STATUS EPILEPTICUS

INTRODUCTION
Status epilepticus is a common cause of admission into the Pediatric Intensive Care Unit. Treating seizures early and with appropriate drugs can improve outcomes.

DEFINITION AND EPIDEMIOLOGY
• In 1989, the International League Against Epilepsy defined status epilepticus as either:
  1. A seizure lasting five minutes
  2. Two or more discrete seizures in between which there is an incomplete recovery of consciousness
• A seizure lasting five minutes or more is very rare and most patients with epilepsy will never have status epilepticus
• The pediatric population is much more likely to be effected by status epilepticus than the adult population. Only 5% of adults and 10-25% of children with epilepsy will have an episode of status epilepticus
• 64 to 85% of cases of status epilepticus occur within the first year of life
• Children are more likely to present with status epilepticus, because many have not been diagnosed with epilepsy when they present with a status epilepticus event, and therefore they are not receiving prophylactic antiepileptic medication

PATHOPHYSIOLOGY
• Any type of seizure (generalized convulsive, non-convulsive, simple, complex, or partial) can progress to status epilepticus if it occurs for longer than five minutes
• Myoclonic status epilepticus which occurs after hypoxia, is a misnomer. Following a significant hypoxic-ischemic event, a patient may have severe myoclonus, and the EEG commonly shows encephalopathy without ongoing seizures
• Seizures start because of an imbalance between excitatory and inhibitory neurotransmission
• The excitatory neurotransmitter that is implicated in almost all seizures is glutamate, and glutamate concentration increases at the site of the seizure focus in the brain at the time of the onset of the seizure (Figure 1)
• Following glutamate release, GABA, the inhibitory neurotransmitter, causes the seizure to cease (Figure 1)
• Patients with intractable epilepsy, who have many seizures in a day, typically go through this cycle many times each day
• When seizures don’t cease after a minute and the seizure is prolonged, GABA receptors change and become less sensitive to innate GABA and benzodiazepines. The appropriate dose of benzodiazepines should be used as early as possible. Benzodiazepines are more likely to be efficacious when the GABA receptors respond appropriately
• The immature brain has more seizures than the mature brain because excitatory synapses mature earlier than inhibitory synapses, and the infant brain has a higher synaptic density.

ELECTROENCEPHALOGRAM (EEG)
• After 30 minutes, the discharge becomes continuous. The EEG demonstrates seizure discharge interspersed with a normal EEG pattern in between (Figure 3). Eventually, these discharges fragment, and between the discharges is a flat, or encephalopathic, EEG pattern (Figure 4)
SYSTEMIC RESPONSE TO STATUS EPILEPTICUS
There are two stages of systemic response to status epilepticus: compensatory and decompensatory (Figure 5).

PATTERNS OF BRAIN INJURY
- Autopsy specimens from patients who have died from status epilepticus demonstrate neuronal loss and a reactive gliosis in several areas of the brain: neocortex, the amygdala of the hippocampus, the dorsal medial thalamic nuclei, and the purkinje cell layer of the cerebellum.
- Initially it was believed that hypoxia and acidosis and metabolic derangements, and even hyperthermia, all led to an ischemic neuronal damage. It has since been shown that glutamate causes injury.
- Excessive glutamate can lead to cell death by necrosis and/or apoptosis.
- The primary receptor involved in this is the NMDA receptor. Glutamate, glycine and d-Serine can bind to this receptor, causing calcium influx, and activating a number of cellular mechanisms leading to cell death.

DEVELOPMENT OF EPILEPSY
- There is a low incidence of neurologic deficits or cognitive impairments in children who have had febrile convulsive status epilepticus, but the risk of subsequent epilepsy has been reported as high as 21% in this group.
- The incidence of developing epilepsy seems to be somewhat dependent on the duration of the initial febrile seizure.
- Development of new neurons may be the mechanism in which how prolonged seizures might initiate epilepsy.

PHARMACOLOGY
- Benzodiazepines are used as a first line agent.
  - They work to enhance the inhibitory transmission of the GABA receptor, thus increasing chloride ion transmission of chloride ions rendering the neurons less excitable.
  - Benzodiazepines used at higher concentrations have an affect on the voltage-activated sodium channels, prolonging the rate of recovery of these channels, therefore limiting the repetitive neuronal firing.
- Barbiturates work by a very similar mechanism to the benzodiazepines, enhancing inhibitory transmission through the GABA receptor and amplifying the chloride transmission.
- Phenytain works through frequency-use and voltage-dependent neuronal sodium channels, slowing their rate of recovery, and thereby limiting the repetitive firing of action potentials.
- In general, drugs which prevent seizures are often not efficacious for stopping status epilepticus.
- The longer the duration of status epilepticus, the less efficacious the drugs are and a greater amount of medication is required to abort status epilepticus.
- Decreased benzodiazepine efficacy during status epilepticus is thought to be related to plastic changes of the GABA receptor, and an inversion of the chloride equilibrium.
- Phenytoin failure during status epilepticus may be related to long term potentiation of excitatory synapses in the dentate gyrus, and translocation in phosphorylation of calmodulin kinase 2 enhancing glutamate release.

SUMMARY
- An algorithm can be helpful to provide medications in the appropriate doses to halt status epilepticus in a timely fashion.
- Benzodiazepines work best early in the seizure.

REFERENCES