OVERVIEW AND EPIDEMIOLOGY

Status epilepticus (SE) was described in the seventh century BC, but its recognition and effective management remain in their infancy. The definitions employed in studies of SE have varied substantially, making comparisons among these reports difficult. Although many researchers have used 30 or 60 minutes as the cutoff for their investigations, clinicians should recognize that most seizures will terminate spontaneously within a few minutes. Seizures which persist longer than five to seven minutes should almost always be treated; whether this is treatment to prevent SE or treatment of SE is largely a semantic question.

A 10 year retrospective study of all patients developing seizures in Mayo Clinic ICUs uncovered seven patients per 1000 ICU admissions.¹ Another two-year prospective study of medical ICU patients acquired 35 with seizures per 1000 admissions.² These studies did not employ comparable methodologies, as the patient populations and methods of detection differed.

Certain ICU patients seem at higher risk for seizures, but the degree of that increase is uncertain. Theophylline frequently produces seizures or SE during rapid administration or when high concentrations occur, but occasionally these complications arise at 'therapeutic' levels. Renal failure or an altered blood-brain barrier pose risks for patients receiving imipenem-cilastatin, but other patients receiving this antibiotic (or GABA antagonists like penicillin) may also experience seizures. Transplant recipients, especially when receiving cyclosporine, are also at increased risk, as are those who become hypo-osmolar rapidly from any etiology. Nonketotic hyperglycemia patients have a strong predisposition to partial seizures and partial SE.

The estimated incidence of generalized convulsive SE (GCSE) in the United States varies from 50,000 to 250,000 cases/year.³⁴ Some of this difference is due to varying definitions, but the latter estimate derives from population-based data and is probably more accurate. Mortality estimates also vary from 1-2 % to 22%. Intermittent SE had a lower mortality rate than continuous SE (20 vs. 31%) in the one study that has addressed this difference.⁵ Within the pediatric age groups (ages 31 days - 16 years), 43% percent of patients less than 4 years of age had a repeat episode of SE within the 2 year study period.
Mortality rate for pediatric patients was 3%, compared to an overall mortality rate of 22%. The most common associations in children were infection, low antiseizure drug levels, and remote etiologies for seizures.\(^6\)

Many risk factors emerged from the population-based study in Richmond VA. SE lasting longer than 60 minutes carried a mortality of 32%; compared with 2.7% for a shorter duration. SE caused by anoxia was associated with 70% mortality in adults but less than 10% in children. The commonest cause of SE in adults was stroke, followed by withdrawal from antiseizure agents; cryptogenic SE; and that related to alcohol withdrawal, anoxia, and metabolic disorders. Systemic infection was the commonest cause of childhood SE, followed by congenital anomalies, anoxia, metabolic problems, antiseizure drug withdrawal, CNS infections, and trauma.\(^7\)

Clusters of seizures in patients with intractable partial epilepsy appears to place these patients at increased risk for SE.\(^8\) Other patients who may be at risk for SE, in whom either underlying disease or treatment may render recognition of difficult, include patients with severe head trauma.\(^9\)

Mitchell notes that four groups represent the majority of treated episodes of SE in children: atypical febrile seizures presenting as SE; acute conditions including meningitis, encephalitis, trauma, tumors, and stroke; idiopathic or remote symptomatic epilepsy; and degenerative or progressive neurologic conditions.\(^10\) Intoxication and recreational drug withdrawal are relatively uncommon causes of SE in children relative to adults. Lacroix reported that over a 10-year period in a PICU, SE accounted for 1.6% of all admissions.\(^11\) Fifty-one percent of cases of SE were in children less than 2 years of age, and the mortality rate for all cases of SE was 6% while in the ICU and 9% at one year. The most common etiologies of SE in this study were underlying epilepsy (32%), atypical febrile convulsion (13.6%), purulent meningitis (13%), and encephalitis (13%). Other specified causes included intoxication, tumor, recent anoxic encephalopathy, systemic hypertensive crisis, and acute or chronic metabolic abnormalities (1.3-5%). The average length of ICU stay was 3.1 +/- 3.6 days. Cat-scratch disease has emerged as an important cause of SE in children.\(^12\)

The recently reported study from Shinnar’s group suggests that recurrent SE occurs in 4.3% of children without and in 19.6% of those with SE at the time epilepsy was diagnosed.\(^13\)

The data in Table 1 are upon twenty years of experience in San Francisco. Approximately 10% of epilepsy patients present with SE,\(^14\) and nearly 20% of seizure patients experience an episode of SE within five years of their first seizure.
Table 1. Etiologies of SE at the San Francisco General Hospital *indicates conditions most likely to result in ICU admission (from Aminoff and Simon, and Alldredge and Lowenstein)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior seizures</td>
<td>No prior seizures</td>
</tr>
<tr>
<td></td>
<td>Total N=98</td>
<td></td>
</tr>
<tr>
<td>Ethanol-related</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Antiseizure drug noncompliance</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Refractory epilepsy</td>
<td>(not used)</td>
<td>8</td>
</tr>
<tr>
<td>CNS infection*</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Trauma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tumor</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Metabolic*</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Stroke*</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Anoxia*</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

Maytal et al studied retrospectively the relationship between antiseizure drug levels or antiseizure drug withdrawal and SE in 51 children with known epilepsy. Drug levels were within standard therapeutic ranges and no acute seizure precipitants such as fever could be identified in 61% of cases.

Many cases of presumed encephalitis in patients with seizures or SE now appear to be consequences of paraneoplastic or autoimmune disorders.

Other less common causes of SE in children include intravenous N-acetylcysteine therapy, camphor ingestion, cerebral malaria, central nervous system lupus erythematosus, human herpes virus 6 infection, cat-scratch disease, thyrotoxicosis, and hypertensive crisis. Proulx et al demonstrated that a highest blood pressure within one hour after cessation of convulsion greater than four SD above the mean for age and sex predicted a 78% probability that hypertension was a cause of seizure rather than its result.

The only population-based study of nonconvulsive SE (NCSE) suggests an incidence of 1.5 per 100,000 per year.

The effect of SE on later development remains debated, but evidence continues to accumulate suggesting a deleterious effect of symptomatic SE (as opposed to simple febrile or ‘idiopathic’ SE).

**PATHOPHYSIOLOGY**

The causes of SE can be divided into predispositions and precipitants. Predispositions are static conditions increasing the likelihood of SE in the presence of a precipitant.
Precipitants are events which can produce SE in most, if not all, people, but tend to affect those with predispositions at lesser degrees of severity (e.g., barbiturate withdrawal). The causes and effects of SE at the cellular, brain, and systemic levels are interrelated, but their individual analysis is useful for understanding them and their therapeutic implications. Longer SE durations produce more profound alterations with an increasing likelihood of permanence, and of becoming refractory to treatment. The pathophysiology of SE has recently been reviewed in detail.20

The ionic events of a seizure follow the opening of ion channels coupled to excitatory amino acid (EAA) receptors. From the standpoint of the intensivist, three channels are particularly important because their activation may raise intracellular free calcium to toxic concentrations: AMPA channels, NMDA channels, and metabotropic channels. These EAA systems are crucial for learning and memory. Many drugs which block these systems are available but are too toxic for chronic use. The deleterious consequences of SE, and the brief period for which they would be needed, suggest that such agents may have a role in SE. Counter-regulatory ionic events are triggered by the epileptiform discharge as well, such as the activation of inhibitory interneurons, which suppress excited neurons via GABA_A synapses. Tachyphylaxis to the benzodiazepines is largely mediated by receptor traffic, which replaces BDZ-sensitive GABAA receptors in the neuronal membrane with BDZ-insensitive ones.21

The cellular effects of excessive EAA channel activity include (1) generating toxic concentrations of intracellular free calcium; (2) activating autolytic enzyme systems; (3) producing oxygen free radicals; (4) generating nitric oxide, which both enhances subsequent excitation and serves as a toxin; (5) phosphorylating enzyme and receptor systems, making seizures likely; and (6) increasing intracellular osmolality, producing neuronal swelling. If ATP production fails, membrane ion exchange ceases, and the neuron swells further. These events produce the neuronal damage associated with SE.

Many other biophysical and biochemical alterations occur during and after SE. The intense neuronal activity activates immediate-early genes and produces heat shock proteins, providing indications of the deleterious effects of SE and insight into the mechanisms of neuronal protection. Absence SE is an exception among these conditions; it consists of rhythmically increased inhibition and does not produce clinical or pathologic abnormalities.

The mechanisms which terminate seizure activity are poorly understood. The leading candidates are inhibitory mechanisms, primarily GABAergic neuronal systems. Clinical observation supports the contention that human SE frequently follows withdrawal from GABA agonists (e.g., benzodiazepines). Intrinsic neuronal properties are also involved, with the calcium-dependent potassium current (IAHP) the most important. Recurrent inhibition via local interneurons and thalamic afferents are probably both important, although their relative strengths may vary in different types of SE. Future therapies may exploit these properties.

Johnston recently reviewed mechanisms that may contribute to the propensity for the developing brain for seizures and for the development of epilepsy.22
These include hypersynchrony of neuronal circuits; increased density of synapses, gap junctions, and excitatory amino acid receptors; and enhanced regenerative responses to injury which may result in the formation of sprouting and abnormal connections, as seen in temporal lobe epilepsy.

The mechanisms producing NCSE are even less well understood. It is increasing recognized as a complication of critical illnesses. Some cases occur in the course of less severe medical illnesses, such as thrombotic thrombocytopenic purpura. The recent report of a familial syndrome involving six patients with an abnormality of chromosome 20 may prove to be instructive. Some drugs have been reported to trigger this form of SE. Although the potential for NCSE to damage neurons has long been debated, the leakage of neuron-specific enolase into the peripheral circulation serves to underscore this possibility.

The electrical phenomena of SE at the whole brain level, as seen in the scalp EEG, reflect the seizure type which initiates SE, e.g., absence SE begins with a 3 Hz wave-and-spike pattern. During SE, there is slowing of this rhythm, but the wave-and-spike characteristic remains. GCSE goes through a sequence of electrographic changes (Table 3). The initial discharge becomes less well formed, implying that neuronal firing is losing synchrony. The sustained depolarizations which characterize SE alter the extracellular milieu, most importantly by raising extracellular potassium. The excess potassium ejected during SE exceeds the buffering ability of astrocytes. Raising extracellular potassium potentiates more seizures.

Table 3. Electroencephalographic-clinical correlations in GCSE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Typical clinical manifestations*</th>
<th>EEG features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tonic-clonic convulsions; hypertension and hyperglycemia common</td>
<td>Discrete seizures with interictal slowing</td>
</tr>
<tr>
<td>2</td>
<td>Low or medium amplitude clonic activity, with rare convulsions</td>
<td>Waxing and waning of ictal discharges</td>
</tr>
<tr>
<td>3</td>
<td>Slight, but frequent, clonic activity, often confined to the eyes, face, or hands</td>
<td>Continuous ictal discharges</td>
</tr>
<tr>
<td>4</td>
<td>Rare episodes of slight clonic activity; hypotension and hypoglycemia become manifest</td>
<td>Continuous ictal discharges punctuated by flat periods</td>
</tr>
<tr>
<td>5</td>
<td>Coma without other manifestations of seizure activity</td>
<td>Periodic epileptiform discharges on a flat background</td>
</tr>
</tbody>
</table>

The clinical manifestations may vary considerably, depending on the underlying neuropathophysiologic process (and its anatomy), systemic diseases, and medications. In particular, stages of the electrographic progression may be sufficiently brief to be overlooked. Partially treating SE may dissociate the clinical and electrographic features. Approximately 20% of patients go from convulsive to nonconvulsive SE with initial treatment (Faught E, personal communication).

The increased cellular activity of SE elevates demand for oxygen and glucose, and blood flow initially increases. After about 20 minutes, however, energy supplies become exhausted. This causes local catabolism to support ion pumps (attempting to restore the internal milieu), which is a major cause of epileptic brain damage.
The brain contains systems to terminate seizure activity; GABAergic interneurons and inhibitory thalamic neurons are both important.

SE produces neuropathology even in patients who are paralyzed, ventilated, and maintained at normal temperature and blood pressure. The hippocampus, a crucial area for memory, contains the most susceptible neurons, but other regions are also vulnerable. In addition to damaging the CNS, GCSE produces life-threatening, systemic effects. Systemic and pulmonary arterial pressures rise dramatically at seizure onset. Epinephrine and cortisol prompt further elevations and also produce hyperglycemia. Muscular work raises blood lactate. Breathing suffers from both airway obstruction and abnormal diaphragmatic contractions. CO2 excretion falls while its production increases markedly. Muscular work accelerates heat production; concomitantly, skin blood flow falls. This combination can raise core temperature dangerously.

The combined respiratory and metabolic acidoses frequently lower the arterial blood pH to 6.9 or lower. The acidosis may produce hyperkalemia; in addition to its deleterious effects on cardiac electrophysiology, the elevated extracellular potassium helps propagate seizure activity. Coupled with hypoxemia and elevated circulating catecholamine concentrations, these conditions may rarely produce cardiac arrest. This sequence probably accounts for some cases of epileptic sudden death; neurogenic pulmonary edema is the likely cause of many others. The severity of the acidosis may prompt consideration of bicarbonate administration.

When this is attempted, however, the likelihood of pulmonary edema is inordinately high. Rapid termination of seizure activity is the most appropriate treatment; the restitution of ventilation and the metabolism of lactate will quickly restore a normal pH.

After about 20 minutes, motor activity begins to diminish, and ventilation usually improves. Body temperature may rise further, however. Hyperglycemia diminishes; after one hour, gluconeogenesis can fail, producing hypoglycemia. GCSE patients often aspirate oral or gastric contents, producing pneumonia. Rhabdomyolysis is common, and may lead to renal failure. Compression fractures, joint dislocations, and tendon avulsions are other sequelae.

**CLINICAL FEATURES**

SE can be classified by a system similar to that of the International Classification of Epileptic Seizures (Table 4). Generalized convulsive SE (GCSE) is the commonest type encountered in the ICU, and poses the greatest risk to the patient. It may either be primarily generalized, as in the drug-intoxicated patient, or secondarily generalized, as in the brain abscess patient who develops GCSE. Nonconvulsive SE (NCSE) in the ICU frequently follows partially treated GCSE. Some use the term for all SE involving altered consciousness without convulsive movements; this blurs the distinctions among absence SE, partially treated GCSE, and complex partial SE (CPSE); which have different etiologies and treatments. However, clinical studies suggest that this scheme is inadequate to properly describe the multitude of manifestations of SE.
Status epilepticus may be difficult to identify, especially in the neonatal age group when seizures activity may appear atypical. Both Clancy and Wical stress the importance of EEG analysis in the high-risk, sick neonate with altered mental status. While the natural history of electrographic neonatal seizures remains unknown, ongoing studies support the notion that electrical seizures may play a role in the future anatomic development of the brain and in the propensity for epilepsy in later life.

In older infants and children, nonconvulsive SE may present in a variety of clinical ways, including impairment of consciousness ranging from a confusional state to stupor, sometimes with poor balance or incoordination, periodic obtundation, behavioral states misdiagnosed as a psychiatric condition, or as an element of particular childhood epileptic syndromes, including electrical SE during slow sleep and the Landau-Kleffner syndrome.

Three problems occur in SE recognition: (1) complex partial SE in patients with preexisting impairment of alertness, (2) SE in patients receiving neuromuscular junction blockade, and (3) misinterpretation of non-epileptiform abnormal movements as SE. Critically ill patients often have altered consciousness without seizures, due to their diseases, their complications (e.g., septic encephalopathy), or medications. A subsequent change in alertness may reflect a seizure, in which case an EEG would be required for diagnosis. Drislane and colleagues recently reviewed the EEG manifestations of partial SE.

Patients receiving neuromuscular junction (NMJ) blocking agents cannot manifest the expected signs of seizures. Since most such patients concurrently receive sedation with GABA agonists, the likelihood of seizures is small.

Table 4. Clinical classification of SE

I. Generalized seizures
   a. Generalized convulsive SE (GCSE)
      i. Primary generalized SE
         1. tonic-clonic SE
         2. myoclonic SE
         3. clonic-tonic-clonic SE
      ii. Secondarily generalized SE
         1. partial seizure with secondary generalization
         2. tonic SE
   b. Nonconvulsive SE (NCSE)
      i. absence SE (petit mal status)
      ii. atypical absence SE (e.g., in the Lennox-Gastaut syndrome)
      iii. atonic SE
      iv. NCSE as a sequel of partially treated GCSE

II. Partial SE
   a. Simple partial SE
      i. typical
      ii. epilepsia partialis continua (EPC)
   b. Complex partial SE (CPSE)

III. Neonatal SE
Autonomic signs of seizures (hypertension, tachy-cardia, pupillary dilation) may also be caused by pain or inadequate sedation. Hence, patients displaying these findings who have a potential for seizures (e.g., intracranial pathology) should have an EEG.

The manifestations of SE depend on the type and, for partial SE, the cortical area of abnormality. Primary GCSE begins as tonic extension of the trunk and extremities without preceding focal activity. No aura is reported and consciousness is immediately lost. After several seconds of tonic extension, the extremities start to vibrate, quickly giving way to clonic (rhythmic) extension of the extremities. This phase wanes in intensity over a few minutes. The patient may then repeat the cycle of tonus followed by clonic movements, or continue to have intermittent bursts of clonic activity without recovery. Less common forms of primary GCSE are myoclonic SE, (bursts of myoclonic jerks increasing in intensity, leading to a convulsion) and clonic-tonic-clonic SE (clonic activity precedes the first tonic contraction). Myoclonic SE is usually seen in patients with anoxic encephalopathy or metabolic disturbances, including some inborn errors of metabolism. Absence SE is an unusual condition that almost always affects adults rather than children. These patients develop periods of impaired responsiveness, sometimes associated with small clonic movements, during which they may attempt to respond to questions. The EEG signature of this condition is a nearly 3Hz wave-and spike discharge which, in contrast to childhood absence, continues for minutes and recurs frequently over hours or days.

Secondarily generalized SE begins with a partial seizure and progresses to convulsive activity. The initial focal clinical activity may be overlooked. This seizure type implies a structural lesion, so care must be taken to elicit evidence of lateralized movements.

Of the several forms of generalized nonconvulsive SE, the one of greatest importance is NCSE as a sequel of inadequately treated GCSE. When a patient with GCSE is treated with antiseizure drugs (often in inadequate doses), visible convulsive activity may stop while the electrochemical seizure continues. In the DVA cooperative study of SE, 20% of patients in whom medication stopped the clinically visible manifestations of SE remained in electrographic SE. Patients who have been adequately treated should begin to awaken within 15 - 20 minutes after the successful termination of SE; many regain consciousness much faster. Those who do not start awakening by 20 minutes should be assumed to have entered NCSE. Careful observation may disclose slight clonic activity. NCSE is an extremely dangerous problem because the destructive effects of SE continue without motor activity. NCSE demands emergent treatment under EEG monitoring to prevent further cerebral damage, since there are no clinical criteria to indicate when therapy is effective. Such cases of NCSE often have a poor outcome, perhaps in part related to delayed diagnosis and difficulty in treatment.

Other forms of NCSE occur de novo, without preceding convulsions. Kaplan recently reported a series of cases, admitted to one hospital (mostly with erroneous psychiatric diagnoses) in whom the delay in recognition was as long as 5 days. Conversely, at least one case of catatonia may have been misdiagnosed as NCSE. Complex partial SE (CPSE) presents with diminished awareness; this diagnosis is often a surprise when an EEG is obtained. A variety of conditions may precipitate it. CPSE is an emergent condition which causes neuronal damage, and in my view should be managed vigorously.
Partial SE in ICU patients typically follows a stroke, or occurs with rapidly expanding focal lesions such as tumors or abscesses. Clonic motor activity is most easily recognized, but the seizure takes on the characteristics of adjacent functional tissue. Therefore, somatosensory or special sensory manifestations may occur, and the critically ill patient may be unable to report such symptoms. Aphasic SE occurs when a seizure begins in a language area, and may resemble a stroke. Epilepsia partialis continua involves repetitive movements confined to a small region of the body. It may be seen with nonketotic hyperglycemia or with focal brain disease; antiseizure drug treatment is seldom useful.

The Journal of Clinical Neurophysiology devoted much of an issue to aspects of NCSE, and provides useful data as well as a debate about the prognostic implications of this condition.

**DIAGNOSIS**

Many forms of SE are clinically apparent, and their treatment should not be delayed to obtain an EEG or other diagnostic studies. Once therapy for SE is in progress, a workup for its etiology should be instituted; the urgency of the workup depends on the clinical situation (e.g., suspected meningitis patients will be approached differently than the noncompliant seizure patient). A variety of findings may be present on the EEG, depending on the type of SE and its duration (see Table 3).

SE itself may produce abnormalities on MRI, including reversible areas of increased T2 signal and diffusion abnormalities on DWI that reverse and are not followed by the development of infarcts or other pathology.

CPSE patients often lack such organized discharges of GCSE, but instead may have waxing and waning rhythmic activity in one or several head regions. A number of other patterns emerge from case reports, such as widespread, invariant alpha. These patients represent some of the most difficult diagnostic problems in electroencephalography. A diagnostic trial of an intravenous benzodiazepine is often necessary to diagnose CPSE. Patients developing refractory SE or having seizures during NMJ blockade require continuous EEG monitoring.

**TREATMENT**

Generalized convulsive status epilepticus (GCSE) constitutes an obvious medical emergency; however, the various forms of nonconvulsive status epilepticus are also emergent but are more difficult to recognize. Certainly in GCSE, and most likely some of the other forms of SE, one must act quickly to prevent additional cerebral damage. Table 1 presents a sample management schema. Patients with simple partial SE or EPC are at less risk of developing widespread cerebral damage, and are also less likely to respond to the aggressive approach outlined in Table 1. In these patients, correcting underlying problems, such as nonketotic hyperosmolar hyperglycemia, is crucial. Errors in terminating SE include (1) inadequate dosing of effective drugs and (2) continued use of drugs that are ineffective in the patient being treated.
The first point most frequently applies to PHT; the proverbial 'gram of Dilantin' is inadequate for those weighing more than 50 kg.

A multicenter trial comparing four treatment arms for adults presenting in SE suggests that lorazepam is currently the best agent to terminate GCSE.\textsuperscript{48} Advantages of LRZ over diazepam (DZ) are its duration of action against SE (4 - 14 hours as opposed to 20 minutes), and its higher initial response rate. One group reported that children receiving DZ for SE more often required intubation and mechanical ventilation than comparable children receiving LRZ.\textsuperscript{49} Europeans often use midazolam (MDZ) or clonazepam initially. MDZ is very useful for refractory SE.\textsuperscript{50,51}

Respiratory depression is the major adverse effect of this class. An interesting view of this area that highlights the limitation of evidence-based medicine techniques has recently been published.\textsuperscript{52}

The DVA trial also highlights the importance of the EEG stage of SE in the likely response to treatment. Preliminary analysis of the data indicates that patients who are in the earliest EEG stage of SE (discrete convulsions) have a 75% chance of success with the initial agent employed. With a waxing and waning pattern, this falls to 30%; at the stage of continuous ictal activity, 25%; with brief suppressions, 8%, and with a suppression-burst pattern, 7%.

Table 5 reviews the success rates of drugs administered in each arm of the DVA trial. It is apparent from these data that only the first drug in such a sequence can be employed in the treatment of SE; after failure of the first conventional anticonvulsant, one should consider eschewing

Table 5.

<table>
<thead>
<tr>
<th>Success rates (% cumulative %)</th>
<th>LRZ arm</th>
<th>PB arm</th>
<th>DZ/PHT arm</th>
<th>PHT arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First drug</strong></td>
<td>LRZ 64.9</td>
<td>PB 58.2</td>
<td>DZ/PHT 55.8</td>
<td>PHT 43.5</td>
</tr>
<tr>
<td><strong>Second drug</strong></td>
<td>PHT 7.2, 72.1</td>
<td>PHT 3.3, 61.5</td>
<td>LRZ 3.2, 59.0</td>
<td>LRZ 13.9, 57.4</td>
</tr>
<tr>
<td><strong>Third drug</strong></td>
<td>PB 2.1, 74.2</td>
<td>LRZ 2.2, 63.7</td>
<td>PB 2.1, 61.1</td>
<td>PB 3.0, 60.4</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td>17.5, 91.7</td>
<td>25.3, 89.0</td>
<td>23.2, 84.3</td>
<td>26.7, 87.1</td>
</tr>
<tr>
<td><strong>Not responding</strong></td>
<td>8.3, 100</td>
<td>11.0, 100</td>
<td>15.8, 100</td>
<td>12.9, 100</td>
</tr>
</tbody>
</table>

PHT is an effective anti-SE agent, but cannot be delivered rapidly enough to be considered a first-line agent. It has a long duration of action when an adequate dose is given (e.g., a 20 mg/kg loading dose yields a plasma concentration above 20 µg/mL for 24 hours). Adding 5 mg/kg if 20 mg/kg fails to stop SE may be useful.\textsuperscript{54} If the patient is no longer in SE during PHT administration, a slower rate may be employed. Fosphenytoin is safer from the standpoints of extravasation and phlebitis, but still produces hypotension and cardiac conduction disturbances when administered quickly. Although it is approved for administration at 150 mg/min, it is prudent to begin the infusion more slowly (e.g., 50 mg/min) and increase the rate as tolerated. An opposing view is available.\textsuperscript{55}
Some advocate PB as a first-line drug, but it is historically a third-line agent, after a benzodiazepine and PHT.

However, we rarely use phenobarbital for the termination of SE for two reasons: only a small percentage of patients who have failed treatment with two antiseizure drugs will respond to a third conventional agent, and at least an additional 20 minutes are required to terminate SE in the few patients who do respond. Phenobarbital remains important in simple partial SE, and in patients who are being weaned from high-dose midazolam or anesthetic barbiturates.

Pentobarbital and thiopental are usually reserved for refractory SE. While these drugs are effective in large enough doses, side effects may limit their utility and are occasionally fatal. However, they are important when other modalities fail. Propofol is effective in refractory SE, but has not been directly compared with other compounds. It may offer a lower risk of ventilatory depression and more rapid awakening when the drug is discontinued. One study suggested a dosage range of 1 – 15 mg/kg/hr. Early fears of a possible proconvulsant effect appear to be unfounded, although withdrawal convulsions may occur if the drug is abruptly terminated. The appropriate role of propofol in pediatric SE remains to be determined. A report of oxygenation difficulties and probable rhabdomyolysis in children suggests the need for caution. We have given this agent to several children without difficulty, but monitor the serum CK as well as oxygen saturation.

We recently reviewed our experience with propofol and midazolam in refractory SE, and discovered that there was a considerable difference in mortality for patients with APACHE II scores ≥ 20 (17% mortality with midazolam vs. 56% for propofol). For this reason, we have returned to midazolam as our initial agent for refractory SE. Mayer’s group recently reported on their experience with midazolam.

Ketamine, an NMDA antagonist, is emerging as a potentially useful agent for refractory SE. A loading dose of 2 mg/kg, followed by an infusion of 10 – 50 µg/kg/min appears to be appropriate, although the available data are limited.

Intravenous valproate has been reported in cases and small series. The appropriate dose for SE probably varies with the type of SE being treated. Venkataraman and Whelless reported that a 20 – 30 mg/kg loading dose could be safely administered at 3 – 6 mg/kg/min, and yielded serum concentrations between 64-204.1 µg/ml (mean 132.6). One report describes hypotension associated with a 30 mg/kg loading dose. Evidence suggesting its value continues to accrue.

Topiramate may also be a valuable agent, primarily for withdrawing patients from intravenous agents. Up to 1600 mg/day via an enteral tube has been used. Although no intravenous form is available, the next generation of this drug should be available parenterally. Levetiracetam may also be useful. Many other agents have been used successfully, such as inhalational anesthetic, and lidocaine.
The critical care consultant should be familiar with these, but in my view it is more important to be able to use a few potent agents quickly and understand them thoroughly than to pick a different drug every time one encounters refractory SE.

As in therapy of adults, the primary concerns in management of SE in children are provision of cardiorespiratory support while achieving rapid control of motor and electrical seizure activity. In the hospital setting, initial pharmacotherapy includes a benzodiazepine for rapid control (lorazepam 0.1 mg/kg IV or PR midazolam 0.05-0.34 mg/kg IV or PR, or diazepam 0.1-0.5 mg/kg IV or PR) followed by a long-acting agent such as phenytoin (20 mg/kg IV), fosphenytoin (20 mg/kg phenytoin equivalents IV), or phenobarbital (10-20 mg/kg IV). 78,79,80

Management of SE in children usually begins before the admission to the ICU. Many prehospital caregivers now have protocols for administration of benzodiazepines in the field as a means of early initiation of therapy. Dieckmann studied rectal vs. IV diazepam in the prehospital setting for treatment of SE, and found both routes to be effective. 81 No child who received rectal diazepam in this study required endotracheal intubation before arrival in the emergency department, while 2 of 15 who received IV drug required intubation. Convulsions recurred in 60% of children who received IV diazepam, as compared to only 30.8% of those who received rectal drug. Alldredge et al found that prehospital therapy was associated with SE of significantly shorter duration (32 minutes vs. 60 minutes) and less likelihood of recurrent seizures in the emergency department (58% vs. 85%). 82

There were no significant differences between groups in the percentage of SE episodes that required endotracheal intubation or ICU admission, and route of diazepam administration (rectal vs. intravenous) was not significantly associated with SE duration, recurrent seizures in the ED, on subsequent in-hospital management. 83 Lorazepam had fewer side effects than diazepam, and either benzodiazepine was superior to placebo with respect to seizure control and need for ICU admission.

Lorazepam has been compared with diazepam for the acute treatment of seizures and SE in children presenting to the emergency setting.84 Both drugs stopped convulsions within 20 - 60 seconds in all responders, however more patients who received diazepam required repeated doses (31%) for seizure control compared to 3% of those receiving lorazepam. Eight of 53 patients receiving diazepam required ICU admission because of respiratory depression, while only one patient receiving lorazepam showed respiratory depression and none required ICU admission, possibly due to the lack of need for repeated doses.

Midazolam infusion is gaining acceptance for the treatment of refractory SE in adults85 and children.86,87,88

Parent and Lowenstein reported achieving a burst-suppression pattern on EEG followed by generalized slowing with infusion rates of 0.3-11 µg/kg/minute in a 26 month boy with seizures after head trauma.89
Rivera et al studied the use of midazolam infusion prospectively in 24 children with SE who were unresponsive to 3 IV doses of 0.3 mg/kg of diazepam, 20 mg/kg of phenytoin, and 20 mg/kg of Phenobarbital. Seizures were controlled in all patients after beginning midazolam infusion.

The mean effective dose was 2.3 µg/kg/min (range 1-18). There were no clinically significant cardiorespiratory changes attributable to the use of midazolam in their study; of particular interest is that in this group of patients, none required endotracheal intubation or mechanical ventilation. Drug was weaned by 1 µg/kg/min every 15 minutes after a 12-hour period free of relapsing episodes of seizure. Midazolam appears associated with a lower mortality in pediatric SE than other agents, although it is more expensive.

Most reviews of SE in children refer to the use of pentobarbital therapy for treatment of refractory SE. While this approach has frequently been used, it should be recognized that few studies of its use in children have been published. Kinoshita et al recently reported experience with a small series of children who achieved a burst-suppression pattern on EEG with dosages of 1.0-3.0 mg/kg/hr. They recommended attempting to taper pentobarbital after 12 hours of sustained burst-suppression in order to minimize the known attendant risks of hypotension and pneumonia. A recent report suggested electroconvulsive therapy as potentially useful for children with NCSE, but reports of NCSE produced by this treatment, and the theoretical concern that ECT would promote rather than disrupt synchrony, argue against its use in the absence of a clinical trial.

Table 6. Suggested protocol for treating SE

I. Establish airway. Often the most rapid way to accomplish this is to rapidly terminate SE. If endotracheal intubation under neuromuscular junction blockade is necessary, use a nondepolarizing agent such as vecuronium (0.1 mg/kg). If increased intracranial pressure is a concern, premedicate with lidocaine (1 mg/kg) or thiopental (4 – 5 mg/kg). If these agents are used, the patient should be considered still to be in SE until neuromuscular transmission is re-established, or an EEG demonstrated that SE is no longer present.

II. Determine blood pressure. If the patient is hypotensive, begin volume replacement and/or vasoactive agents as clinically indicated. GCSE patients who present with hypotension will usually require admission to a critical care unit. (Hypertension should not be treated until SE is controlled, since terminating SE will usually substantially correct it, and many of the agents used to terminate SE can produce hypotension).

III. Unless the patient is normo- or hyper-glycemic, administer dextrose and thiamine.

IV. Terminate SE. These drugs can eliminate visible convulsive movements while leaving the patient in NCSE. Patients who do not begin to respond to external stimuli 15 minutes after the apparent termination of GCSE undergo emergent EEG monitoring.

   a. LRZ 0.1 mg/kg, diluted in an equal volume of the IV solution. The latency of effect is debated, but lack of response after five minutes should be considered a failure.
b. If SE persists, some begin PHT, 20 mg/kg. If the patient tolerates this infusion rate, increase up to a maximum of 50 mg/min. Many investigators believe that an additional 5 mg/kg dose of PHT should be administered before advancing to the next line of therapy. If fosphenytoin is used instead of phenytoin, the rate of infusion may be up to 150 mg PHT equivalent/min. However, the data from the VA cooperative trial do not support this approach.

c. Instead, begin MDZ with a loading dose of 0.2 mg/kg followed by an infusion of 0.2 – 2.0 mg/kg/hr. This wide dosage range is necessary because of the development of tachyphylaxis. The appropriate goal is seizure suppression regardless of the EEG background; the background may need to be diffuse slowing, suppression-burst, or flat.97

d. If SE persists, administer propofol 3-5 mg/kg as a bolus, then 1-15 mg/kg/hr to achieve seizure control (as determined by EEG monitoring). Intubate patients at this stage if this has not already been accomplished. Patients reaching this stage should be treated in a critical care unit. Other agents (ketamine, valproate) may be considered based on their favorable adverse effect profiles.

e. Should the patient not be controlled with propofol, or is intolerant of it, administer pentobarbital 12 mg/kg at 0.2 - 0.4 mg/kg/min as tolerated, followed by an infusion of 0.25

f. 2.0 mg/kg/hr as determined by EEG monitoring. Most patients will require systemic and pulmonary arterial catheterization, with fluid and vasoactive drug therapy as indicated to maintain blood pressure.

V. Prevent recurrence of SE. The choice of drugs depends greatly on the etiology of SE and the patient’s medical and social situation.

VI. Treat complications.

a. Rhabdomyolysis should be treated with a vigorous saline diuresis to prevent acute renal failure; urinary alkalinization may be a useful adjunct. If definitive treatment of GCSE takes longer than expected because of hypotension or arrhythmias, neuromuscular junction blockade under EEG monitoring might be considered.

b. Hyperthermia usually remits rapidly after termination of SE. External cooling usually suffices if the core temperature remains elevated. In rare instances, cool peritoneal lavage or extracorporeal blood cooling may be required. High dose pentobarbital generally produces poikilothermia.

c. The treatment of cerebral edema secondary to SE has not been well studied. When substantial edema is present, one should suspect that SE and cerebral edema are both manifestations of the same underlying condition. Hyperventilation and mannitol may be valuable if edema is life threatening. Edema due to SE is vasogenic in origin, so steroids may be useful as well.
REFERENCES


SEIZURES AND EPILEPSY: UPDATE

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Outline of Dr. Bleck’s review and updated review

I. Epidemiology
   a. Seizures in critical care population
      i. Mayo clinic study (Wijdicks 1993) – 7 pts/1000 ICU admission
      ii. Bleck study (1993) – 35 pts/1000 admissions, most commonly in non-primary neurological diagnoses
   b. Status epilepticus – 50,000-250,000 incidence/year or 10-20/100,000
      i. Mortality – 22% overall, 3% in peds population (Richmond study 1996), 32% in SE lasting > 60min, 70% in adults with anoxic etiology
      ii. Risk factors
         1. Adults: stroke, withdrawal from AEDs, cryptogenic, alcohol withdrawal, anoxia, metabolic
         2. Children: systemic infection, congenital anomalies, anoxia, metabolic, AED withdrawal, CNS infections, trauma (Richmond study)
         3. Peds: (Lacroix study 1994); 32% due to underlying epilepsy, 13.6% atypical febrile convulsions, 13% purulent meningitis, 13% encephalitis.
   c. Non-convulsive status epilepticus – 1/5/100,000/year (Tomson 1992)

II. Pathophysiology
   a. Cells of the cerebral cortex, hippocampus, thalamus
      i. Pyramidal cells of cortical layer V
      ii. CA3 neurons of hippocampus
   b. Intracellular paroxysmal depolarizing shifts (PDS) manifest on scalp EEG as interictal spike
   c. Bursts of depolarization mediated by Na and Ca slow action potentials
      i. Enhanced by low Mg
      ii. Enhanced by low K
   d. Excitatory amino acid receptors (EAA) – important in learning and memory
      i. Ionic channels coupled to excitatory receptors
         1. AMPA channels
         2. NMDA channels
         3. Metabotropic channels
      ii. Cellular effects of EAA channel activity
         1. Toxic levels intracellular free calcium
         2. Activate autolytic enzymes
         3. oxygen free radical production
4. Nitric oxide production
5. Enzyme and receptor phosphorylation - enhance seizure activity
6. Increase intracellular osmolality – neuronal swelling
7. Failure of ATP pumps leads to cellular death
   iii. Longer duration can lead to permanent neuronal injury
e. Inhibitory systems
   i. Recurrent inhibitory interneurons – GABAergic pathways
   1. Tachyphylaxis to benzodiazepine receptors – BDZ-sens R replaced by BDZ-insens R (Goodkin 2008)
   ii. Intrinsic neuronal inhibition via K channel (calcium dependent)
   iii. Thalamic afferents
f. Non-convulsive status epilepticus
g. Clinical correlates: progression of GCSE by stage – 20% progress to NCSE
   i. GTC convulsions – discrete seizures with interictal slowing
   ii. Low amplitude clonic activity – waxing and waning ictal discharges
   iii. Slight clonic activity of the eyes, face, hands – continuous ictal discharge
   iv. Rare slight clonic activity – continuous ictal discharge with int. periods of suppression
   v. Coma – no clinical manifestation – periodic epileptiform discharges on a flat background
h. Neuropathology in status epilepticus
   i. Increase oxygen and glucose, cerebral blood flow initially – 20min
   ii. Local catabolism to meet energy demand after 20min
   iii. Neuronal damage can occur even in ventilated, paralyzed and fully supported patients – hippocampus most vulnerable
i. Systemic effects in status epilepticus
   i. Systemic BP and pulmonary art pressure rise during seizure onset
   ii. Hyperglycemia due to epinephrine and cortisol stimulation
   iii. Elevated lactate from muscle contractions, rigidity
   iv. Respiratory insufficiency – airway obstruction, aspiration, abnormal diaphragmatic contractions, CO2 retention due to hypoventilation
   v. Increase in body temp – muscular contraction, decreased peripheral blood flow
   vi. Metabolic and respiratory acidosis – hyperkalemia
   vii. Increased circulating catecholamines – sudden death cardiac arrest, takotsubo cardiomyopathy, neurogenic pulmonary edema
   viii. Rhabdomyolysis – myoglobinuria, renal failure
   ix. Compression fractures, shoulder dislocations, other ortho injuries
   x. Cerebral edema – usually vasogenic so may respond to steroids
III. Clinical Features of status epilepticus
a. Classification:
   i. Generalized convulsive SE
      1. Primary generalized SE – tonic/clonic, myoclonic, clonic
      2. Secondarily generalized SE (symptomatic) – focal onset
   ii. Partial SE
1. Simple partial SE – epilepsia partialis continua
2. Complex partial SE – can cause focal neuronal injury
iii. Nonconvulsive SE
   1. Absence SE (petit mal status)
   2. Atonic SE
   3. Atypical absence
   4. Sequellae of partially treated GCSE
iv. Neonatal SE – clinical presentation often atypical, important to recognize and treat as electrographic seizures may affect future brain development and development of epilepsy
b. Pediatric SE
   i. Infants, children – altered mental status, incoordination, imbalance, periodic obtundation and behavioral states, often misdiagnosed
c. NCSE as a sequel of treated GCSE
   i. Most will awaken in 15-20min if GCSE is stopped
   ii. Electrographic seizure activity persists in 20% despite cessation of motor activity
   iii. Emergent treatment under continuous EEG monitoring to prevent ongoing neuronal injury
   iv. Atypical presentations: catatonia, psychiatric, altered mental status
d. Partial SE in ICU patients
   i. Post stroke or other focal lesions (tumor, abcess)
   ii. Aphasic SE
   iii. Isolated sensory symptoms
   iv. Epilepsia partialis continua – may be difficult to treat. Can occur from metabolic such as non-ketotic hyperglycemia
IV. Diagnosis
a. Stat EEG – usually 20-30min recording
   i. Non-comatose – 95% of seizures detected with 24 hrs of cEEG
   ii. Comatose – 87% of seizures detected within 48 hrs of cEEG, and 97% by 168 hrs
c. QEEG (see Stewart reference)
   i. Amplitude integrated EEG (aEEG)- 81% sensitivity in detecting seizures
   ii. Compressed density spectral array (CDSA)- 83% sens sz detection
   Low false positive rates. Dec sensitivity in detection of low amplitude or short duration focal seizures.
d. Artifacts in EEG – increase in source of artifacts from recording in special care units. Video recording necessary to time-lock sources of artifact.
e. Encephalopathy patterns – triphasic waves and ictal-interictal continuum of
f. BIS monitoring – good correlation of BIS and continuous EEG excellent*
   i. BIS of 30 = 99% sens and 98% spec for burst suppression

g. MRI – reversible diffusion, FLAIR and T2 abnormalities on MRI, non-vascular distribution.
V. Treatment of status epilepticus
   a. Do not delay treatment waiting on an EEG if clinically apparent seizures
   b. Protocol
      i. Airway
         1. Cessation of seizure often accomplishes this
         2. Intubation
            a. Vecuronium – 0.1mg/kg
            b. Premedicate with lidocaine (1mg/kg) if increased ICP
            c. Premed with thiopental (4-5 mg/kg) if increased ICP
      ii. Blood pressure
         1. Hypotension – IVF or pressors
         2. Hypertension – no need to treat unless ICH/SAH as it usually corrects once seizure terminates
      iii. First line agents to terminate SE (Stage 1: < 30min)
         initial drug showed 43-65% success in DVA trial
         1. IV Lorazepam (0.1mg/kg – 4mg IVP): drug of choice
            a. Higher initial response rate – 65%
            b. Longer duration of action (4-14 hrs)
            c. If no response after 5min – move to second line agents
         2. Diazepam
            a. IV - shorter duration of action (20min)
               i. More respiratory depression in children
            b. Rectal – more effective than IV in children
      iv. Second line agents (Stage 2: 30-60min)
         much lower response rate (7%) if first line agent fails, so it would be reasonable to go to a continuous IV drip instead (see below)
         1. Phenytoin – 20mg/kg iv, administer at rate of 50mg/min. + additional 5mg/kg iv before moving to another AED
            a. Advantage – long duration of action
         2. Fosphenytoin – 20mg/kg PE iv + 5 mg/kg PE, rate <150mgPE/min
            a. Advantage – can be administered faster than phenytoin, but still watch for cardiac arrhythmia.
            b. Less phlebitis than phenytoin
         3. Depakote – 20 mg/kg load at rate of 3-6mg/kg/min
            a. 20 studies totaling 533 adults/children showed equal efficacy to phenytoin/fosphenytoin as second line therapy to benzos, or as first line therapy*
            b. Side effects: hypotension, dizziness, thrombocytopenia, rarely acute encephalopathy
            c. Advantage – no cardiorespiratory depression
      v. Continuous drip – alternative second line agents or refractory status
         1. cIv midazolam – 0.2mg/kg load, then 0.2 – 2.0 mg/kg/hr
            a. Titrate EEG background to burst-suppression (diffuse slow, flat ok)
            b. Tachyphylaxis commonly develops

*References:
c. lower mortality in pts with APACHE II > 20; 17% vs 56% with propofol (Prasad 2001)

2. cIV propofol: 3-5mg/kg bolus, 1-15mg/kg/hr drip
   a. titrate to EEG background – burst suppression if poss
   b. pt must be intubated
   c. watch for rebound withdrawal convulsions
   d. prolonged use associated with increased morbidity and mortality.

vi. Alternative second line agents
1. Levatiracetam – 2000 – 4000 mg daily (divided Q 12 –Q8 hrs)
   a. Multiple open label studies have shown excellent efficacy with low toxicity (Shorvon – 18 studies referenced)
   b. No randomized controlled trials however
2. Lacosamide – 400mg IV bolus
   a. Only approved as adjunctive oral therapy for partial sz
   b. Few case reports using IV bolus promising and well tolerated side effects
   c. Slow inactivation of voltage gated Na channel
3. Phenobarbital – rarely used to terminate SE
   a. May be more effective in simple partial SE
   b. Use to wean pts off high-dose midazolam or anesthetic barbiturates

Other considerations
i. Correct obvious metabolic abn: dextrose, thiamine, potassium, Mg
ii. Obtain stat EEG if pt does not awake after clinical seizure activity stops
iii. Continuous EEG monitoring for persistent altered mental status (24 hrs) or comatose (48hrs), or to titrate continuous drip therapies

vi. Treatment of refractory status epilepticus, GCSE (Stage 3: > 60min)
   a. RSE = no response to first (BDZ) or second line agents (phenytoin, valproate, phenobarb, +/- propofol)
   b. First RCT in RSE by Rossetti 2010 showed termination of RSE in 43% by propofol and 22% by barbiturates (not significant), longer mech ventilation times for pts on barbiturates though mortality and recovery to baseline similar in both groups. Study group size was small (24 pts)
   c. Agents to consider
      i. Pentobarbital - 12mg/kg at rate of 0.2-0.4mg/kg/min load, then infusion of 0.25-2.0 mg/kg/hr to titrate to burst suppression. Hemodynamic monitoring and support likely needed.
      ii. Thiopental – 100-250mg over 20sec, then additional 50mg boluses every 2-3min until sz stop, infusion 3-5mg/kg/h to titrate to burst suppression
      iii. Ketamine – NMDA antagonist
      iv. Inhalational anesthetics – isoflurane, desoflurane
         1. End-tidal concentrations of 1.2-5%
2. Reports of use up to 10 days longer use associated with T2 signal change in the thalamus/cerebellum.
3. Consider use when IV anesthetics fail, not for prolonged use
4. No organ toxicity but hypotension and rebound seizure can occur
v. Magnesium – blocks NMDA receptor
vi. Lidocaine – stabilizes cell membranes
1. IV bolus of 1.5-2 mg/kg over 2min, then 3-4 mg/kg/hr for max of 12 hrs.
2. Risk of significant toxicity and exacerbation of sz with prolonged use
vii. Therapeutic hypothermia – reduce energy demands and exitotoxic transmission
viii. Vagal nerve or deep brain stimulation – case reports
ix. IV gammaglobulin – autoimmune etiology
x. IV steroids – autoimmune etiology
xi. Plasmapheresis – autoimmune etiology

VII. Treatment of refractory complex partial status epilepticus (CPSE)
aggressiveness of treatment is controversial and non-anesthetic agents may be preferred

VIII. Pediatric treatment of SE
a. Prehospital treatment
   i. Shorter duration of SE (32 min vs 60min), less recurrent sz in the ED (58% vs 85%), and no difference in intubation with route of administration in children treated prehospital (Alldredge 1995)
   ii. Diazepam – rectal and IV equally efficacious (Dieckmann 1994)
      1. No children required intubation with rectal form
      2. Rectal form: 30% recurrent convulsions vs 60% for IV form
   iii. Midazolam – 0.5mg/kg buccal form showed better seizure cessation (56%) than rectal diazepam (27%). (McIntyre 2005)
b. Cardiorespiratory support
c. Termination of seizure activity
   i. First line agents
      1. Lorazepam – 0.1mg/kg IV
         a. Less repeat doses (3%) needed than diazepam (31%)
      2. Midazolam – 0.05-0.34 mg/kg PR or IV
      3. Diazepam – 0.1-0.5 mg/kg PR or IV
   ii. Follow with long acting agents
      1. Phenytoin 20mg/kg IV
      2. Fosphenytoin 20 mg/kg PE IV
      3. Phenobarbital 10-20 mg/kg IV
   iii. Refractory status in children
      1. midazolam infusion gaining acceptance
         a. Mean effective dose 2.3 mcg/kg/min (range 1-18)
b. No significant cardiorespiratory changes noted (Rivera 1995)
c. Lower mortality in peds SE than other agents

2. Pentobarbital – few published studies in children
   a. 1.0-3.0 mg/kg/hr achieved burst suppression on EEG
   b. Taper after 12 hours of sustained burst suppression

3. Propofol – unclear role in children with SE
   a. may cause rhabdomyolysis, so monitor serum CK
   b. oxygenation difficulties reported with use

IX. Outcome in SE
   a. Short term outcomes estimate 25% overall mortality in pts with CSE. Predictors of mortality were continuous or refractory sz activity, and cerebral insult.
   b. Residual symptoms are cognitive dysfunction, motor deficits, worsening of previous epilepsy or residual epilepsy if new onset SE.
   c. Retrospective study showed better outcomes with adherence to strict treatment protocol; pt with adequate first line treatment were 7x more likely stop szs
   d. Prospective study (Legriel 2010) results
      i. Of 248 patients admitted to ICU with SE (excluding postanoxic SE), 18.8% mortality within 90 days
      ii. 42% had a good recovery; GOS = 5.
      iii. Factors assoc with poorer 90 day outcome
         1. Seizure duration > 120min
         2. Refractory SE
         3. Presence of cerebral insult
         4. Older age

X. Autoimmune epilepsy
   a. VGKC complex ab – assoc with limbic encephalitis; seizures, confusion, amnesia with generalized or temporal lobe seizures and medial temporal lobe signal changes on MRI in 60%. These abs found mostly in serum rather than CSF.
      i. CASPR2 Ab – assoc with neuromyotonia, paraneoplastic, thymomatous
      ii. LGI1 – most pts with limbic associated mediotemp lob epilepsy
      iii. Contactin 2 proteins
      iv. Faciobrachial dystonic seizures – assoc with LGI1 subset of VGKC complex Ab. 40% of these patients had myoclonus. Also unexplained falls.
   b. NMDA-R Ab – originally described as a paraneoplastic encephalopathy syndrome in young women with ovarian teratoma. Ab higher in serum than CSF.
      i. Now mostly assoc with non-paraneoplastic disease
      ii. Seizures seen in 80% and also neuropsychiatric features, choreoathetoid mvs, dysautonomia, dec level of consciousness, NCSE, refractory seizures.
      iii. May be a common cause of encephalitis lethargic
   c. GABA-R Ab syndrome – drug refractory seizures and limbic symptoms
   d. AMPA-R Ab syndrome – low association with seizures (3/10)
Rasmussen’s encephalitis – unihemispheric synd starting in childhood with intractable partial seizures, secondary generalization progressing to cortical inflammation and subsequent neurologic deficits with intractable seizures. Historically treated with hemispherectomy, though rituximab has been reported to be successful.

GAD-R Ab – may be more of a marker of underlying autoimmune disease

Post-infectious

SUDEP: Sudden unexpected death in epilepsy

1. 1 in 1000 with epilepsy and 1 in 150 with refractory epilepsy dies of SUDEP
2. Definite SUDEP requires postmortem examination that shows no cause of death
3. Many patients with SUDEP found prone, similar to SIDS
4. Cardiac arrhythmia, autonomic hyperactivity, central apnea, genetic factors (Dravet syndrome) may play a role

ADDITIONAL REFERENCES