UF HEALTH FLAGLER HOSPITAL CONVULSIVE STATUS EPILEPTICUS PROTOCOL (CSE)

BACKGROUND

CLASSIFICATION

Status epilepticus (SE)

- Convulsive or non-convulsive
- Focal or generalized onset

Convulsive SE (CSE)

Prominent motor symptoms

- Generalized convulsive SE (GCSE)
  - Obvious bilateral tonic and clonic motor activity and loss of consciousness
- Focal SE
  - Jerking movements restricted to one area of the body, usually with preserved consciousness.
    - Myoclonic*
      - Rapid, but lower amplitude, jerking muscle activity.
    - Tonic
      - Sustained contractions and posturing of the limbs
    - Clonic
      - Repeated, short contractions of various muscle groups characterized by twitching movements or rhythmic jerking
    - Hyperkinetic
      - Involves predominantly proximal limb or axial muscles in irregular sequential ballistic movements
    - Automatisms
      - Coordinated, repetitive motor activities such as lip-smacking, tapping, or swallowing

*Not all episodes of persistent myoclonus are epileptic in origin

- Many are better labeled as "status myoclonicus" rather than truly epileptic
- The cause is usually an acute, severe encephalopathy, particularly anoxia

Nonconvulsive SE (NCSE)

Seizure activity detected on an EEG without observable motor symptoms

- With coma
  - Generalized nonconvulsive status epilepticus (GNCSE)
- Without coma
  - Generalized (Absence SE)
  - Focal

DEFINITIONS

Generalized convulsive SE (GCSE) is defined as:

- ≥5 minutes of continuous seizures, or
- ≥2 discrete seizures between which there is incomplete recovery of consciousness between ictal events in a 30-minute period

Other types

- The most appropriate time has not been well defined

The International League Against Epilepsy (ILAE) defines various types of SE according to the responsiveness to treatment

- Two critical time points in the evolution of SE
  - t1: transition from likely self-terminating seizure into SE
    - It is the time at which ongoing seizure activity should be regarded as abnormally prolonged, unlikely to stop spontaneously, and when treatment for SE should be started.
  - t2: time point after which SE activity likely becomes harmful to the brain
    - It is the time after which the ongoing seizure activity poses a significant risk of long-term complications.

	t1	t2
Tonic-clonic SE	5 min	30 min
Focal onset with impaired consciousness	10 min	>60 min
Absent SE	10-15 min	Unknown

Refractory SE (RSE)
- SE persists despite the administration of one first line benzodiazepine and one second line anti-epileptic drug

Super-refractory SE (SRSE)
- Ongoing SE that continues 24 h or more after the onset of anesthesia
    - Include those cases in which the SE recurs on the reduction or withdrawal of anesthesia

Prolonged SRSE
- Ongoing SE for more than 7 seven days
    - With ongoing general anesthesia in convulsive SE
    - Without ongoing general anesthesia in non-convulsive SE

New onset refractory SE (NORSE)

ETIOLOGY

Once SE is confirmed, diagnostic efforts should be targeted towards the underlying etiology to maximize the chance of seizure termination through treatment of the causative disease

Five most common and relatively easy-to-identify causes of SE
- Stroke
- Brain trauma
- Common CNS infections
- Alcohol- drug-related events, hypo/hyperglycemia, and electrolytes abnormalities (hyponatremia, hypernatremia, hypocalcemia, and hypomagnesemia)
- Pre-existing epilepsy with breakthrough seizures or non-compliance with anti-epileptic drugs

Other causes
- Brain tumors
- Anoxic encephalopathy
- Hypertensive encephalopathy
    - Posterior reversible encephalopathy syndrome (PRES)
- Uremia, hepatic encephalopathy

Less common causes
- Autoimmune disorders
- Mitochondrial pathologies
- Less common infections, genetic syndromes, and drugs or metabolic toxins

DIAGNOSIS

CSE

Diagnosed clinically
- Should be distinguished from:
    - Exacerbation of movement disorders
    - Functional neurological presentations

NCSE

Providers need to be familiar with common manifestations of NCSE

May require EEG confirmation

EEG considerations

A single EEG
- Detects interictal epileptiform discharge in 20 to 50% of cases

During GCSE

- The EEG is often obscured by muscle and movement artifacts, but it may show continuous spike and wave activity indicative of generalized seizure activity

In many cases of focal motor SE

- EEG evidence of seizure activity is subtle or absent
    - This is generally thought due to a deeper seizure focus or orientation of the seizure discharges such that they are not evident on surface EEGs
    - The seizures of focal status epilepticus can also be intermittent and thereby absent on a short EEG recording

In myoclonic status epilepticus

- There may be background slowing and less rhythmic and broader spikes, sometimes with periodic discharges
- May show focal slowing or more widespread background slowing indicative of an encephalopathy
- Cases due to anoxia may show a very disturbed, nearly flat background EEG, indicative of an extremely severe encephalopathy and predictive of a poor prognosis

Indications for continuous video EEG (cEEG) in patients with or suspected seizures

- Patients with persistently abnormal mental status for more than 30 min following GCSE or other clinically-evident seizures to identify NCS and NCSE
- Patients with clinical paroxysmal events suspected to be seizures, to determine whether they are ictal or nonictal
- Unexplained coma or altered consciousness
- Requirement for muscle paralysis in patients undergoing targeted temperature management (TTM) protocol
- All patients with RSE

Neuroimaging indications

CT brain and MRI (has superior yield) should be considered once seizures have stopped and the patient has stabilized in the following conditions:

- First presentation of seizures without obvious etiology
- Suspected focal onset
- No recovery as expected

Lumbar puncture (LP)

- LP should be considered in the following conditions:
    - Clinical presentation is suggestive of an acute CNS infection
    - Concern for leptomeningeal metastases
- In other circumstances, LP is less likely to be helpful and may even be misleading because prolonged seizure itself can cause cerebrospinal fluid pleocytosis (although usually only minor).
- LP should only be performed after a space-occupying brain lesion has been excluded by appropriate brain imaging studies.
- Blood cultures should be obtained, and empiric antibiotics should be started prior to brain imaging if there is concern for infection.

Differential diagnosis

- Psychogenic status epilepticus
- Encephalopathies with unresponsiveness and myoclonus
- Movement disorders
    - Tremors and dystonia

CONVULSIVE STATUS EPILEPTICUS (CSE) PROTOCOL

As with any protocol, this protocol serves to provide evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize as necessary to meet individual patient needs. This protocol is not intended to replace the practitioner's judgment; it is intended to provide guidance to the physician for the group of patients described in the protocol.

OBJECTIVE:

- In patients with SE is very important to develop a strategy to prevent, detect and correct secondary insults.

    - Development of standardized protocols reduces practice variations and facilitate the care of critically ill patients.
- All patients admitted to the ICU with suspected or confirmed diagnosis of CSE will be eligible to be included in the protocol.

MONITORING:
On admission to the ICU a Neurology consult, a single EEG, and the following tests will be requested, if not already done.

- ABGs with lactate, CBC, INR, PTT, CMP, CK, serum electrolytes (Na, K, Cl, Mg, Ca, and P), anti-seizures drug levels if applicable, and UDS.
- CT brain or MRI once seizures have stopped and the patient has stabilized in the following conditions:
    - First presentation of seizures without obvious etiology
    - Suspected focal onset
    - No recovery as expected
- cEEG will be instituted to guide anti-seizure treatment in patients with refractory RSE
    - To monitor the efficacy of continuous IV antiseizure drugs
    - To target seizure suppression, burst-suppression, or complete EEG suppression
    - To wean off anti-seizure treatment
    - Frequency of review and interpretation
        - cEEG will be reviewed as often as logistically and technically feasible and interpreted by electroencephalographers at least twice daily (i.e., about every 12 hours)
        - If frequent nonconvulsive seizures are identified, more frequent interpretation will be provided until seizures are controlled

INTERVENTIONS:
Patients will be managed in collaboration with the Neurologist.

General Care
The general care and physiological neuroprotection will be characterized by maintaining the following variables:

- Blood pressure (BP) control – MAP >65 mmHg
- Maintenance of normothermia - Temperature less than 37.8 ℃ and evaluation and treatment of fever source
- Maintenance of euvolemia
- Maintenance of normoxemia: SaO2 greater than 94%
- Maintenance of normocapnia: PaCO2 35 to 40 mmHg
- Maintenance of normonatremia: sodium 135 to 145 meq/L
- Maintenance of glycemia: glucose 110 to 200 mg/dL
- Venous thromboembolism prevention
- Aspiration precautions – HOB 30^0
- Early nutrition
- Management of specific conditions
    - Lumbar puncture (LP) will be considered if:
        - Clinical presentation is suggestive of an acute CNS infection
        - Concern for leptomeningeal metastases
    - LP will be performed only after a space-occupying brain lesion has been excluded by appropriate brain imaging studies
    - If acute CNS infection is suspected, will obtain blood cultures and initiate empiric antibiotics with ceftriaxone, vancomycin, and acyclovir and de-escalate according to cultures and LP analysis including HSV PCR.

Treatment of Seizures
The treatment of GCSE and focal motor SE is similar with the same antiseizure drugs

- Focal motor treatment is somewhat less urgent than that of GCSE and with higher priority given to the avoidance of oversedation and intubation
- Myoclonus SE (MSE) is frequently much more refractory to antiseizure drugs and often has a grave prognosis, especially after anoxia

Stage 1 - SE

Administration of one first line benzodiazepine and one second line anti-epileptic medication even if seizures have ceased following benzodiazepine treatment.

- Benzodiazepines
    - Lorazepam (Ativan) 0.1 mg/Kg IV bolus with repeated doses if still seizing, allowing three to five minutes to assess its effect before deciding whether additional doses are necessary
        - There is no definite maximum dose of lorazepam so it will be guided by the clinical effect (including blood pressure and respiratory status) and seizure control.
    - If Lorazepam is not available, will use Diazepam 0.15 mg/Kg IV up to 10 mg per dose
    - If IV access is not immediately available, will use Midazolam 10 mg IM

- Anti-epileptic medications
    - Levetiracetam at a loading dose of 60 mg/kg (maximum 4500 mg) infused over 5 to15 minutes with maintenance dose of 500 up to 1500 mg IV q12h
    - Alternatives
        - Valproic acid at a loading dose of 40 mg/kg infused over four minutes with maintenance dose of 8 mg/kg every 8 h
        - Fosphenytoin infusion of 20 mg/kg at a maximum rate of 150 mg/min with a maintenance dose from 4 – 8 mg PE/Kg/d IV in 1 hr divided doses
            - If junctional rhythm or bradycardia develops will reduce rate of infusion or stop it
        - Lacosamide 200 mg IV q12h
            - EKG should be performed before its use and during maintenance to monitor for PR prolongation since rare serious adverse events including second degree and complete atrioventricular block can occur

    - If patient already on chronic therapy prior to the onset of SE
        - With levetiracetam, will be reloaded with levetiracetam or loaded with Valproate or Fosphenytoin
        - With Valproate or Fosphenytoin will be loaded with Levetiracetam

- Patients will need (if availability allows it) cEEG monitoring for up to 24 hours after cessation of clinical seizures
- Neurologist will determine further adjustments of anti-epileptic drugs and when to switch IV to oral/enteral route

Stage 2 - Refractory SE (RSE)

If seizures persists despite the administration of one first line benzodiazepine and one second line anti-epileptic medication, contrary to the previous practice of introducing an additional anti-epileptic drug, it is now accepted to start IV continuous infusion treatment (anesthesia level) targeting seizure suppression.

- Patient will be intubated and placed on mechanical ventilatory support with continuous BP monitoring and use IVF and vasopressor support as necessary to keep MAP >65 mmHg and UO >0.5 ml/Kg/h
- Patient will require cEEG monitoring with the aim to document the cessation of electrographic seizures
- Propofol or Midazolam IV infusions will be initiated
    - Propofol
        - Initial dose of 1 to 2 mg/kg IV bolus over 5 minutes
            - Additional boluses of 0.5 to 2 mg/kg can be given every three to five minutes until seizures stop (up to a maximum total dose of 10 mg/Kg)
        - This will be followed by continuous infusion starting at 20 mcg/Kg/min and titrate over 20 to 60 min targeting seizures control to a maximum of 200 mcg/Kg/min
            - Additional boluses for breakthrough seizures can be given every three to five minutes until seizures stop (up to a maximum of 200 mg)
            - Propofol IV continuous infusion >50 mcg/Kg/min will be allowed for a maximum of 48 hours
    - Midazolam
        - Initial dose of 0.2 mg/kg IV bolus given at a rate of 2 mg/min
            - Additional boluses can be given every five minutes until seizures stop (up to a maximum of 2 mg/kg)
            - This will be followed by continuous infusion of 0.1 mg/kg/hour, which can be titrated upwards to as high as 3 mg/kg/h targeting seizures control

If seizures persist after 60 minutes despite Propofol *or* Midazolam IV infusions, considering adding:

- Ketamine 1-2 mg/kg bolus, followed by continuous infusion of 1 to 5 mg/kg/h
    - Usual Ketamine dose for SE is 2.5 to 7 mg/h with pharmacy to concentrate at 10mg/cc to prevent fluid overload if high rates of infusion needed

If seizures persist despite Propofol *and* Ketamine or Midazolam *and* Ketamine IV infusions, considering adding:

- Either Midazolam or Propofol accordingly

Patient will require IV maintenance of at least 2 of the following anti-epileptic medications

- Levetiracetam (see maintenance dose above)
- Valproic acid (see maintenance dose above)
- Fosphenytoin (see maintenance dose above)

Will continue the antiseizure IV infusions for 24 h before starting tapering. Then gradually taper over 12 to 24 hours. Patient will continue receiving the anti-epileptic medications.

Stage 3 - super refractory status epilepticus (SRSE) and prolonged SRSE

If seizures (electrographic and/or clinical) persist after stopping IV anesthetic infusions or if seizures continue despite the anesthetic infusions, the patient is defined as having SRSE and will need to be transferred to UF Health Jacksonville.

REFERENCES

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