

**Status Epilepticus (SE)**

Last updated: April 12, 2020

**DEFINITIONS**

SEIZURE CLUSTER (S. ACUTE REPETITIVE SEIZURES CRESCENDO SEIZURES, SEIZURE FLURRIES) – acute episodes of consecutive seizures that occur within a short period of time with a patient regaining consciousness during the interictal period. These clusters are distinct from a person’s typical seizure pattern.

- when left untreated, can progress to status epilepticus.

**Status Epilepticus (SE)** by 2015 ILAE task force:

- seizure **lasting > 5 minutes** for generalized tonic-clonic seizures
- seizure **lasting > 10 minutes** for focal seizures
- seizure **lasting > 10-15 minutes** for absence seizures

Other definitions:

- persistent seizure activity after sequential administration of appropriate **first and second-line AEDs**
- **continuous** seizure activity (clinical or electrical) ≥ 30 min.
- **repetitive** seizures with incomplete neurological recovery interictally for period ≥ 30 min.

**Refractory SE** – if seizures continue despite two AEDs after **30 minutes** (for generalized seizures) or 60 minutes (for focal seizures) - mortality as high as 38%.

**Super-refractory SE** – if SE continues beyond **24 hours** despite treatment.

**EPIDEMIOLGY**

- **INCIDENCE** - 15-20 cases per 100,000 people.
most cases (70%) occur in **young children** (among children, 73% are < 5 yrs old)
next most affected group is patients > 60 yrs age.

**ETIOLOGY**

1. **Acute CNS insults** (50%) - anoxia, head injury, stroke, neoplasm, infection, ethanol withdrawal or intoxication (!!!).
2. **Therapy related** (20%) - medication adjustments, **noncompliance** (most common cause in pre-known epileptic patients! esp. with abrupt phenobarbital withdrawal), intercurrent illness (preventing PO intake of meds), drug-drug interactions (lowering effectiveness of AEDs)
3. **Undetermined cause** (30%); may be as first manifestation of idiopathic epilepsy.

- in > 50% of cases, SE is **patient's first seizure** (i.e. > 50% SE patients do not have history of epilepsy); 1 out of 6 patients presenting with first time seizure will present in SE.
- 5-15% epileptic patients have had one or more SE episodes at some time.

**ADULTS**
- most common cause - subtherapeutic AED levels in patient with known seizure disorder.
- **cerebrovascular disease** predominates (25%) in **OLDER ADULTS**
- structural lesion is more likely than in pediatric subgroup.

**CHILDREN**
- in children < 1 yr age, 28% are secondary to **CNS infection**, 30% due to **electrolyte disorders**, 19% associated with **fever**.

  **Fever & infection** are most common precipitants in children!

**PATHOLOGY**

- in animals, neurons begin to die **after 20-60 minutes of continuous discharging** (precise time period in humans is unknown but irreversible changes begin to appear in neurons after as little as 20 minutes of convulsive activity; cell death is very common after 60 mins)
  - mean duration of SE in patients without neurologic sequelae is 1.5 hrs.
- significant increases in cerebral blood flow and metabolic rate during SE.
- neuron death may result from:
  1) metabolic **exhaustion**
  2) damage by **excitatory neurotransmitters**
- **most vulnerable areas** - hippocampus, amygdala, cerebellum, middle cortical areas, thalamus.
- **acute MACROSCOPIC changes** - venous congestion, small petechial hemorrhages, edema.
- **MICROSCOPIC changes**: ischemic cellular changes → microglial proliferation, neuronophagia → cell loss → increased numbers of reactive astrocytes.

**CLASSIFICATION & CLINICAL FEATURES**

a) **generalized** or **partial**
b) **convulsive** or **nonconvulsive**.
**Generalized convulsive SE (GCSE)** - convulsive activity accompanied by coma and epileptiform activity on EEG (EEG is not required for diagnosis):

*Most frequent (75%) and most dangerous type of SE!*

1) tonic-clonic
2) tonic
3) clonic
4) myoclonic

**Nonconvulsive SE** (clouding* of consciousness ± minor motor manifestations; i.e. abrupt-onset sustained confusional-delirious state):

*not complete loss (so sometimes called "twilight" form of SE)

1) **absence SE** (75% patients < 20 yrs; most other – older adults) - usually presents as one continuous episode (twilight state).
2) **complex partial SE** - usually recurring cycles of 2 distinctly separate phases (ictal and interictal).

N.B. patients can appear totally functional - clinical picture may be so subtle that only recognizable to friends and family!

- if patient is comatose, it most likely represents “burned-out” GCSE (i.e. subtle SE).
- **EEG is required** for diagnosis (and to distinguish two types):
  - absence SE – continuous 1-2.5 Hz generalized spike-wave activity ("spike-wave stupor");
  - complex partial SE - ictal activity is localized (usually to frontal or temporal lobes).

**Simple partial SE** – rare; diagnosis clinical (EEG frequently negative).

- clonic simple partial SE is called **EPILEPSIA PARTIALIS CONTINUA**. see p. E9 >>

GCSE manifestations change over time - paradoxical evolution of apparent clinical improvement (inexperienced clinician may stop treatment because of apparent improvement):

- SE begins with series of generalized tonic, clonic, or tonic-clonic seizures (**OVERT SE**);
  - each seizure is discreet; motor activity stops abruptly, coincident with end of electrographic seizure.
  - each convulsion is followed by gradual recovery, and then next seizure occurs.
- if SE is not treated, discrete convulsions give way to increasingly subtle clinical manifestations (**SUBTLE SE**); e.g. only nystagmoid jerks of eyes or shoulder twitching may be seen.
  - occasionally, subtle SE occurs without prior convulsive activity (e.g. in severe diffuse cerebral dysfunction).
- eventually, coma without motor activity is all that remains, although electrographic seizures persist (**ELECTRICAL SE**).

N.B. status epilepticus should be suspected in any unexplained coma (e.g. patient stops having overt seizures, yet remains comatose)

**Treatment should be continued until electrographic seizure activity** has resolved completely!

*CNS injury can occur even when patient is paralyzed with neuromuscular blockade but continues to have electrographic seizures.

**GCSE produces SYSTEMIC EFFECTS:**

*Permanent brain damage* is caused more by **ongoing seizure activity** than by **systemic factors**!
1) **hypoxia**, respiratory and metabolic **acidosis**
   - convulsive SE affects mechanical aspects of breathing (respiratory fatigue) + can cause neurogenic pulmonary edema + aspiration.
   - medications used for treating SE (esp. benzodiazepines and barbiturates) inhibit respiratory drive.
2) cerebral dysautoregulation, **BP instability** (↑ then ↓)
3) **hyperpyrexia** up to 42°C (motor activity + central sympathetic drive)
4) acute hypercatecholaminemia may trigger fatal cardiac arrhythmias.
5) hyperazotemia; hypokalemia; hyponatremia; hyperglycemia → hypoglycemia.
6) **rhabdomyolysis** → myoglobinuria, acute tubular necrosis, renal failure.
7) ↑↑↑ of plasma prolactin, glucagon, growth hormone, ACTH.
8) **leukocytosis** (bands should not be seen in absence of infection); modest **CSF pleocytosis**.

### NEW-ONSET REFRACTORY STATUS EPILEPTICUS (NORSE), FEBRILE INFECTION-RELATED EPILEPSY SYNDROME (FIRES)

- a clinical presentation, not a specific diagnosis:
  - NORSE - a clinical presentation in a patient without active epilepsy or other preexisting relevant neurological disorder who has NORSE without a clear acute or active structural, toxic, or metabolic cause.
  - FIRES – NORSE preceded by a febrile infection.
  - pathophysiology is largely unknown (autoimmune encephalitis in only half of cases); high levels of cytokines (IL-6 and TNFα), in the serum and CSF.
    - one study identified an association between FIRES and polymorphisms in the IL-1 receptor antagonist gene.
  - treatment - immune therapies:
    - steroids, intravenous immunoglobulins, and plasma exchange – disappointing.
    - ketogenic diet (anti-inflammatory effects) - more efficacious.
    - **ANAKINRA** - successful in a single case report.
    - **TOCILIZUMAB** (humanized monoclonal antibody against the IL-6 receptor) - SE was terminated after 1 or 2 doses of tocilizumab in 6 patients (out of 7) with a median interval of 3 days from the initiation

### DIFFERENTIAL DIAGNOSIS

SE diagnosis depends on demonstrating ictal patterns in EEG!

Neuroimaging has no impact on immediate management until seizures are controlled.

**MRI-DWI** shows diffusion restriction (up to 3 days after status)

1. **Nonepileptic phenomena** (tremor, myoclonus, eye and oral-buccal movements that follow anoxia, brain stem or bilateral cerebral ischemia, drug overdose, severe metabolic disturbances) - difficult to differentiate clinically from nonconvulsive SE.

2. Prolonged **psychogenic seizures**.

### MANAGEMENT

Acute life-threatening emergency that **demands prompt diagnosis and treatment** if severe neurological sequelae (pathologic brain changes) and death are to be minimized!
N.B. **SE duration** is major determinant of morbidity and mortality!

“Time is brain” - the sooner treatment is initiated, the better the chances of success, and the lower the risk for adverse consequences!

Nasal **MIDAZOLAM** (Nayzilam®) - nasal spray CIV, FDA approved for the acute treatment of **seizure clusters** in patients ≥ 12 years. see p. E3 >>

- **seizure activity ≥ 5-10 minutes** - treat as status, because most seizures must terminate spontaneously within 1-2 minutes.

  If seizure lasts > 2 minutes, place **intravenous line** and **draw blood** for tests. If seizure continues **beyond 5 minutes**, begin treatment with **benzodiazepine**

- **impending status epilepticus** - 3 or more TCS within 24-hour period (esp. if this represents increase from typical frequency); H: home treatment with one dose rectal **DIAZEPAM** gel (Diastat®) 10-20 mg (0.05-0.1 mg/kg) should be considered before transfer to ED.

  N.B. infusing buccal **MIDAZOLAM** into mouth (between gums and cheek) is twice as effective as rectal DIAZEPAM!

  If seizures continue, EMS can give IV/IM* **FOSPHENYTOIN**

  *gets absorbed in 5 mins, therapeutic level in 10 minutes

  - admit to ICU, set a clock in motion.
  - relapsing seizures in patient with **known seizure disorder** and subtherapeutic AED levels usually responds to bolus of maintenance AEDs, however, SE still should be treated by standard protocol.

N.B. use of neuromuscular blockers is inappropriate (unless needed for intubation – use short acting agent) because they do not stop seizure activity in brain (which is cause of brain damage!).

**Treatment for GCSE**

**STEP 1 – ABC + Coma** see p. S30 >>

1. **ABC** - secure oral airway (e.g. tongue may cause obstruction in younger patient - place nasopharyngeal airway), prevent aspiration (turn head to side, suction secretions), administer 100% O₂ (via properly fitting face mask); intubate if respirations compromised or if seizure persists > 30 min.
2. **Monitor** - ECG, SaO₂, vital signs.
3. **Blood tests** - bedside (fingerstick) glucose test; AEDs levels (if indicated), CBC, chemistries (electrolytes, Ca²⁺, Mg²⁺, BUN, creatinine, LFT), toxicological screens.
4. **Establish intravenous line** with normal saline.
5. **THIAMINE** 50-100 mg IV → **DEXTROSE** 50% 50 ml IV (D25 2 ml/kg in children).
6. Search for probable cause of SE (tests should not impede rapid and aggressive treatment!):

   1) obtain **history**
   2) perform **examination**
   3) some authors feel that **EEG monitoring** should be routine part of treatment; others use EEG only selectively (e.g. when GCSE diagnosis in doubt, assessing treatment adequacy).

   In general, EEG has no role in management of GCSE!
   4) **neuroimaging** should be done in all patients (except children with febrile SE); CT is sufficient to exclude acute brain lesion; MRI should be obtained later if CT was normal.
   5) **lumbar puncture** is performed in any febrile patient (even if signs of meningitis are not present); if ICP↑ or mass lesion are suspected, antibiotics should be given immediately and CT scan obtained first.
WBC pleocytosis (up to 80) can occur following SE (benign postictal pleocytosis), but these patients should be treated with antibiotics until infection is ruled out by negative cultures!

**STEP 2** – intravenously administer **ANTICONVULSANTS** (terminate 80-97% cases):
- continuously monitor for respiratory depression, hypotension, cardiac arrhythmias.
- advanced cardiac life support must be ready!

1. **Rapid-acting** anticonvulsant – **BENZODIAZEPINE**
   a) **LORAZEPAM** – preferred agent (aborts SE in 97% cases, provides coverage for 12 hours)
   - 0.1 mg/kg (0.02-0.5 mg/kg in children); in general:
     - < 40 kg → 2 mg
     - > 40 kg → 4 mg (or 2+2 mg).
   - at < 2 mg/min - less respiratory depression, less fat soluble - slower, but **longer duration of action** – up to 2-3 hours!!
     N.B. even though lorazepam has much shorter T1/2 than diazepam, its effective half-life in brain is longer.
   - wait 1 minute for response; if seizures continue → given additional doses up to max 9 mg (adult)
   b) **MIDAZOLAM**
     N.B. IM midazolam 10 mg (5 mg for those < 40 kg) is more effective and faster to terminate seizures than IV lorazepam (at least in prehospital setting – RAMPART trial).
   c) **DIAZEPAM** 0.1-0.2 mg/kg (0.1-1.0 mg/kg in children) at 1-5 mg/min up to 10 mg; repeat once or twice q5-30min if seizures persist (aborts SE in 68% cases)
     - diazepam (high lipid solubility and rapid CNS entry) frequently abolishes seizure activity within minutes, only for seizures to recur within 30 minutes (as drug redistributes to other fatty tissues).
     N.B. DIAZEPAM enters CNS slightly faster than LORAZEPAM but affords only 30 minute protection (vs. 12 hrs by LORAZEPAM).
     - if IV access is not obtainable, DIAZEPAM is drug of choice - may be given rectally (0.5 mg/kg, maximum 20 mg), endotracheally, intraosseously.

2. Immediately next step (to prevent seizure recurrence) – **long-acting** anticonvulsant **PHENYTOIN** 15-20 mg/kg load (up to 50 mg/min or 1 mg/kg/min); if seizures persist → additional 5-10 mg/kg boluses q20min (up to 30 mg/kg total or 30 μg/ml level).
   N.B. phenytoin is incompatible with glucose-containing solutions!
   - use **continuous ECG and BP monitoring** during infusion! (phenytoin is contraindicated in heart block).
   - better alternative - **FOSPHENYTOIN** 15-20 mg PE/kg (up to 150 mg PE/min – i.e. can be infused 3 times faster); PE = phenytoin equivalents.
   - alternative (in hypersensitive to PHT or patients who already are taking PHT but in whom blood level of PHT is not yet known*) - IV **VALPROATE** (slow onset of action is drawback).
     *administering FOSPHENYTOIN to patient who is taking PHT may raise level to point at which PHT actually becomes proconvulsant and cause cardiac arrest!
     **VALPROIC ACID** is drug of choice for MYOCLONIC STATUS; can add lorazepam or clonazepam to help with acute control.

N.B. most common cause of treatment failure - appropriate medication administered in **inadequate dosages** via **inappropriate route**!
- **Acidosis** should not be treated (acidosis does not correlate with degree of neuronal injury + acidosis is anticonvulsant).
- **Hyperthermia** should be treated aggressively (correlates with poor neurological outcome) - fans and antipyretics.

Convulsive Status Epilepticus Pediatric Trial (ConSEPT)
- randomly assigned 233 children to receive either levetiracetam or phenytoin.
- clinical cessation of seizure activity - 50% of the levetiracetam group and 60% of the phenytoin group (however, when the drugs were administered sequentially, the rate of seizure cessation rose to approximately 75%).

Emergency treatment with Levetiracetam or Phenytoin in convulsive Status Epilepticus in children trial (EcLiPSE)
- randomly assigned close to 300 children experiencing CSE to receive either levetiracetam or phenytoin.
- no statistically significant difference between the two groups was found in either the termination of the episode (CSE was terminated by levetiracetam in 70% of participants, and by phenytoin in 64% of participants) or the median time to seizure cessation, although there was a trend in favor of levetiracetam in both outcomes.

**STEP 3**
1. Elective intubation (because benzodiazepine + barbiturate will cause respiratory depression) using rapid sequence technique (because all patients are considered as having full stomach).
2. Place arterial line + draw arterial blood gases.
3. 3rd line AED (only 7% of patients who have not responded to above will respond to 3rd line drug, so some experts skip straight to Step 4):
   a) **Phenobarbital** IV 20 mg/kg q20min (100 mg/min or 3 mg/kg/min in children) up to total 1-2 g; takes 15-20 min to work.
      N.B. monitor for respiratory and cardiac depression! - assisted ventilation is usually required!
   b) **Sodium Valproate** 15-30 mg/kg IV bolus (max rate: 6 mg/kg/min) → maintenance 500 mg TID
   c) **Levetiracetam** 20 mg/kg IV bolus (over 15 minutes) → maintenance 1500 mg BID
- SE that is not controlled with standard dosages of benzodiazepines, phenytoin, phenobarbital is considered **Refractory SE**.

**STEP 4 – Pharmacological Coma** (administered by anesthesiologist):

   **Pentobarbital** 3-15 mg/kg load → 0.5-5 mg/kg/hr maintenance (titrated to burst-suppression near-electrocortical silence).

- treatment is continued for 6-48 hours.
- continuously monitor EEG (for recurrence of seizure activity).
- high risk of hypotension - ventilatory assistance and vasopressors are invariably required.
- other drugs used for refractory SE:
  a) **Propofol** (1-2 mg/kg → 2-10 mg/kg/h)
  b) **Midazolam** (0.2 mg/kg → 0.75-45 μg/kg/min)
  c) **Carbamazepine**
  d) **Oxcarbazepine**
e) **Lacosamide**
   40-60% success rate in SE, with low toxicity; TRENdS trial, which compared lacosamide with fosphenytoin in adults with nonconvulsive SE, showed success rates of 63% and 50%, respectively (no significant difference), with similar rates of adverse effects.

f) **Brivaracetam** (30% response rate and low toxicity).

g) **Perampanel**: there’s not yet IV formulation, and the few available data in refractory SE show low effectiveness (5-20%).

h) **Stiripentol**: moderate efficacy (30-50%) and low toxicity, though no IV formulation is available

i) **Topiramate** (initial dose of 100 mg/d and high median maintenance dose of 400 mg/d); response rate 27.4%; hyperammonemia was a frequent adverse event (35.8%), mainly in combination with the administration of valproate.

   *Anne Fechner et al. Treatment of refractory and superrefractory status epilepticus with topiramate: A cohort study of 106 patients and a review of the literature. Epilepsia Nov 2019*

j) **Lamotrigine**

k) **Diazepam** drip ≈ 2–3 mg/hr.

l) **Paraldehyde** 5% (150-200 mg/kg IV slowly for 15-20 min → 20 mg/kg/hr in concentration in glass bottle); if administered rectally or IM can produce tissue damage and sloughing!

m) **Lidocaine** (may cause seizures in toxic doses)

n) **Ketamine** - reserved for super-refractory SE (in 26 studies involving 303 super-refractory patients, ketamine treatment worked in 74%)

**STEP 5 – general anesthesia** using inhaled anesthetic (**Halothane** < **Isoflurane**).

- novel therapeutic options (no systematic studies): transcranial magnetic stimulation, electroconvulsive therapy (shock therapy).

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**Sequence of medications**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Sequence</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Lorazepam (0.075 mg/kg IV at 2 mg/min)</td>
</tr>
<tr>
<td>10</td>
<td>Proceed immediately to:</td>
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<tr>
<td>20</td>
<td>Phenytion (20 mg/kg IV at 50 mg/min), or Fosphenytoin (20 mg/kg IV at 150 mg/min)</td>
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<tr>
<td>30</td>
<td>Seizures continuing</td>
</tr>
<tr>
<td>40</td>
<td>Phenytion (5-10 mg/kg IV at 50mg/min), or Fosphenytoin (5-10 mg/kg IV at 150 mg/min)</td>
</tr>
<tr>
<td>50</td>
<td>Seizures continuing</td>
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<tr>
<td>60</td>
<td>Phenobarbital (20 mg/kg IV at 50–100 mg/min)</td>
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<tr>
<td>70</td>
<td>Seizures continuing</td>
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<tr>
<td>80</td>
<td>Phenobarbital (5–10 mg/kg IV at 50–100 mg/min)</td>
</tr>
<tr>
<td></td>
<td>Seizures continuing</td>
</tr>
<tr>
<td></td>
<td>Admit to ICU for barbiturate or benzodiazepine anesthesia</td>
</tr>
</tbody>
</table>
**STEP 6 – emergency surgery** (seizure focus resection, VNS at high stimulation parameters, etc).

- use intraop ECoG to delineate need to resect cortex.

Treatment for NONCONVULSIVE STATUS - *may be treated less aggressively* - risk of neurological sequelae is significantly lower!

- good guideline is not to worsen patient's level of consciousness by pharmacologic means.

**Absence SE**: low doses of benzodiazepine → dramatic improvement in mental state → VALPROATE IV or rectally (20-25 mg/kg in 50-mL solution over 10 minutes; repeat after 3 hours, then q6h) or oral ETHOSUXIMIDE.

- no deaths or long-term morbidity have been reported!
- differentiation from other causes is important - many mimics of absence SE can lead to irreversible neuronal damage if not aggressively treated!

**Complex Partial SE** – treatment as for GCSE:
  a) intravenous benzodiazepines.
  b) FOSPHENYTOIN (IM or IV)
  c) oral anticonvulsants

- negative outcomes can occur!

**Simple Partial SE** – treatment less aggressive as for GCSE (e.g. if first-line drugs are ineffective, clinician may elect not to use general anesthetic agent to stop simple partial SE).

**Management Following Status Epilepticus**

- *idiopathic status epilepticus in previously healthy patient* → maintain AED therapy for 3 months → discontinue if remains asymptomatic.
- *other cases* – as general principles require. see p. E5 >>

**Prognosis**

Morbidity & mortality depend on:

1. **intervention speed** (duration > 1 hour carries poor prognosis)
2. **age** (outcome is better in children)
3. **etiology** (outcome is better with pre-existing idiopathic epilepsy, drug-induced SE).

**Mortality** (within 30 days): 20% (1-65%); 38% for refractory SE

- 27% for overt GCSE vs. 65% for *subtle GCSE*
- 4-6% in children, 13% in young adults, 38% in elderly, > 50% in *those > 80 years*.

1% of patients die during episode itself.

Morbidity and mortality is due to:

1. CNS injury from repetitive electric discharges
2. Systemic stress from seizure (cardiac, respiratory, renal, metabolic)
3. CNS injury by acute etiological insult

StEp Audit (2015):

BIBLIOGRAPHY for ch. “Epilepsy and Seizures” → follow this LINK