Status Epilepticus (SE)

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EPIDEMIOLOGY 1
ETIOLOGY 1
PATHOLOGY 2
CLASSIFICATION & CLINICAL FEATURES 2
DIFFERENTIAL DIAGNOSIS 3
MANAGEMENT 4
MANAGEMENT FOLLOWING STATUS EPILEPTICUS 7
PROGNOSIS 8

STATUS EPILEPTICUS (SE):

a) seizure **lasting > 5 minutes**
b) persistent seizure activity after sequential administration of appropriate **first and second-line AEDs**

Other definitions:

a) **continuous** seizure activity (clinical or electrical) ≥ 30 min.
b) **repetitive** seizures with incomplete neurological recovery interictally for period ≥ 30 min.

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*!

EPIDEMIOLOGY

- INCIDENCE - 150,000 new cases/year in the U.S. in the outpatient setting.
- 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**.

DIFFERENTIAL DIAGNOSIS

SE diagnosis depends on demonstrating ictal patterns in EEG!

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

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

- **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% O_2 (via properly fitting face mask); intubate if respirations compromised or if seizure persists > 30 min.
2. ***Monitor*** - ECG, SaO_2, vital signs.
3. ***Blood tests*** - bedside (fingerstick) glucose test; AEDs levels (if indicated), CBC, chemistries (electrolytes, Ca^{2+}, Mg^{2+}, 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 $T_{1/2}$ 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).

   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!
     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.

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**.

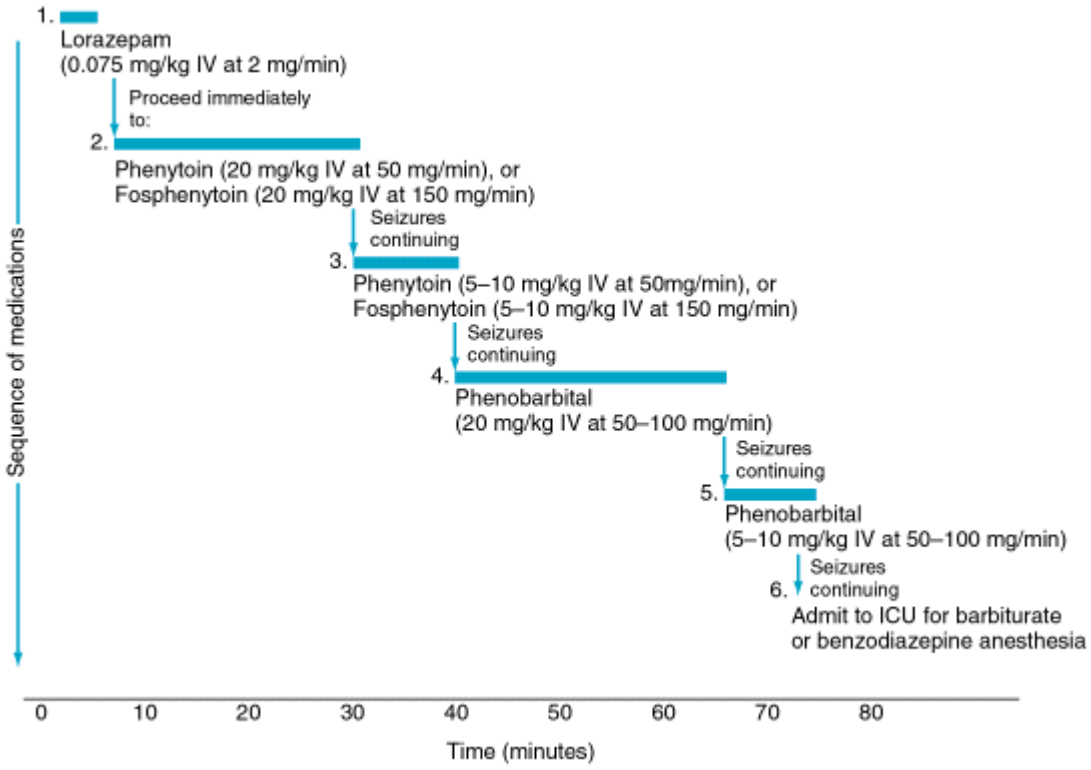
STEP 4 – pharmacological COMA (administered by anesthesiologist):

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) TOPIRAMATE
    f) LAMOTRIGINE
    g) DIAZEPAM drip ≈ 2-3 mg/hr.
    h) 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! *drug is incompatible with plastic
    i) LIDOCAINE (may cause seizures in toxic doses)
    j) KETAMINE

STEP 5 – general anesthesia using inhaled anesthetic (HALOTHANE < ISOFLURANE).

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



STEP 6 – emergency surgery (seizure focus resection, VNS at high stimulation parameters, etc).

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)
1) **age** (outcome is better in children)
2) **etiology** (outcome is better with pre-existing idiopathic epilepsy, drug-induced SE).

Mortality (within 30 days) ranges 1-65% (death caused directly by SE per se occurs in 2-10% cases)

- 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

BIBLIOGRAPHY for ch. "Epilepsy and Seizures" → follow this LINK