Status Epilepticus

- Status epilepticus (SE) is any seizure lasting longer than 30 minutes whether or not consciousness is impaired, or recurrent seizures without an intervening period of consciousness between seizures.

- SE is a medical emergency with significant morbidity and mortality, and aggressive treatment of seizures which last 5 minutes or more is strongly recommended.

International Classification of Status Epilepticus (SE)

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

- Seizure initiation is likely caused by an imbalance between excitatory (e.g., glutamate, calcium, sodium, substance P, and neurokinin B) neurotransmission and inhibitory (γ-aminobutyric acid, adenosine, potassium, neuropeptide Y, opioid peptides, and galanin) neurotransmission.

- Seizure maintenance is largely caused by glutamate acting on postsynaptic *N-methyl-D-aspartate and* α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate/akinate receptors. Sustained depolarization can result in neuronal death.

- There is evidence that γ-aminobutyric acid A receptors may be modified during SE and become less responsive to endogenous agonists and antagonists.

- Two phases of GCSE have been identified. During **phase I**, each seizure produces marked increases in plasma epinephrine, norepinephrine, and steroid concentrations that may cause hypertension, tachycardia, and cardiac arrhythmias.

- Muscle contractions and hypoxia can cause acidosis, and hypotension, shock, rhabdomyolysis, secondary hyperkalemia, and acute tubular necrosis may ensue.

- **Phase II** begins 60 minutes into the seizure, and the patient begins to decompensate. The patient may become hypotensive, and cerebral blood flow may be compromised.

- Glucose may be normal or decreased, and hyperthermia, respiratory deterioration, hypoxia, and ventilatory failure may develop.

- Younger children, the elderly, and those with preexisting epilepsy have a higher propensity for sequelae.

- Recent estimates suggest a mortality rate of up to 10% in children, 20% in adults, and 38% in the elderly.

- Variables affecting outcome are (1) the time between onset of GCSE and the initiation of treatment, and (2) the duration of the seizure.

CLINICAL PRESENTATION AND DIAGNOSIS:

SYMPTOMS:

- Impaired consciousness (e.g., ranging from obtunded to markedly lethargic and somnolent).

- Disorientation (once GCSE is controlled)
- Pain associated with injuries (e.g., tongue lacerations, shoulder dislocations, head and facial trauma)

SIGNS:

Early/

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

Late Signs:

- Clinical seizures may or may not be apparent
- Pulmonary edema with respiratory failure
- Cardiac failure (dysrhythmias, arrest, cardiogenic shock)
- Hypotension/hypertension
- Disseminated intravascular coagulation, multiorgan failure
- Rhabdomyolysis
- Hyperpyremia

DIAGNOSIS:

Initial Laboratory Tests

- Complete blood count (CBC) with differential
- Serum chemistry profile (e.g., electrolytes, calcium, magnesium, glucose, serum creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST])
- Urine drug/alcohol screen
- Blood cultures
- Arterial blood gas (ABG) to assess for metabolic and respiratory acidosis
- Serum drug concentrations if previous anticonvulsant use is suspected or known

Other Diagnostic Tests:

- Spinal tap if CNS infection suspected.
- Electroencephalograph (EEG) should be obtained immediately and once clinical seizures are controlled.
- Computed tomography (CT) with and without contrast.
- Magnetic resonance imaging (MRI).
- Radiograph if indicated to diagnose fractures.

DESIRED OUTCOME:

The goals of treatment are

(1) terminate clinical and electrical seizure activity,

(2) minimize side effects,

(3) prevent recurrent seizures, and

(4) Avoid pharmacoresistent epilepsy and/or neurologic sequelae.

TREATMENT:

- For any tonic-clonic seizure that does not stop automatically or when doubt exists regarding the diagnosis, treatment should begin during the diagnostic workup.

- Concurrent with initiation of anticonvulsants, vital signs should be assessed and an adequate airway should be established and ventilation maintained.

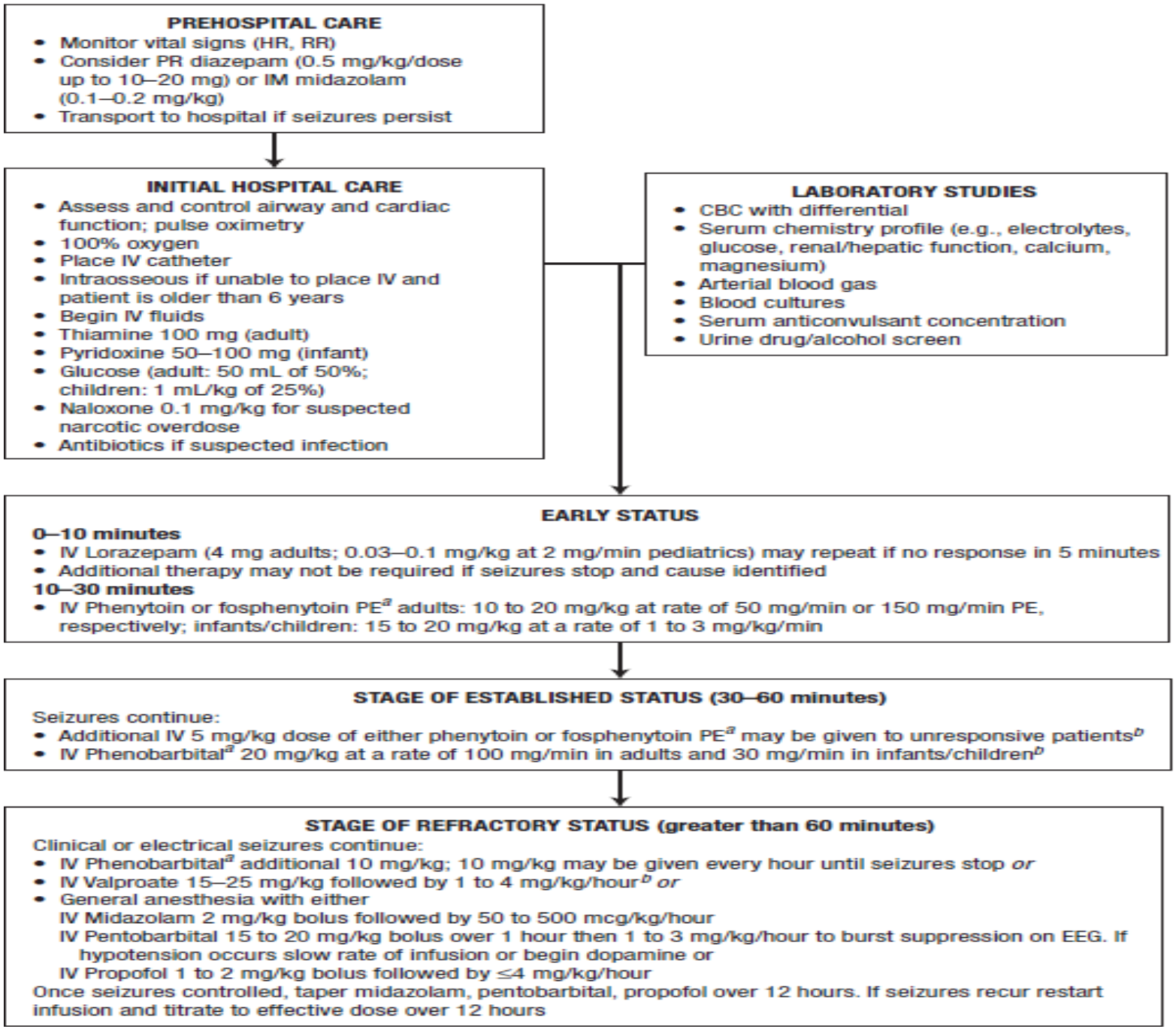
- Oxygen should be administered.

- If there is poor air exchange, the patient should be intubated and ventilated mechanically. Temperature should be monitored frequently.

- Normal to high blood pressure should be maintained.
- All patients should receive IV glucose, and **thiamine (100 mg IV) should** be given prior to glucose in adults.

- Metabolic and/or respiratory acidosis should be assessed by ABG measurements to determine pH, PaO_2, $PaCO_2$, and HCO_3.

- If pH is less than 7.2, secondary to metabolic acidosis, sodium bicarbonate should be given.


PREHOSPITAL CARE
• Monitor vital signs (HR, RR)
• Consider PR diazepam (0.5 mg/kg/dose up to 10–20 mg) or IM midazolam (0.1–0.2 mg/kg)
• Transport to hospital if seizures persist
INITIAL HOSPITAL CARE
• Assess and control airway and cardiac function; pulse oximetry
• 100% oxygen
• Place IV catheter
• Intraosseous if unable to place IV and patient is older than 6 years
• Begin IV fluids
• Thiamine 100 mg (adult)
• Pyridoxine 50–100 mg (infant)
• Glucose (adult: 50 mL of 50%; children: 1 mL/kg of 25%)
• Naloxone 0.1 mg/kg for suspected narcotic overdose
• Antibiotics if suspected infection
LABORATORY STUDIES
• CBC with differential
• Serum chemistry profile (e.g., electrolytes, glucose, renal/hepatic function, calcium, magnesium)
• Arterial blood gas
• Blood cultures
• Serum anticonvulsant concentration
• Urine drug/alcohol screen
EARLY STATUS
0–10 minutes
• IV Lorazepam (4 mg adults; 0.03–0.1 mg/kg at 2 mg/min pediatrics) may repeat if no response in 5 minutes
• Additional therapy may not be required if seizures stop and cause identified
10–30 minutes
• IV Phenytoin or fosphenytoin PE[a] adults: 10 to 20 mg/kg at rate of 50 mg/min or 150 mg/min PE, respectively; infants/children: 15 to 20 mg/kg at a rate of 1 to 3 mg/kg/min
STAGE OF ESTABLISHED STATUS (30–60 minutes)
Seizures continue:
• Additional IV 5 mg/kg dose of either phenytoin or fosphenytoin PE[a] may be given to unresponsive patients[b]
• IV Phenobarbital[a] 20 mg/kg at a rate of 100 mg/min in adults and 30 mg/min in infants/children[b]
STAGE OF REFRACTORY STATUS (greater than 60 minutes)
Clinical or electrical seizures continue:
• IV Phenobarbital[a] additional 10 mg/kg; 10 mg/kg may be given every hour until seizures stop or
• IV Valproate 15–25 mg/kg followed by 1 to 4 mg/kg/hour[b] or
• General anesthesia with either
IV Midazolam 2 mg/kg bolus followed by 50 to 500 mcg/kg/hour
IV Pentobarbital 15 to 20 mg/kg bolus over 1 hour then 1 to 3 mg/kg/hour to burst suppression on EEG. If hypotension occurs slow rate of infusion or begin dopamine or
IV Propofol 1 to 2 mg/kg bolus followed by ≤4 mg/kg/hour
Once seizures controlled, taper midazolam, pentobarbital, propofol over 12 hours. If seizures recur restart infusion and titrate to effective dose over 12 hours

- A benzodiazepine (BZ) should be administered as soon as possible if the patient is actively seizing. Generally one or two IV doses will stop seizures within 2 to 3 minutes.

- Diazepam, lorazepam, and midazolam are equally effective. If seizures have stopped, a longer-acting anticonvulsant should be given.

- With BZ administration, a brief period of **cardiorespiratory depression** (less than 1 minute) may occur and can necessitate assisted ventilation or require intubation, especially if BZs are used with a barbiturate. **Hypotension** may occur with high doses of BZs.

- Phenytoin has a long half-life (20 to 36 hours), but it cannot be delivered fast enough to be considered a first-line agent.

- It takes longer to control seizures than do the BZs because it enters the brain more slowly.

- It causes less respiratory depression and sedation than the BZs or phenobarbital, but it is associated with ***administration-related cardiovascular toxicity*** (the vehicle is 40% propylene glycol).

- Phenytoin should be diluted to less than or equal to 5 mg/mL in normal saline. The maximum rate of infusion is 50 mg/min in adults (25 mg/min in the elderly) and 3 mg/kg/min in children less than 50 kg.

- Vital signs and ECG should be obtained during administration. If arrhythmias or hypotension occurs or if the QT interval widens, the rate should be slowed.

- Maintenance doses should be started within 12 to 24 hours of the loading dose.

- **Fosphenytoin**, the water-soluble phosphate ester of phenytoin, is a phenytoin prodrug.

- The dose of fosphenytoin sodium is expressed as phenytoin sodium equivalents (PE).

- Adverse reactions include nystagmus, dizziness, and ataxia. Paresthesias and pruritus typically disappear within 5 to 10 minutes after the infusion.

- In adults, the rate of administration should be 100 to 150 mg PE/min. Pediatric patients should receive fosphenytoin at a rate of 1 to 3 mg PE/kg/min.

- Continuous ECG, blood pressure, and respiratory status monitoring is recommended for all loading doses of fosphenytoin. Serum phenytoin concentrations should not be obtained for at least 2 hours after IV and 4 hours after intramuscular administration of fosphenytoin.

- The Working Group on Status Epilepticus recommends that **phenobarbital** be given after a BZ plus phenytoin has failed.

- Most practitioners agree that phenobarbital is the long-acting anticonvulsant of choice in patients with hypersensitivity to the hydantoins or in those with cardiac conduction abnormalities.

- In order to avoid overdosing, estimated lean body mass should be used in obese patients.

- Peak brain concentrations occur 12 to 60 minutes after IV dosing. On average, seizures are controlled within minutes of the loading dose.

- If there is inadequate response to high doses of **midazolam, anesthetizing** is recommended.

- Intubation and respiratory support are mandatory during **barbiturate coma, and continuous monitoring of vital signs is** essential.

- A short-acting barbiturate (e.g., **pentobarbital or thiopental) is** generally preferred.

- Serum concentrations of 30 to 40 mg/L are necessary to induce an isoelectric EEG. If hypotension occurs, the rate of administration should be slowed or dopamine should be administered.

- The loading dose should be followed immediately by an infusion increasing gradually until there is burst suppression on the EEG or adverse effects occur.

- Propofol is very lipid soluble, has a large volume of distribution, and has a rapid onset of action. It has comparable efficacy to **midazolam for** refractory GCSE.

- It has been associated with metabolic acidosis, hemodynamic instability, and bradyarrhythmias that are refractory to treatment.

- Lidocaine is not recommended unless other agents have failed. It has a rapid onset of action. Fasciculations, visual disturbances, and tinnitus may occur at serum concentrations between 6 and 8 mg/L.

- Seizures and obtundation may develop when serum concentrations exceed 8 mg/L.

- *Levetiracetam, topiramate,* and the general anesthetics, halothane, isoflurane, and ketamine are being evaluated for refractory GCSE, but their efficacy, safety, or overall suitability have not been established to date.