than 10 hours, 60% of patients returned home. In contrast, when NCSE lasted more than 20 hours, none returned home and

85% died.[25] One mechanism underlying the worse outcome may be that nonconvulsive seizures result in elevated intracranial pressure and metabolic dysfunction. A recent study in adults with traumatic brain injury (TBI) undergoing continuous EEG monitoring demonstrated that patients with nonconvulsive seizures had higher intracranial pressure and higher lactate to pyruvate ratios than those without nonconvulsive seizures, and in patients with nonconvulsive seizures, the intracranial pressure and lactate to pyruvate ratios were higher during seizures than between seizures.[32] In adults with intracerebral hemorrhage, nonconvulsive seizures have been associated with hemorrhage expansion,[33] although a causal relationship has not been established. Studies in neonates have demonstrated an association between neonatal seizures, especially more prolonged and harder to control seizures, and poor outcome, although the associations between etiology, seizures, and outcome remains unclear.[34] One study demonstrated an association between seizures and death related to neurologic instability and that higher numbers of electrographic seizures are associated with higher morbidity including microcephaly, cerebral palsy, and failure to thrive.[35] A study demonstrated that infants with less than 14 electrographic seizures were normal at follow up, whereas several with more than 14 were delayed on follow up.[36] In a study of preterm and term neonates, those with SE had a significantly higher incidence of neurologic sequelae than those with only repetitive seizures.[37] In an outcome study of 82 neonates with seizures, outcome was worse in those when multiple medications were needed to treat the seizures.[38] Although non-convulsive seizures and NCSE have been associated with elevated markers of neuron injury and worse outcome, studies have not yet investigated whether treatment improves outcome.

With increasing recognition that nonconvulsive seizures are common and associated with worse outcome, there is an increasing need for EEG monitoring techniques that allow real-time bedside interpretation of EEG. However, at most hospitals, many more critically ill patients are at risk for nonconvulsive seizures than those that can be monitored given the required EEG equipment, technologists, and neurophysiologists. More automated seizure detection methods are required, and these must allow for real-time management.[39] To date, although there is no perfect seizure detector, methods such as synchronization ratios,[40] envelope trend analysis,[41] and hairline EEG[42] may be used. Furthermore, many of the EEG patterns recorded in critically ill patients are quite different than traditional EEG patterns.[43,44] Many epileptiform patterns occur which do not meet criteria for seizures but may affect prognosis. Categorization of these patterns is underway,[45] but it remains unclear which of these patterns affect prognosis and require treatment.[46]

New Pathophysiological Understanding

Most seizures terminate spontaneously within several minutes,[6] possibly because of γ-aminobutyric acid (GABA) mediated inhibition of neurotransmission that occurs in response to seizures. However, with continuing seizures, inhibitory GABA receptors are internalized in clathrin-coated endocytic vesicles, some of which are recycled to the plasma membrane and some of which are destroyed in lysosomes within the neuron. At the same time, excitatory *N*-methyl-D-aspartate receptors may be mobilized to the plasma membrane. This receptor trafficking results in decreased inhibitory control and increased excitation of neurotransmission that may lead to continuing SE. Alterations in neuropeptide and other gene expression over hours may also contribute to sustained SE.[47] The internalization of GABA receptors may explain the clinical findings that benzodiazepines, which work via GABA-mediated mechanisms, are less effective as seizure duration increases[8–10] and may suggest a role for *N*-methyl-D-aspartate-modulating medications like ketamine, although further research is needed.

Importance of Rapid Treatment

There is increasing evidence that the longer SE persists, the more resistant it is to treatment with current anticonvulsant medications. In 157 children with SE, a treatment delay of more than 30 minutes was associated with delayed seizure control.[8] In a study of 27 children, first- (benzodiazepine) and second-line (phenytoin or phenobarbital) medications were effective in terminating SE in 86% when seizure duration was less than 20 minutes at presentation and only 15% when seizure duration exceeded 30 minutes.[9] In a retrospective study of 358 children with SE who received midazolam, treatment effectiveness decreased as the time to treatment increased. Efficacy was significantly lower when treatment was initiated more than 3 hours after seizure onset, and there was a trend toward reduced efficacy even at 1 hour, especially when the etiology was epilepsy and not acute symptomatic seizure.[10] In adults, SE lasting more than 30 minutes is associated with a 10-fold greater mortality than when duration is 10 to 29 minutes.[7] Together, these studies suggest that seizures must be treated quickly before they become resistant to treatment and are associated with higher mortality.

NEWER ANTICONVULSANT MEDICATIONS AND FORMULATIONS

Fosphenytoin

Phenytoin is a traditional anticonvulsant used to treat SE and acute repetitive seizures and is often used for seizure prophylaxis in the PICU. Phenytoin causes a use-dependent inhibition in action potential firing by stabilizing the inactive form of sodium channels in the neuron.[48] After intravenous (IV) administration, it reaches peak brain levels in about 15 minutes. Precipitation may occur in the IV line, so it should be administered directly into the vein or into an IV line close to the venous access point. Keeping phenytoin in solution requires alkaline pH and high concentration of the solvent propylene glycol. This combination may cause metabolic acidosis and infiltration may cause irritation and tissue destruction or in rare cases, purple glove syndrome (edema, pain, discoloration at the infusion site).[49] Intramuscular (IM) administration is not possible because of muscle destruction and unpredictable absorption.[50] In addition, IV phenytoin infusion may result in hypotension or cardiac arrhythmias, especially in children with pre-existing cardiac disease.

Thus, ECG and blood pressure must be monitored before, during, and after the infusion.

In terms of monitoring serum phenytoin levels, free phenytoin levels are generally more reliable than total phenytoin levels. A retrospective study of critically ill children demonstrated that 10% of children had free levels in the toxic range, although total levels were low. Free fractions were especially elevated in children with low albumin or with coadministration of valproic acid or cefazolin.[51] It may be reasonable to follow free levels or, if following total levels, to occasionally check both to be sure there is a reasonable correlation.

Fosphenytoin, the disodium phosphate ester of phenytoin, is a prodrug of phenytoin that can be administered intravenously. Unlike phenytoin, it is freely soluble in aqueous solutions and is less likely to result in tissue injury if there is IV infiltration. It can also be administered by the IM route. Upon administration, fosphenytoin is converted by phosphatases to phenytoin. The half-life of this reaction is 8 to 15 minutes. However, the concentration of free phenytoin, which is the active portion that enters the brain, increases more rapidly, because before being hydrolyzed, fosphenytoin displaces phenytoin from protein-binding sites. Intravenous fosphenytoin may be administered more rapidly than phenytoin (maximum of 150 mg fosphenytoin/min or 3 mg/kg/min in children vs 50 mg phenytoin/min in adults or 1 mg/kg/min in children) and thus, despite the need for conversion from the prodrug, it is expected to reach therapeutic concentrations in the brain in the same amount of time as phenytoin, which is about 15 minutes. With IM administration, the dosing of fosphenytoin is the same. A study in adults demonstrated that after IM injection of fosphenytoin, serum concentrations of 10 μg/mL were obtained in 26% after 10 minutes and half in 30 min.[52] Injection site reactions are uncommon, and no serious events have been reported to date.[52,53] Fosphenytoin is prescribed in equimolar amounts of phenytoin called phenytoin equivalents and thus the dosing may be considered in the same manner as traditional phenytoin dosing, with initial loading doses of about 25 mg phenytoin equivalent/kg.

Fosphenytoin IV infusion causes fewer infusion-related adverse reactions than phenytoin. Hypotension is less common, but is reported to occur after the infusion is completed. Although fosphenytoin is less likely than phenytoin to cause cardiac arrhythmias, there are rare reported cases. A recent review of the Food and Drug Administration adverse event reporting system from 1997 to 2002 identified 29 adverse cardiac events and 10 deaths related to fosphenytoin administration. These included children with cardiac arrest, atrioventricular block, and bradycardia.[54] It is less likely to cause infusion site irritation, and no reports of purple glove syndrome have been reported to date.[55] Fosphenytoin was reported to cause hyperphosphatemia in a child with end-stage renal disease.[56]

Aside from infusion issues, the adverse effects of fosphenytoin are the same as phenytoin. These include antiepileptic drug hypersensitivity syndrome which consists of rash, fever, lymphadenopathy, and sometimes visceral organ involvement (especially hepatic and renal) and is estimated to occur with 1 in 3000 exposures. There is cross-reactivity between phenytoin/fosphenytoin and phenobarbital, primidone, and carbamazepine. Idiosyncratic reactions may also occur in isolation, including rashes (maculopapular exanthem, Stevens-Johnson syndrome, generalized exfoliative dermatitis, toxic epidermal necrolysis), fever, serum sickness, hepatic and renal dysfunction (including hepatitis), blood dyscrasias (thrombocytopenia, agranulocytosis, anemia), polymyositis, and pseudolymphoma. Dose-related side effects include nystagmus (total level 15–25 mg/L), and ataxia and mental status change (total level >30 mg/L). Movement disorders including bradykinesia and choreoathetosis may rarely occur. Long-term effects of phenytoin include gingival hyperplasia, hirsutism, reduced vitamin D levels and bone demineralization, cerebellar atrophy, and rarely phenytoin-induced encephalopathy and dementia.[57]

As fosphenytoin is rapidly converted to phenytoin, it has the same pharmacokinetic disadvantages as phenytoin, many of which are especially problematic in the pediatric emergency department or PICU. These include nonlinear (zero order) kinetics (as the dose increases elimination mechanisms are saturated leading to progressive accumulation of phenytoin), high protein binding (90%), hepatic induction, and frequent drug interactions. Phenytoin is a potent inducer of the hepatic cytochrome P450 drug metabolizing system and thus reduces levels of other antiepileptic medications metabolized by this system (benzodiazepines, barbiturates, valproic acid, carbamazepine, topiramate, lamotrigine, felbamate) in addition to steroids, oral contraceptive medications, antiarrhythmic medications, antiviral protease inhibitors, β-blockers, calcium-channel blockers, digoxin, coumadin, chloramphenicol, vitamin D, folic acid, vitamin K, and some chemotherapy agents. Phenytoin levels may increase when co-administered with aspirin, leucovorin, methotrexate, rifampin, and cisplatin. Co-administration of barbiturates and phenytoin may be quite difficult because each is affected by the other and often frequent monitoring of levels is required. One study suggested that children with febrile illnesses may have a 50% reduction in phenytoin levels for unclear reasons.[58] In renal disease such as nephrotic syndrome, protein binding may be reduced leading to large increases in unbound phenytoin and the unbound fraction of phenytoin may be reduced with dialysis. Hepatic disease may reduce serum protein levels leading to an increase in free phenytoin and may also reduce metabolism of phenytoin. Other conditions resulting in hypoalbuminemia include severe malnutrition, burns, and pregnancy-free phenytoin levels must be followed in these patients.

Although phenytoin and fosphenytoin are effective in treating most types of SE, it may be ineffective in treating SE related to generalized epilepsy, such as absence status (spike wave stupor) and myoclonic SE.

Valproic Acid

Valproic acid is effective against both partial and generalized seizures, a broad spectrum anticonvulsant. It is a mainstay of outpatient epilepsy treatment and is often considered as a first-line medication for generalized epilepsy. Valproic acid has high protein binding (70–93%). Valproic acid inhibits hepatic P450 enzymes and thus leads to increased levels of many anticonvulsants (phenytoin,

barbiturates, benzodiazepines), free warfarin, and nimodipine. Valproic acid is thought to modulate sodium channels such that high-frequency repetitive firing is blocked and also increases inhibitory GABA transmission[48] in the neuron. It is available in an IV formulation. Although the package prescribing information recommends administering valproic acid over 60 minutes at less than 20 mg/min, studies have demonstrated that more rapid infusion is safe in adults and children. A recent study of 40 adults with epilepsy (but not actively seizing) administered a faster infusion (6–10 mg/kg/min) demonstrated that infusion site pain, burning, and paresthesias were common (occurred in 81%) but these only lasted several minutes and were not associated with signs of redness, irritation, or phlebitis. There were no changes in vital signs or in the level of consciousness.[59] A study of 18 children reported that when valproic acid was administered intravenously at 1.5 to 11 mg/kg/min, there was no severe infusion site complications, but that 1 child experienced burning pain at the infusion site. There were no vital sign changes reported.[60]

Several studies have reported that valproic acid is highly effective in 78% to 100% of children with RSE with no adverse effects.[61,62] One study of 18 children used an IV loading dose of 25 mg/kg at an average infusion rate of 2.8 mg/kg/min and reported 100% seizure termination within 30 minutes with no adverse reactions.[61] A second study in which 41 children were loaded with 20 to 40 mg/kg IV over 1 to 5 minutes and then infused with 5 mg/kg/h reported that 78% had termination of clinical and EEG seizures, with 66% achieving control within 6 minutes. There were no adverse effects.[62] However, there are other case reports of hypotension with IV valproic acid infusion (30 mg/kg over 1 hour) for SE.[63] Valproic acid may also induce encephalopathy with or without elevated ammonia levels, and this must be considered in patients with persisting encephalopathy.

Valproic acid rarely causes hepatotoxicity, but risk factors include young age (especially less than 2–3 years), anticonvulsant polypharmacy, and metabolic disease. The estimated risk in children receiving poly-pharmacy is 1 in 600 children less than 3 years, 1 in 8000 from 3 to 10 years, and 1 in 10,000 for children 11 to 20 years.[64] This generally occurred after 2 to 3 months of treatment and has not been reported after a first loading dose. A recent practice parameter on SE in children noted that data from 9 class III studies revealed that an inborn error of metabolism was diagnosed in 4.2% of children with SE when metabolic testing was performed.[65] Valproic acid often causes a mild elevation in liver enzymes, and severe hepatotoxicity is not usually preceded by a progressive increase in liver enzymes, suggesting the effect is idiopathic and not preventable by laboratory monitoring. Administration of L-carnitine may improve survival in patients with severe valproate-induced hepatotoxicity,[66] and it is recommended that L-carnitine be supplemented in children with multiple risk factors (which commonly includes many children in the PICU) and younger children.[67]

Levetiracetam

Levetiracetam is a second generation anticonvulsant medication considered to be effective in a broad spectrum of seizure types. It is rapidly absorbed from the gastrointestinal tract (peak levels within 1 hour) or can be administered intravenously. In adults, IV infusion and oral tablets are bioequivalent,[68,69] and IV infusion is well tolerated.[68] Bioavailability is 100%, and absorption is not affected by food. It is only about 10% protein bound. Levetiracetam exhibits linear pharmacokinetics. Elimination is via renal excretion. There is no liver metabolism and so it neither affects nor is affected by other medications affecting the hepatic cytochrome P450 system.[70] Given that children with SE often have associated systemic disorders such as coagulopathy, liver failure, and hypotension that could be complicated by traditional anticonvulsants, levetiracetam may have an increasing role in the management of critically ill children with seizures and SE in the emergency department and intensive care unit, although further pediatric studies are warranted.

Levetiracetam is thought to have multiple sites of action including inhibition of calcium dependent neurotransmitter release and GABA modulation (via a negative allosteric modulator).[48] Recent animal studies have demonstrated that levetiracetam treatment during the maintenance phase of SE diminished or aborted seizures,[71] is neuroprotective in culture[72] and in animals experiencing SE,[73] and may reduce the epileptogenic effects of SE.[74]

Levetiractem is available as oral (tablet and liquid) and IV formulations, although the IV form is not approved for use in children (see below). Dosing must be adjusted with renal dysfunction. It may cause sedation, especially when initiated at high doses. Increased aggression and rarely psychosis are reported with use in the outpatient setting. This is not clearly dose-dependent and is reversible upon discontinuation of the medication. In outpatient studies, small decreases in red blood cell and white blood cell counts were noted, but these did not require medication discontinuation and were not associated with infection. A large retrospective study in adults suggests levetiracetam is safe in critically ill patients and that levetiracetam monotherapy was associated with fewer complications compared with other anticonvulsants (primarily phenytoin).[75]

A study of 6 patients with RSE (mostly adults but 1 adolescent with static encephalopathy), indicated that nasogastric doses of 500 to 3000 mg/d controlled seizures within 12 to 96 hours with no noted adverse effects.[76] In 8 adults with NCSE, there was cessation of ictal EEG activity and clinical symptoms of NCSE after initiation of levetiracetam within 3 days without side effects.[77] A study of 23 adults (39% with RSE) receiving nasogastric levetiracetam at a median dose of 2000 mg (range 750–9000 mg) revealed that 43% responded (SE resolved within 72 hours of the start of or an increase in levetiracetam administration, without recurrence of seizures longer than 10 seconds or more frequent than 2 per hour). All responders received levetiracetam within 4 days of SE onset and were administered doses of less than 3000 mg daily. These data suggest that levetiracetam may be efficacious when administered early and that high doses are unlikely to provide benefit in adults.[78]

Although pediatric data are lacking, and IV levetiracetam is not currently approved for use in children, our pediatric neurology epilepsy specialists, with parental consent,

have begun to study IV levetiracetam administration and have used it in 6 children in RSE, achieved expected serum levels, noted no adverse events, and noted termination or temporary reduction in seizures. A 9-year-old patient with refractory epilepsy developed NCSE that resolved with a 2-week titration of levetiracetam from 10 mg/kg/d to 40 mg/kg/d.[79] However, with this long titration, the seizure may have terminated spontaneously. Further pediatric studies are needed to determine the role of levetiracetam in RSE.

Older anticonvulsants with enzyme induction are known to increase the hepatic clearance of chemotherapy medications and are associated with reduced survival (see section on Brain Tumors below).[80,81] Although further studies are warranted, levetiracetam (which does not induce hepatic metabolism) may be a good medication for children receiving chemotherapy who require anticonvulsants.

Topiramate

Topiramate is a second-generation anticonvulsant considered to be effective in a broad spectrum of seizure types. It has rapid absorption from the gastrointestinal tract (90% maximal plasma concentration achieved within 2 hours), 80% bioavailability, and absorption is not affected by food. It is only 9% to 17% bound to plasma proteins. Topiramate exhibits linear pharmacokinetics. Elimination is primarily via renal excretion. It is not extensively metabolized in the liver, although it has been reported to cause some elevation in phenytoin levels, presumably via an effect on the P450 isozyme CYP2C19. It does not have important effects on the levels of other anticonvulsant medications. Topiramate levels may be increased when enzyme inhibitors like valproic acid are administered and reduced when enzyme inducers like phenytoin or barbiturates are administered. There are reports that topiramate administration results in slight reductions in digoxin, lithium, and amitryptiline levels and slightly increase metformin levels.[82]

Topiramate has several mechanisms of action including blockage of voltage-sensitive sodium and calcium channels, enhancement of GABA activity, and modulation of glutamate receptors via interaction with kainate and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors.[48] Because it has mechanisms independent of GABA modulation, topiramate may be effective later in RSE once GABA receptors have been targeted by other anticonvulsant drugs and may have internalized. Furthermore, animal models have also suggested that topiramate may be neuroprotective and antiepileptic.[83–85]

In children, topiramate has been reported to be effective in controlling seizures such that coma-inducing medications to treat RSE could be weaned using various dosing regimens.[87–89] Some protocols have slowly titrated the medication resulting in seizure control in 3 to 6 days,[87,89] whereas others started at a higher dose which resulted in seizure control within 1 day[88] without noted side effects. Three adult reports totaling 10 patients, including 5 without prior epilepsy, have described control of RSE with nasogastric topiramate at doses of 300 to 1600 mg/d.[90–92] Although topiramate has not been shown to be useful in initial SE management, these studies suggest it may be a useful additional medication once patients have been treated with coma-induction agents for RSE. Studies have shown safety of rapid dose escalation in children being treated for infantile spasms.[86]

Topiramate is not available in an IV formulation. It is available as tablets which can be crushed for use with feeding tubes. It is also available as sprinkle capsules, but these may plug feeding tubes. Dosing must be adjusted with renal dysfunction. Common side effects include lethargy and ataxia. Topiramate is a carbonic anhydrase inhibitor and may result in metabolic acidosis by preventing bicarbonate formation. Predisposed patients include those with renal disease, severe respiratory disorders, diarrhea, or those on the ketogenic diet. Measurement of baseline and periodic bicarbonate levels is indicated. Nephrolithiasis may occur with topiramate, especially when used in combination with acetazolamide, zonisamide, or the ketogenic diet. Rare adverse reactions include pancreatitis, acute angle closure glaucoma, and oligohydrosis with resulting hyperthermia. Reversible hyper-ammonemic encephalopathy has been reported with concurrent valproic acid administration.

SE MANAGEMENT

Several principles guide medication choices for SE. Ideal medications can be administered rapidly and penetrate the brain quickly and should not cause systemic side effects. Employing medications with different mechanisms of action at successive steps may be useful, although to date this type of rational "poly-therapy" has not been demonstrated to be more effective. Importantly, in addition to the pediatric neurologist, a multidisciplinary team effort involving, but not limited to, pediatric emergency and critical care specialists are necessary for general supportive care, such as attending to the airway, breathing, circulation, treat underlying causes, and to prevent and treat systemic complications. Hypoglycemia, hyponatremia, hypocalcemia, and hypomagnesemia can all result in seizures and require specific therapy. A recently developed evidence-based guideline for the management of children with decreased level of consciousness that is available online recommends that hypoglycemia be treated with 5 mL/kg IV bolus of 10% glucose, hyponatremia be treated with 5 mL/kg infusion of 3% saline IV over 1 hour, hypocalcemia be treated with 0.3 mL/kg of 10% calcium gluconate IV over 5 minutes, and hypomagnesemia be treated with 50 mg/kg of magnesium sulfate IV over 1 hour.[93] A study of children with hyponatremia (serum sodium concentrations less than 125 mmol/L) and seizures demonstrated that anticonvulsants were generally ineffective in terminating seizures but IV administration of 4 to 6 mL/kg bolus of 3% saline was safe and effective in terminating seizures.[94]

There is clear evidence that earlier treatment of SE is beneficial and that out of hospital treatment is safe and effective. Treatment may begin before arriving at the hospital with IM midazolam,[95,96] buccal midazolam,[97–100] intranasal midazolam,[101–103] or rectal diazepam.[104–107] Some of these studies have suggested midazolam is superior to diazepam.[96,97,99,102,103] For children with prior prolonged seizures or SE, a home plan should be developed that takes into account the seizure history, distance to medical care, and the medical sophistication of the family. It should include

TABLE 1. Convulsive SE Algorithm

Stage	Management
Impending SE <5 minutes	Out-of-hospital
	Consider IM midazolam (0.2 mg/kg to maximum 10 mg) or buccal midazolam (0.5 mg/kg to maximum of 10 mg) or rectal diazepam (0.2–0.5 mg/kg to maximum of 20 mg)
	Benzodiazepines
	Lorazepam 0.1 mg/kg IV (max 5 mg) over 1 min
	Diazepam 0.2 mg/kg IV (max 10 mg) over 1 min
	Allow 5 minutes to determine whether seizure terminates.
	Give oxygen. Support airway, breathing, and circulation. Obtain IV access. Check bedside glucose. Continue ECG and vital sign monitoring. Continue neurologic assessments.
Established SE 5–10 min	Repeat benzodiazepine administration.
	Do not wait for seizure termination.
	Administer fosphenytoin 30 mg/kg IV at 2–3 mg/kg/min (max 150 mg/min)
	[or phenytoin 30 mg/kg IV at 1 mg/kg/min (max 50 mg/min)]
	If <2 yr, consider pyridoxine 100 mg IV push.
	Administer bolus of 2 mL/kg IV 50% glucose if hypoglycemic.
	Consider thiamine 100 mg IV first.
	Testing:
	Bedside glucose / Complete blood cell count / Cultures
	BMP, Mg, Phos / LFT / Toxicology (serum, urine)
	AED levels / PT, PTT / Head CT
	Other tests, as clinically indicated
	Draw phenytoin level (10 minutes after infusion)
	Support airway, breathing, and circulation. Continuous vital sign and ECG monitoring. Continue neurologic assessments.
	Consult pediatric neurology service.
Initial RSE	If seizure continues 10 minutes after fosphenytoin infusion then patient has RSE regardless of time elapsed.
	Administer third line medication: Levetiracetam 20–30 mg/kg IV at 5 mg/kg/min (max 3g) or Valproate 20 mg/kg IV at 5 mg/kg/min (if no specific concern for liver or metabolic disease)
Later RSE	If seizure continues 5 minutes after levetiracetam or valproate, administer phenobarbital 30 mg/kg IV at 2 mg/kg/min (max rate 60 mg/min).
	Admit to PICU. Continue to support airway, breathing, and circulation. Obtain central venous access and continuous hemodynamic monitoring through arterial line.
	Once clinical seizure terminates will likely need EEG monitoring to assess for subclinical seizures.
Coma Induction	If seizure continues 10 minutes after completion of phenobarbital infusion, then initiate coma with IV midazolam 0.2 mg/kg bolus (max 10 mg) over 2 minutes and then initiate infusion at 0.1 mg/kg/hr.
	If clinical seizures persist 5 minutes after initial midazolam bolus then administer additional midazolam bolus of 0.2 mg/kg bolus. Continue infusion.
	If clinical seizures persist after another 5 minutes, then administer another midazolam bolus of 0.2 mg/kg and increase infusion to 0.2 mg/kg/h. Repeat as needed.
	If seizure persist at maximum midazolam (generally 2 mg/kg/h) or midazolam infusion is not tolerated, then consider transition to isoflurane. In addition, consider IV pentobarbital, NG topiramate, NG or IV valproic acid or NG or IV levetiracetam.
Coma Phase	Continue pharmacologic coma for 24 hours after last seizure with EEG goal of burst-suppression.
	Continue EEG monitoring.
	Continue initial medications (total phenytoin goal level 20–30 μg/mL, phenobarbital goal level 40–50 μg/mL). Daily phenobarbital and free and total dilantin levels.
	Continue levetiracetam at 40–80 mg/kg IV divided Q8 or Q12 (max 3 g).
Weaning Phase	Reduce midazolam by 0.05 mg/kg/hr every 3 hours with frequent EEG review. If no clinical or electrographic seizures then wean until off.
	Continue EEG for at least 24 hours after end of infusion to evaluate for recurrent electrographic seizures.

BMP indicates basic metabolic panel; LFT, liver function test; AED, anti-epileptic drug; PT, prothrombintine; PTT, partial thromboplastin time; NG, nasogastric.

TABLE 2. Interactions of Antiepileptic Drugs Commonly Used in the PICU

Antiepileptic Drug	Hepatic Enzyme Effect	Effect on Other Antiepileptic Drugs.	Effect on Other Drugs	Other
Levetiracetam	None	None	None	None
Phenobarbital	Induces CYP 1A2, 2B6, 2C, 3A4 and EH and UGT	Enzyme induction results in reduced levels of phenobarbital, phenytoin, carbamazepine, valproate, lamotrigine, tiagabine topiramate, and zonisamide.	Enzyme induction results in reduced levels of acetaminophen, chloramphenicol, cyclophosphamide, cyclosporine, dexamethasone, doxycycline, felodipine, fluconazole, folic acid, furosemide, itraconazole, ketoconazole, methadone, meperidine, methotrexate, methylprednisolone, nifedipine, nimodipine, prednisolone, theophylline, verapamil, and warfarin.	Use with cefotaxime results in higher incidence of exanthematous skin rashes. Level reduced with chloramphenicol and activated charcoal. Reduces levels of many chemotherapeutics and free/total thyroxine.
Phenytoin/ Fosphenytoin	Induces CYP 1A2, 2B6, 2C, 3A4 and EH and UGT	Enzyme induction results in reduced levels of phenobarbital, phenytoin, carbamazepine, valproate, lamotrigine, tiagabine topiramate, and zonisamide.	Enzyme induction results in reduced levels of acetaminophen, chloramphenicol, cyclophosphamide, cyclosporine, dexamethasone, doxycycline, felodipine, fluconazole, folic acid, furosemide, itraconazole, ketoconazole, methadone, meperidine, methotrexate, methylprednisolone, nifedipine, nimodipine, prednisolone, theophylline, verapamil, and warfarin.	Levels decreased with activated charcoal, acyclovir, antacids, and rifampin. Levels increased with amiodarone, diltiazem, chloramphenicol, cimetidine, disulfiram, fluconazole, isoniazid, miconazole, omeprazole, propoxyphene, and ticlopidine. Unpredictable pharmacokinetics with warfarin. Reduces levels of many chemotherapeutics.
Valproate	Inhibits CYP2C9 and EH and UGT	Enzyme inhibition results in increased phenytoin, phenobarbital, lamotrigine, and carbamazepine levels. Protein binding leads to increased free phenytoin levels.	Reduces zidovudine.	Levels increased by cimetidine and isoniazid. Levels reduced by methotrexate, rifampin, meropenem.

CYP indicates cytochrome P450; EP, epoxide hydroxylase; UGT, UDP-glycosyltransferase.

appropriate medications that can be administered by parents or caretakers and education must be provided regarding the appropriate use of the medication.[108]

In our institution, our neurology specialists have recently adopted the SE algorithm that is shown in Table 1. During the impending and established SE phases, the initial medications should be given rapidly and in close succession, allowing 5 minutes between benzodiazepine doses and 10 minutes after fosphenytoin administration is completed to judge response. We use a single large dose of fosphenytoin rather than repeated smaller doses to allow for more rapid intervention. Fosphenytoin was chosen as the second antiseizure medication because phenobarbital's main mechanism of action, GABA enhancement, is similar to the mechanism of action of benzodiazepines whereas fosphenytoin acts on voltage-gated sodium channels. In addition, phenobarbital is more likely to lead to respiratory and cardiovascular compromise. However, there are no studies directly comparing fosphenytoin and phenobarbital as a second-line medication.

If seizures persist after adequate doses of a benzodiazepine and fosphenytoin, then RSE is diagnosed. We define RSE as a seizure of any type (convulsive, subtle, or solely electrographic) that continues despite treatment with adequate doses of a benzodiazepine and fosphenytoin. We define treatment efficacy as termination of all seizures (convulsive and electrographic) within 30 minutes without seizure recurrence for 24 hours.

Children who are diagnosed with RSE need rapid treatment, but initiation of coma-inducing medications are clearly associated with a high incidence of systemic side

TABLE 3. General Issues Related to Antiepileptic Drugs Commonly Used in the PICU

Antiepileptic Drug	Phamacokinetic Impact on Other AEDS	Pharmacokinetic Impact on Other Drugs	Use in Renal Dysfunction	Use in Hepatic Dysfunction	Other	Possible Contraindications	Main Side Effects
Levetiracetam	None	None	Dose adjustment	No effect			Behavior change including aggression or psychosis
Phenobarbital	Common	Common	No dose adjustment	Variable effect	Hepatic enzyme inducer	Severe liver dysfunction	Respiratory depression, sedation, hepatotoxicity, hypotension (especially when given with benzodiazepines), skin rash (including Stevens-Johnson), and blood dyscrasias
Phenytoin/ Fosphenytoin	Common	Common	No dose adjustment	Variable effect	Hepatic enzyme inducer High protein binding	Heart block	With phenytoin and fosphenytoin: Hepatotoxicity, pancytopenia, and skin rash (including Stevens-Johnson)
					Phenytoin cannot be mixed with glucose/dextrose due to precipitation and should not be given in small peripheral veins		Less common with fosphenytoin: Cardiac arrhythmias, hypotension, phlebitis, soft tissue injury from extravasation, purple glove syndrome
Valproate	Common	Common	No dose adjustment	Caution and may be contraindicated.	Hepatic enzyme inhibitor High protein binding	Severe liver dysfunction, thrombocytopenia, active bleeding	Hepatotoxicity, thrombocytopenia, pancreatitis, hypotension (rare), skin rash (including Stevens-Johnson), and hyper-ammonemic encephalopathy.

effects and the need for PICU admission. In the initial RSE stage, we have therefore recommended a trial of a third anticonvulsant before initiation of coma-inducing medications. We have used IV levetiracetam in several patients with RSE and found that there was at least a temporary termination of seizures without adverse effects. Alternatively, in patients without known risk factors for hepatotoxicity, such as known liver disease or metabolic disease, there are data to suggest that IV valproic acid may be a useful third-line medication.

If seizures persist, then in the later RSE phase, we proceed to a trial of IV phenobarbital, generally as plans are being made to induce coma with IV midazolam, if phenobarbital does not terminate the seizure. We use IV midazolam because there is more published data available for midazolam compared with IV pentobarbital, and published series and our experience suggest that midazolam is less associated with hypotension than pentobarbital. After an initial bolus, an infusion is increased every 5 to 10 minutes with the goal of burst suppression (approximately 50% burst, 50% suppression) on EEG. We maintain burst suppression for 24 hours, with EEG reviews and medication adjustment, as needed. Coma induction is then weaned over about 24 hours. If there is recurrence of SE, then the midazolam is restarted and high-dose topiramate is added. Epilepsy surgery is considered if a focal area of ictal onset is clear. Weaning is again attempted after 24 hours of burst suppression.

MEDICALLY COMPLEX CHILDREN

Children requiring intensive care often have underlying chronic or acute medical conditions that may lead to seizures or affect the appropriate management of seizures. Although there has been little study of optimal management of these patients, some data are available and are summarized below. These issues have been discussed in a recent compilation of reviews.[109] In addition, the important drug interactions and side effects of the commonly used antiseizure medications are listed in Tables 2 and 3.

Brain Tumors and Leukemia

Seizures are common in patients with brain tumors. Seizures may be the initial presenting sign of tumor, and these patients are prone to refractory epilepsy. Studies have demonstrated that prophylactic antiepileptic medication administration does not reduce the occurrence of seizures and is associated with frequent adverse effects. A practice parameter focused on adults by the American Academy of Neurology suggests that in adults, prophylaxis not be used and that if prophylactic antiepileptic drugs are used after neurosurgery, they should be discontinued after a week if there have not been seizures.[110] In patients with seizures and brain tumors, interactions between antiepileptic medications and chemotherapy medications must be considered. Hepatic enzyme inducing antiepileptic medications may accelerate the metabolism of chemotherapeutics leading to reduced plasma concentrations and lower anticancer activity. Enzyme-inducing antiepileptic medications stimulate the metabolism of cyclophosphamide, ifosfamide, busulfan, teniposide, etoposide, paclitaxel, methotrexate, and some vinca alkaloids.[111] In adults with glioblastoma multiforme, the administration of enzyme inducing antiepileptic medications is associated with significantly shorter survival.[80] In 566 children with B-lineage leukemia, anticonvulsant therapy with enzyme-inducing medications was significantly related to worse event-free survival (defined as the time from the start of therapy to the first adverse event, including failure to achieve complete remission, leukemic relapse, second malignant disorder, or death) and central nervous system relapse. Clearance of teniposide and methotrexate was faster in children receiving anticonvulsants.[81] Enzyme-inducing antiepileptic medications may also increase steroid metabolism[111] and reduce the efficacy of corticosteroids in reducing brain edema.[111] Valproate, a hepatic enzyme inhibitor, may lead to increased chemotherapeutic levels with resulting toxicity.[112] Some chemotherapeutic agents such as fluorouracil and tamoxifen can reduce phenytoin metabolism and cause toxicity.[111] If anticonvulsant medications are required, levetiracetam, gabapentin, and lamotrigine may be appropriate choices as these drugs do not induce hepatic enzymes.

Renal Dysfunction

Renal failure may result in seizures as a component of uremic encephalopathy, acute dialysis disequilibrium, or in association with pH imbalance, hyponatremia, hypomagnesemia, hypocalcemia, sepsis, intracranial hemorrhage (due to clotting defects), and posterior reversible leukoencephalopathy syndrome (related to malignant hypertension or immune suppressant medications after renal transplant). Renal failure also affects epilepsy treatment. Albuminuria leads to increased free fractions of protein bound medication and reduced glomerular filtration, which results in increased half-lives of renally excreted anticonvulsant medications (levetiracetam, topiramate, vigabatrin, and gabapentin). As a result, in conditions requiring loading of antiseizure medications, the usual loading dose is unchanged but subsequent maintenance doses must be smaller or less frequent. Hemodialysis may remove medications with low protein binding, necessitating a post-dialysis dose (gabapentin, vigabatrin, topiramate, phenobarbital, and levetiracetam).[113]

Hepatic Dysfunction

Hepatic failure because of multiple etiologies may result in seizures, most often during the more severe stages of encephalopathy. D-Penicillamine used to treat Wilson disease may reduce pyridoxine levels and cause seizures. In patients with porphyria, hepatic enzyme-inducing antiseizure medications may increase heme synthesis and precipitate liver failure and should be avoided. Several antiseizure medications are associated with hepatotoxicity including phenobarbital, phenytoin, carbamazepine, valproic acid, felbamate, and topiramate. Generally, valproic acid should not be used in patients with hepatic dysfunction. Anticonvulsant medications not associated with hepatotoxicity include lamotrigine, gabapentin, oxcarbazepine, levetiracetam, zonisamide, and pregabalin. Medications that require dose adjustment with liver dysfunction include phenytoin, carbamazepine, phenobarbital, valproic acid, topiramate, oxcarbazepine, and zonisamide. Reduced circulating albumin due to hepatic dysfunction may lead to increased free fractions of highly protein bound medications

including phenytoin, carbamazepine, valproic acid, and benzodiazepines.[113] Levetiracetam may be a good drug in patients with hepatic dysfunction because it has low protein binding, no hepatic metabolism, and has not been associated with hepatotoxicity to date.

Solid-Organ Transplant

Acute symptomatic seizures occurring near the time of transplantation are not often associated with later epilepsy and thus long-term antiseizure medications may not be indicated. When antiseizure medications and immunosuppressant medications must be co-administered, interactions must be considered. Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin may reduce levels of cyclosporine, tacrolimus, sirolimus, and corticosteroids.[111,114] Antiseizure medications do not significantly affect levels of azathioprine, mycophenolate, and muromonab.[114]

Congenital Heart Disease

Seizures are common in the postoperative period, occurring in 21 (11.5%) of 183 infants who underwent postoperative EEG monitoring after heart surgery.[115] In addition, brain injury (hypoxic-ischemic or stroke) related to congenital heart disease is a common cause of later remote symptomatic seizures including non-convulsive seizures[116] and SE.[30] Studies have not investigated the optimal treatment of seizures in these patients. Medications such as phenytoin may induce arrhythmias and if used, slower infusion with continuous ECG and vital sign monitoring are indicated. As discussed previously, there is lower risk for arrhythmias with fosphenytoin, but arrhythmias have been reported in children so continuous ECG and vital sign monitoring are still recommended. Furthermore, hepatic enzyme inducing antiseizure drugs, such as phenytoin and phenobarbital, may reduce the levels of some antiarrhythmic medications such as digoxin, disopyramide, mexilitine, quinidine, and amiodarone and antihypertensive medications such as propranolol, metoprolol, nifedipine, nimodipine, and verapamil.[111] Both levetiracetam and valproate can be administered intravenously and may be a reasonable alternatives for use in patients with congenital heart disease, although they have not been studied in this group. No significant changes in blood pressure or heart rate were noted in studies in which 40 children with SE or acute repetitive seizures were loaded with valproate[61] or 41 children with RSE were loaded with valproate.[62] Levetiracetam has not been associated with arrhythmias and seems to be safe in critically ill adults[75] but has not been extensively studied in children.

Anticoagulation

Seizures are common in children with indications for anticoagulation such as ischemic stroke and sinovenous thrombosis. Hepatic enzyme inducing antiseizure medications may increase warfarin metabolism.[111] Interestingly, there can initially be an increase in anticoagulant action of warfarin when phenytoin is co-administered, but then a decrease in anticoagulant activity due to an increase in warfarin metabolism.[117] Thus, anticonvulsant levels and international normalized ratio (INR) must be followed.

TBI/Subarachnoid Hemorrhage

Post-traumatic seizures (PTS) in adults are common, especially with a Glascow Coma Scale score <10, cortical contusion, depressed skull fracture, subdural or epidural or intracerebral hematoma, penetrating brain injury, or with a seizure occurring within 24 hours of TBI[118] and may be divided into early PTS occurring within 7 days and late PTS occurring after 7 days. Class I studies in adults have suggested that prophylactic anticonvulsant medications reduce the incidence of early PTS but do not reduce the incidence of late PTS[119,120] and that valproate may be associated with higher mortality than phenytoin.[121] Thus, in adults, anticonvulsant medications are often used for 7 days after TBI but not continued long term.

There is little data available in children. One study of 102 children with moderate to severe blunt head injury demonstrated that in the first 48 hours, seizures occurred in 5% of children who did not receive phenytoin prophylaxis and 7% of children who did receive phenytoin prophylaxis. Their conclusion was that prophylactic phenytoin was not associated with any change in early PTS, and there were no differences between the treatment groups in survival and neurologic outcome at 30 days.[122] In another study of 194 children with TBI, prophylactic phenytoin was shown to reduce the incidence of early PTS in children with severe TBI.[123] Both low Glascow Coma Scale scores (severe TBI) and young age (infants and toddlers) are associated with increased risk of early PTS.[124] Therefore, prophylactic anticonvulsant therapy to prevent the occurrence of early PTS in high-risk children is recommended as a treatment option, but not recommended to prevent late PTS.[124] There are no data regarding the use of newer anticonvulsants for seizure prophylaxis after pediatric TBI.

Although no data exist in the pediatric population regarding seizure prophylaxis and subarachnoid hemorrhage, a recent study of 453 adults with subarachnoid hemorrhage compared a 3-day course of phenytoin to a multiweek regimen and demonstrated no significant change in the incidence of seizures and a significant reduction in the rate of phenytoin-related complications with the shorter course.[125]

CONCLUSIONS

Seizures are common in critically ill children. Prolonged seizures are known to be associated with lower response to treatment and worse outcome and thus aggressive treatment is indicated. Many anticonvulsants now in use were not available when many SE algorithms were developed and further study is needed to elucidate the role of these newer medications and possibly redesign SE treatment algorithms. Furthermore, there is increasing evidence that seizures in critically ill patients may be subclinical and are likely associated with worse outcome. Further study is needed to determine which children are at high risk for subclinical seizures and require EEG monitoring and how these seizures should be treated. Treatment with anticonvulsant medications must be carefully considered because each has side effects and drug-drug interactions that may complicate critical care management and significantly impact the outcome of the

underlying condition. Studies directed at evaluating the optimal management for specific patient populations will lead to improved care because seizure management may be different in subpopulations of critically ill children.

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CME EXAM
Instructions for the *Pediatric Emergency Care* CME Program Examination

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CME EXAMINATION
October 2008

Please mark your answers on the ANSWER SHEET.

Anticonvulsant Medications in the Pediatric Emergency Room and Intensive Care Unit, *Abend et al*

1. Status epilepticus in children refers to seizures that persist for at least:
   a. 1 minute
   b. 5 minutes
   c. 15 minutes
   d. 30 minutes
   e. 60 minutes
2. Fosphenytoin, as compared with phenytoin:
   a. Reaches peak serum levels sooner
   b. Should not be given intramuscularly
   c. Can be administered at a more rapid rate
   d. Causes nystagmus less frequently
   e. Produces hypotension more often
3. Valproic acid:
   a. Is available only as an oral formulation
   b. Is more effective for focal than for generalized seizures
   c. Often causes hepatotoxicity in older patients
   d. Should be used cautiously in patients on warfarin
   e. Has a high rate of adverse effects in children with SE
4. Levetiracetam:
   a. Requires a dosage adjustment with renal failure
   b. Is eliminated via the hepatic route
   c. Has poor oral absorption
   d. Should be used cautiously in patients on warfarin
   e. Is the drug of choice for SE in infants
5. The initial drug for treating SE is a 5-year-old child is:
   a. Topiramate
   b. Lorazepam
   c. Valproic acid
   d. Levetiracetam
   e. Thiamine

ANSWER SHEET FOR THE *PEDIATRIC EMERGENCY CARE* CME PROGRAM EXAM

October 2008

Please answer the questions on page 719 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

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City/State/Zip _____

Daytime Phone _____

Specialty _____

1. (A) (B) (C) (D) (E)
2. (A) (B) (C) (D) (E)
3. (A) (B) (C) (D) (E)
4. (A) (B) (C) (D) (E)
5. (A) (B) (C) (D) (E)

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CME EXAM ANSWERS

Answers for the Pediatric Emergency Care CME Program Exam

Below you will find the answers to the examination covering the review article in the July 2008 issue. All participants whose examinations were postmarked by September 15, 2008 and who achieved a score of 80% or greater will receive a certificate from Lippincott CME Institute, Inc.

EXAM ANSWERS
July 2008

1. C
2. B
3. A
4. D
5. C