Status epilepticus

SOROOR INALOO

PEDIATRIC NEUROLOGIST

SHIRAZ UNIVERSITY OF MEDICAL SCIENCES

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Objective

*Definition

*Classification

*Epidemiology

*Pathophysiology

*Etiology

*Outcome

*Management

Definition of status epilepticus

The International League Against Epilepsy (ILAE) and others defined SE as a single epileptic seizure of >30 minutes duration or a series of epileptic seizures during which function is not regained between ictal events in a 30-minute period

For the purposes of treatment decisions, however, a shorter time window >5 to 10 minutes of continuous seizures

For generalized tonic-clonic seizures, SE is defined as continuous convulsive activity or recurrent generalized convulsive seizure activity without regaining of consciousness (t1 = 5 min, t2 ≥ 30 min).

The definition differs for SE consisting of focal seizures with impaired awareness (t1 = 10 min, t2 = 60 min) and absence SE (t1 = 10-15 min, t2 = unknown).

RSE :If convulsive status epilepticus (SE) persists for 30 minutes after (immediate benzodiazepine treatment followed by second therapy with an antiseizure drug)

SRSE occurs when SE persist for 24 h or more after administration of anesthesia

Classification of status epilepticus(SE)

●Focal SE without impairment of consciousness or awareness (simple partial SE) – Continuous or repeated focal motor or sensory seizures without impaired consciousness.

●Focal SE with impairment of consciousness or awareness (complex partial SE) – Continuous or repeated episodes of focal motor, sensory, or cognitive symptoms with impaired consciousness. This is also called nonconvulsive SE. In some patients the clinical manifestations of seizure activity are subtle and not apparent to the clinician.

●Generalized convulsive SE including tonic-clonic, tonic, and clonic – Always associated with loss of consciousness.

●Absence SE – Generalized seizure activity, characterized clinically by altered awareness, but not necessarily unconsciousness

Other rare SE – Myoclonic SE ,Psychogenic

Epidemiology

The **incidence** of SE ranges between 10 and 60 per 100,000

SE is most common in children younger than 5 yr of age, with an incidence in this age-group of > 100 per

100,000 children. **10 to 40%** developed **refractory status epilepticus**

Approximately 12- 30% of patients presenting with SE are having their first seizure, and approximately 20-40% of these later develop epilepsy

Febrile status epilepticus is the **most common** type of SE in children.

In the 1950s and 1960s, **mortality** rates of 6–18% after SE

Currently, with the recognition of SE as a medical emergency, **mortality rate 4 -5 %**

Most of it secondary to the underlying etiology rather than to the seizures

SE carries an approximately 14% risk of new neurologic deficits, most of them (12.5%) secondary

to the underlying pathology

Risk factor of SE

History of epilepsy

Age under 5 year or elderly

Genetic predisposition

Mental handicap

Structural brain pathology (abnormal brain imaging)

History of prior SE

Pathophysiology

Status epilepticus occurs because of failure of the normal mechanisms that limit the spread and recurrence of isolated seizures .

Failure occurs because excitation is excessive and/or inhibition is ineffective

Excitatory neurotransmitters that contribute to SE include glutamate(most important), aspartate and acetylcholine .

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, and antagonists to its effects or alterations in its metabolism in the substantia nigra may contribute to SE

In a rat model, GABA synthesis in the substantia nigra declined significantly during induced SE

Other inhibitory mechanisms include the calcium ion-dependent potassium ion current and blockage of N-methyl-D-aspartate (NMDA) channels by magnesium.

Cause of status epilepticus

SE may occur in the setting of underlying, premorbid epilepsy or as the first manifestation of epilepsy

Virtually any cause of epilepsy may have a first presentation with SE.

- **Central nervous system infections and inflammation (autoimmune encephalitis)**
- **Acute hypoxic-ischemic insult**
- **Metabolic disease (eg, hypoglycemia, inborn error of metabolism)**
- **Electrolyte imbalance**
- **Traumatic brain injury**
- **Drugs, intoxication, poisoning**
- **Cerebrovascular event**

Febrile infection-related epilepsy syndrome (FIRES) ➢

Febrile infection-related epilepsy syndrome (FIRES)

New onset refractory SE in the setting of a **prodromal febrile illness** starting between two wk and

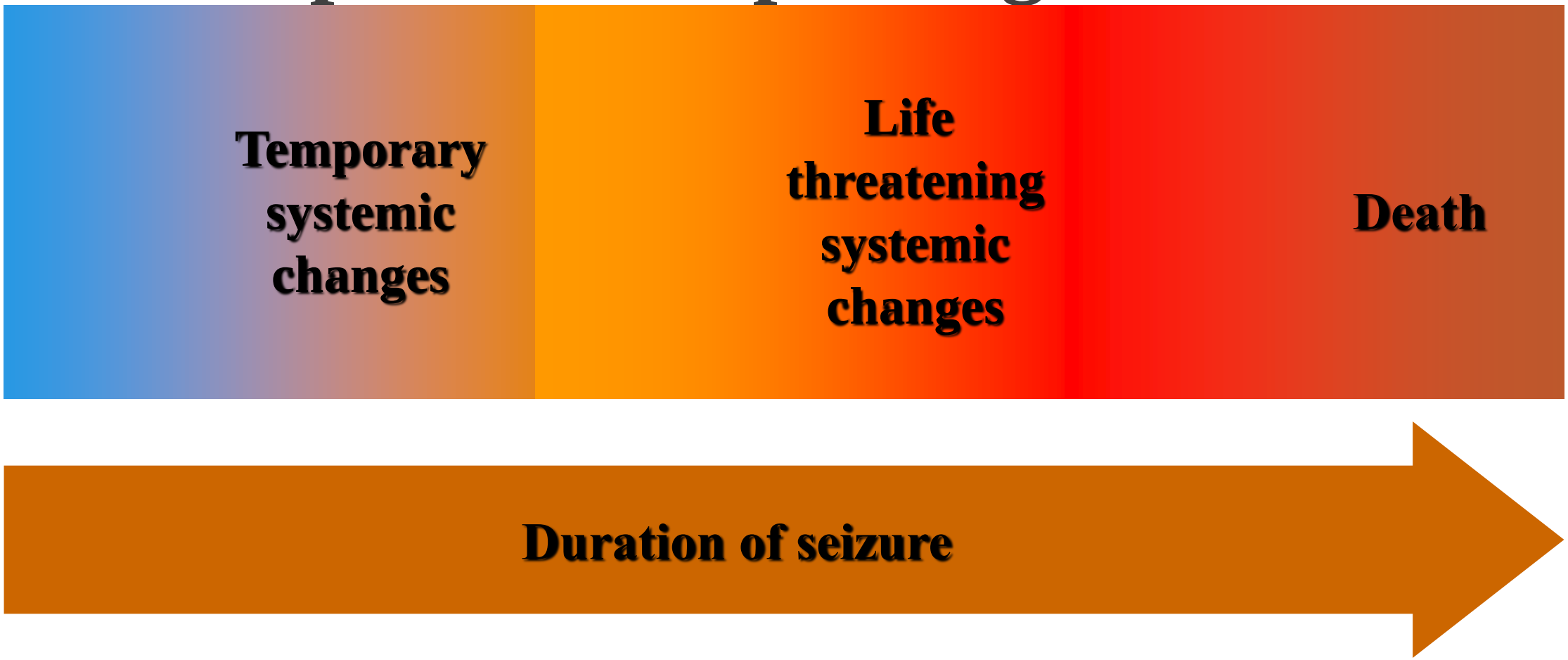
24 hours prior to onset of refractory SE, with or without fever at onset of SE .

FIRES is considered a subcategory of new-onset refractory status epilepticus (NORSE), which is characterized by the absence of a clear acute or active structural, toxic or metabolic cause for SE in a patient without active epilepsy or another preexisting relevant neurologic disorder .

This has been described in adults as well as children

The mechanism is unclear, and the infectious agent is generally not identified. Some cases may actually represent an autoimmune or paraneoplastic encephalomyelitis due to autoantibodies against synaptic proteins such as the N-methyl-D-aspartate (NMDA) receptor, in which case immunomodulatory therapies may be effective

Complication of prolonged seizures



Systemic alternation in SE

Hypoxemia

Acidosis

Increased intracranial pressure

Hyper &hypoglycemia

Myocardial supresssion

Hyper &hypotension

Fever

Leukocytosis

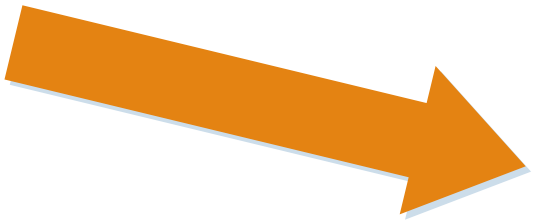
Rhabdomyolysis (hyperkalemia ,myoglobinuria,increased CPK)

CSF pleocytosis

Hemodynamics

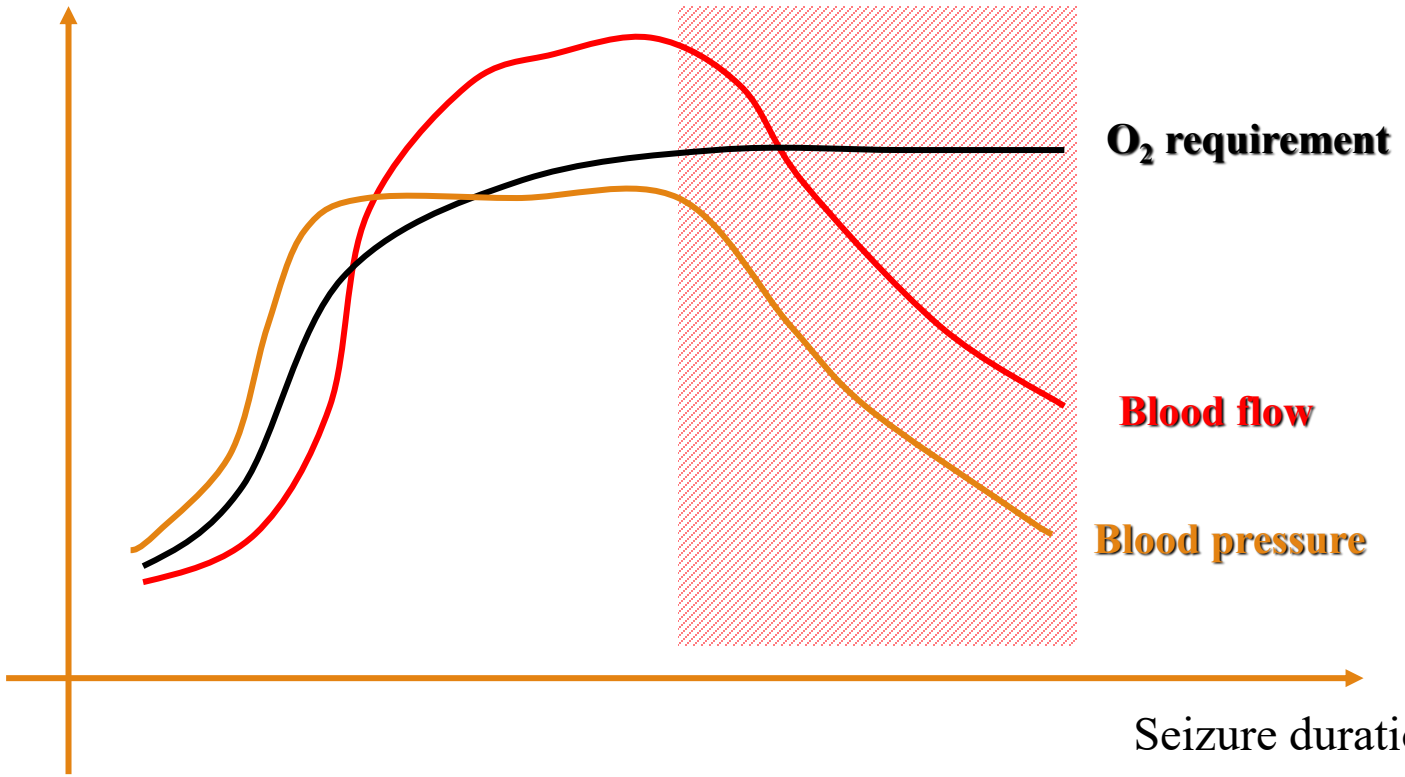
Sympathetic overdrive

- Massive catecholamine / autonomic discharge
- Hypertension
- Tachycardia
- High CVP



- **Exhaustion**
  - **Hypotension**
  - **Hypoperfusion**

Cerebral blood flow - Cerebral O_2 requirement



Hyperdynamic phase

- CBF meets $CMRO_2$

Exhaustion phase

- CBF drops as hypotension sets in
- Autoregulation exhausted
- Neuronal damage ensues

Outcome

Neuronal loss — Though the outcome of SE generally is favorable in the absence of an underlying neurologic condition, minor amounts of neuronal loss are thought to occur with every episode, particularly if prolonged Over time.

When neurons are depolarized, calcium enters the cell through NMDA channels and causes injury or death.

Other possible contributing factors include **hypoxia**; excessive release of excitatory amino acids and calcium; increases of various proteins, including those that promote apoptosis (programmed cell death);

Abnormalities on magnetic resonance imaging (MRI) and release of the neuron-specific enolase (NSE) are markers of neuronal damage.impairment.

Disturbance of the NMDA channels appears to be an important mechanism of neuronal damage

Management

General consideration

Previous response — If the child has a history of previous status epilepticus (SE), knowing which antiseizure drug was effective in arresting the seizures is helpful

Missed medication — If the child is on long-term antiseizure drug therapy, it should be determined whether medication has been recently missed or if prescriptions have not been refilled

for example, VPA has provided good seizure control, and the child is known to have missed one or more doses, intravenous VPA, rather than phenytoin

Initial treatment

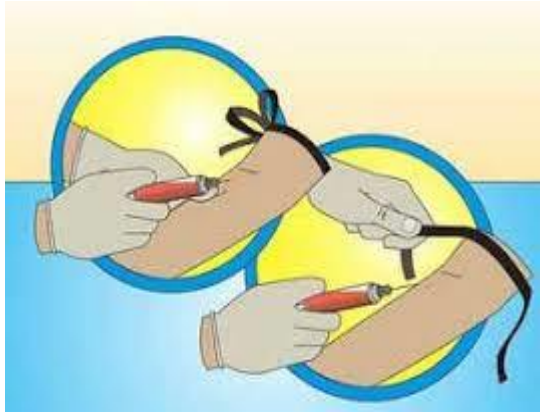
A Oxygen, oral airway. Avoid hypoxia!

B Consider bag-valve mask ventilation. Consider intubation

C IV/IO access. Treat hypotension, but NOT hypertension

Initial investigations

Labs



- Pulse oximetry
- ABG
- Na, Ca, Mg, PO_4 , glucose
- CBC
- Liver function tests, ammonia, renal function test
- Anticonvulsant level
- Toxicology (5cc blood, 50 cc urine)
- **Blood cultures and lumbar puncture (LP)** should be obtained if there is evidence of systemic or central nervous system infection

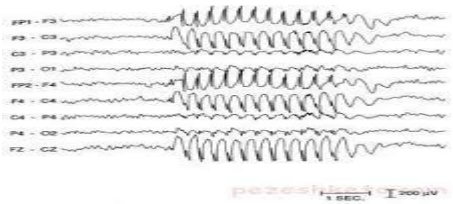
Initial investigations

Lumbar puncture

- Always defer LP in unstable patient, but never delay antibiotic/antiviral Rx if indicated
- Serum and CSF : Auto-antibodies including ANA, anti-dsDNA, ANCA, APS & ENA panel Serum anti-neuronal antibodies including anti-NMDAR, –AMPA & –VGKC, –GABA Lumbar puncture with oligoclonal bands, and CSF anti-neuronal antibodies

- **Metabolic studies** for inborn errors of metabolism should be considered if there are other suggestive indicators.

Neuroimaging —
first presentation of epilepsy
in children whose recovery from SE does not follow the expected course
if LP is considered,
CT is generally recommended to exclude a mass lesion, but MRI has superior yield for determining the underlying etiology.



Cardiac monitoring

EEG urgent electroencephalogram (EEG) should be obtained in emergency room

If an urgent EEG cannot be obtained, an EEG should be done to evaluate background activity as soon as possible after the seizure stops, ideally within one to two hours.

If the patient has not regained a relatively normal mental state within a few hours after SE has stopped, an EEG should be performed to evaluate the possibility of subclinical electrographic seizures

Studies of critically ill children who undergo continuous EEG monitoring indicate that electrographic seizures are present in approximately 30 to 40 percent of recordings, often without clinical accompaniment

First line therapy

- **Benzodiazepine** – Lorazepam 0.1 mg/kg (IV) maximum of 4 mg , slow IV push over one minute and its effect assessed over the next five to ten minutes.

Alternative is diazepam 0.2 mg/kg IV (maximum dose 8 mg)

If seizures continue after five minutes, additional doses of lorazepam or diazepam can be given

- midazolam 0.15 – 0.3 mg/kg

When IV access is unavailable — When IV and IO access cannot be achieved within the first three minutes, alternative first-line agents include:

- Buccal midazolam 0.2 mg/kg, maximum 10 mg
- IM midazolam 0.2 mg/kg, maximum 10 mg
- Rectal diazepam 0.5 mg/kg, maximum 20 mg

Second therapy: Antiseizure drugs

If seizures continue for 10 minutes after at least two injections of lorazepam or diazepam, a second therapy with a long-acting antiseizure drug is indicated. phenytoin/fosphenytoin, levetiracetam, and valproate (VPA) are all equally

phenytoin : initial dose of 20 mg/kg IV at a rate of 1 mg/kg per minute (maximum rate 50 mg/min).dilute in N/S Max 1500 mg

levetiracetam **:**40 mg/kg IV infusion (IV or IO) over 5 minutes Max 4500 mg/dose , may be prefer over phenytoin because of ease of use, more rapid administration, and equivalent efficacy

Valproate : loading dose of 20 to 40 mg/kg IV (diluted 1:1 with N/S or 5 percent DW) over 5 to 10 minutes Max 3000mg/dose and may be repeated after 10 to 15 minutes

Phenobarbital : loading dose of 20 mg/kg IV,Max 1000 mg slowly infused (maximum infusion rate 2 mg/kg per minute with a ceiling of 50 mg/min) and followed by repeated increments of approximately 8 to 10 mg/kg every 30 min

phenobarbital is considered a second-line long-acting agent after levetiracetam, fosphenytoin or phenytoin, and valporate, and usually is used only when these agents are not effective .

Vit B6 also recommended in patient < 2 y 100 mg IV

Refractory status epilepticus

RSE :If convulsive status epilepticus (SE) persists for 30 minutes after (immediate benzodiazepine treatment followed by second therapy with an antiseizure drug)

further pharmacologic therapy (third therapy) is required, usually in the form of continuous infusional therapy

Third therapy

Midazolam :initial bolus infusion of 0.2 mg/kg IV followed by a continuous infusion of 0.05 to 2 mg/kg per hr (1 - 30 mcg/kg/min)

Pentobarbital : initial bolus infusion of 5 to 15 mg/kg IV followed by a continuous infusion of 0.5 to 5.0 mg/kg per hr

Significant side effects : respiratory depression, hypotension, myocardial depression, and reduced cardiac output.

Thus, intubation and mechanical ventilation with intravascular pressure monitoring are required prior to treatment, and inotropic agents frequently are needed

Propofol initial bolus 2mg/kg then continuous infusion 5-10 mg/kg/hr

Sodium valporate 20-40 mg/kg IV & enema (Dilute 1:1 with N/S or D/w 5%) 3 mg/kg/min Maintenance 5 mg/kg/hr

Duration of continuous infusions

Suppressive therapy with pentobarbital, midazolam, or propofol is generally used to induce a suppression-burst pattern on EEG for 24 to 48 hours.

The dose is then slowly reduced to see if seizures reappear. If seizures are still present, the patient is placed back into suppression-bust for another 24 to 48 hours and then reassessed.

Other therapies

In addition to levetiracetam, observational data suggest that other antiseizure drugs including lacosamide, and topiramate

Other emerging therapies include ketamine (0.5–3 mg/kg Infusion rate: 1–10 mg/kg/h)

Ketogenic diet

Anesthesia with Isoflurane

Pulse methylprednisolone 20-30 mg/kg

IVIG

Plasmapheresis 5 exchanges over 5 days

Electroconvulsive therapy vagus nerve stimulation hypothermia

POSTICTAL ASSESSMENT

Most children begin to recover responsiveness within 20 to 30 minutes after generalized convulsions, although there is a broad range of duration

If child does not begin to respond to **painful stimuli** within 20 - 30 minutes after tonic - clonic SE, suspect non - convulsive SE

(urgent EEG)

Close monitoring during this period is critical.

The two most common reasons for delayed postictal recovery are sedation from medications and ongoing nonconvulsive seizures

Non - convulsive SE ?

Neurologic signs after termination of SE are common:

- Pupillary changes
- Abnormal tone
- Babinski
- Posturing
- Clonus
- May be asymmetrical

Non - convulsive SE ?

Up to 20% of children with SE have non - convulsive SE after tonic - clonic SE

Non convulsive status epilepticus

Presentation

confusional state,personality change ,agitation,blinking automatism,ataxia dementia, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking, fluctuating mental status, hallucinations, paranoia, aggressiveness ,coma

13% of neuro ICU patients 16% sever head injury have NCSE

Diagnosis → EEG

Treatment: Diazepam with EEG monitoring PB, PHT, valporate

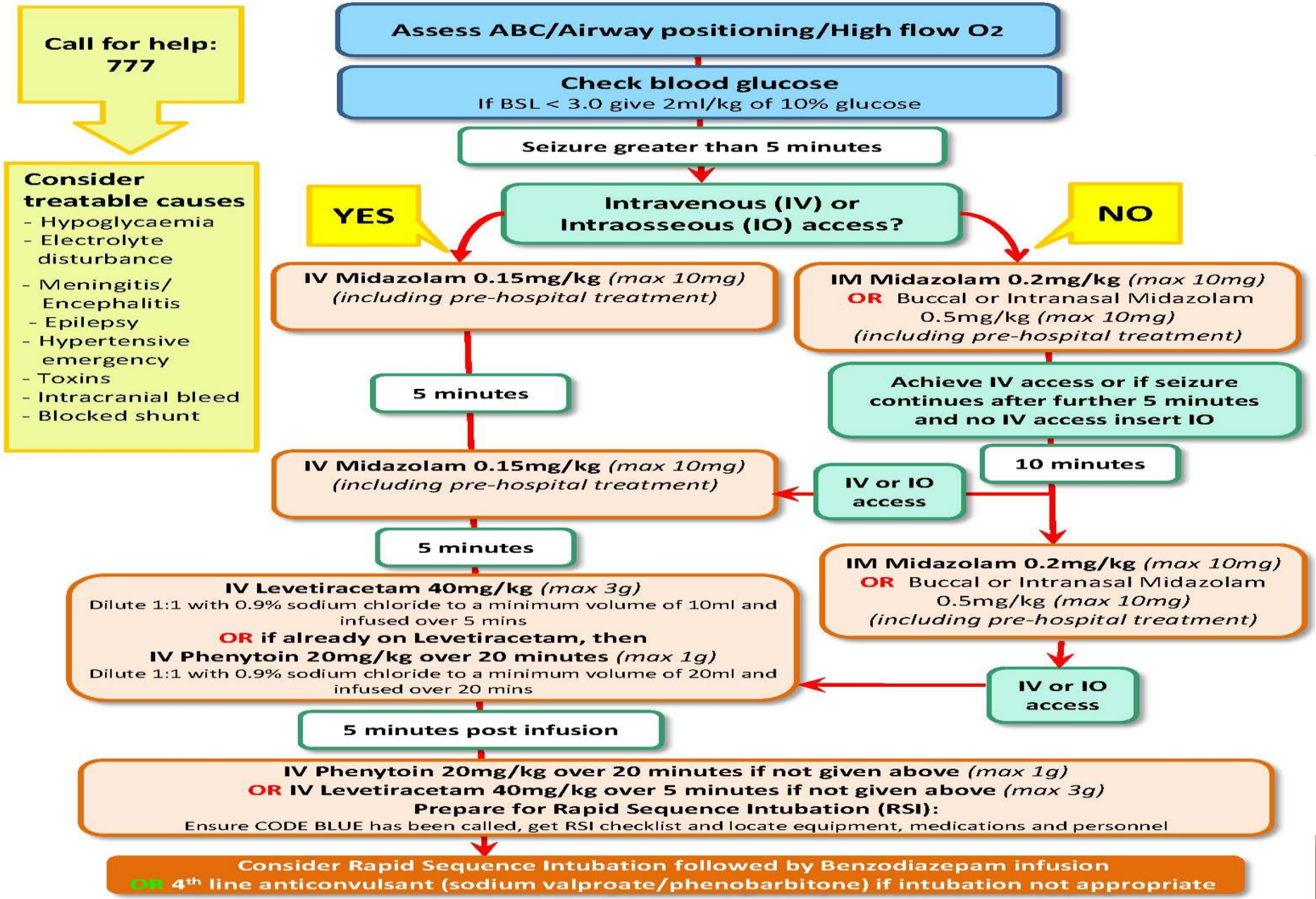
Out-of-hospital/prehospital treatment

Treatment of SE out-of-hospital by paramedics appears to be safe and effective in children.

IM midazolam (**5** mg for children whose weight is 13 to 40 kg and **10** mg for those over 40 kg)

Rectal Diazepam **0.3 – 0.5 mg/kg** (5 mg age <3 y and 10 mg >3 y)

Paediatric Status Epilepticus



Status Epilepticus Guideline

Shiraz University of Medical Sciences, Jan 2019

Treatment Algorithm for Status Epilepticus for Children Older Than Neonates

Time Line From Arrival	
0-5 min Stabilization Phase	1. Stabilize patient (airway, breathing, circulation, disability-neurologic exam) 2. Time seizure from its onset, monitor vital signs 3. Access oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed 4. Initiate ECG monitoring 5. Collect finger stick blood glucose. If glucose<60 mg/dl then children receive 5 ml/Kg D10W, wt>60 kg receive 50 ml D50W 6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels
	Does Seizure continue? YES / NO
5-10 min First Therapy Phase	Choose one of the following 2 equivalent first line options: Intravenous diazepam[1] (0.2 – 0.3 mg/Kg/dose, max 10 mg/dose, repeat once if necessary) OR Intramuscular midazolam (0.1 – 0.15 mg/Kg, max 10 mg/dose) If none of 2 options above are available, choose one of the following: Rectal diazepam (0.2 – 0.5 mg/Kg, max 20 mg/dose, single dose) OR Intranasal midazolam (0.2 – 0.3 mg/Kg, max 10 mg), OR buccal midazolam (0.3 – 0.5 mg/Kg, max 10 mg/dose) If patient at baseline, then symptomatic medical care
	Does Seizure continue? YES / NO
10-30 min Second Therapy Phase	Second line of anti-seizure drugs: Intravenous phenytoin (20 mg/Kg, max 1500 mg), with ECG monitoring, infusion rate 1 mg/Kg/min. Dilute by normal saline. If patient at baseline, then symptomatic medical care
	Does Seizure continue? YES / NO
>30 min Third Therapy Phase	Third line of anti-seizure drugs: Choose one of the following second line options and give as a single dose: Intravenous valproic acid[2] (40 mg/Kg, max 3000 mg/dose) OR Intravenous levetiracetam[3] (60 mg/Kg, max 2500 mg/dose) OR Intravenous phenobarbital[4] (20 mg/Kg, max 1000 mg/dose) If patient at baseline, then symptomatic medical care
	Does Seizure continue? YES / NO
Patient should be intubated and admitted in PICU & consult with neurologist or intensivist	Continue infusion/anesthetics (preferably with EEG monitoring). ECG monitoring is required. Consult with neurologist or intensivist Midazolam[5] (0.2 mg/Kg/dose, max 10 mg/dose) then infusion with 0.5 - 1 µg/Kg/min every 5 min increased dose till max dose 33 µg/Kg/min). If seizure continue, choose one of the following options Thiopental (5 mg/Kg loading dose followed by 1 – 5 mg/Kg/hr infusion rate) OR Propofol[6] (2.5 - 3.5 mg/Kg loading dose followed by 7.5 – 15 mg/Kg/hr infusion rate) OR Intravenous ketamine (0.5 – 2 mg/Kg), then continuous IV infusion 5 – 20 µg/Kg/min If patient at baseline, then symptomatic medical care

1 Infusion rate is 2 mg/min. The only repeatable drug as the first line is IV diazepam.

2 Infusion rate is 3 – 6 mg/Kg/min.

3 Infusion rate is 5 mg/Kg/min.

4 The usual loading dose is 20 mg/Kg. Additional dose 5 - 10 mg/Kg, max 40 mg/Kg. Infusion rate is 2 mg/Kg/min.

5 Simple calculation method: 3×wt (kg) Midazolam diluted in 50 cc D5W (max 50 mg in 50 cc D5W). 1 cc/hr of this solution = 1 µg/Kg/min midazolam.

6 Propofol infusion with the rate of 25 mg/Kg/hr is not recommended for more than 2 days in the children.

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Thank you for Attention