STATUS EPILEPTICUS GUIDELINE FOR CHILDREN

BACKGROUND

Seizures lasting longer than 5 minutes should probably be treated as status epilepticus, despite conventional definitions of status being a duration of seizures > 30 min.

Non-convulsive status should be similarly treated, except in children with known difficult to control and chronic seizure syndromes.

HOME MANAGEMENT

Intranasal (INM) [1] [4] [5] or buccal midazolam [6] has been shown to be more effective and easier to use than rectal diazepam for the management of prolonged seizures and is increasingly being used in the home setting[8]

INITIAL PRESENTATION TO HOSPITAL

Check for important treatable causes:

- Hyponatremia – seizures due to hyponatremia (usually NA < 125 mmol/L): give 5 mL/kg of 3% Saline bolus (1 cc raises ~ Na 1 meq), repeat if required [9].
- Hypoglycemia:
    - Dextrose 10% 5 mL/kg (max 250 mL)
    - Dextrose 25% 2 mL/kg (max 100 mL)
    - Neonates: Dextrose 10% 2 mL/kg (max 250 mL)

- Hypocalcemia – give calcium gluconate: 50 mg/kg (MAX 2000 mg) slow IV.
- Hypertensive encephalopathy (usually due to acute nephritis, main treatment is to use antihypertensive agents with furosemide if needed).

There is evidence that lorazepam is more effective than phenobarbital, phenytoin, and diazepam/phenytoin combined in adult subtle and overt status epilepticus (>10 min). [10] Seizure recurrence and side effects were no different between the drugs. [11] A Cochrane review supported this conclusion and added that lorazepam was more effective than diazepam alone. [12] At least one study has reported reduced seizure recurrence with lorazepam. [13]

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One study of out-of-hospital status in adults compared IV lorazepam and IV diazepam and placebo. Success rates on arrival at hospital were 59, 43 and 21% respectively. Respiratory or circulatory compromise was most common in the placebo group (10, 10 and 23% respectively). [14]

A Cochrane review of treatment of tonic-clonic status in children concluded there was insufficient evidence to conclude lorazepam was better than diazepam for generalized tonic clonic convulsions > 30 min duration. However, there was a trend towards a reduced rate of recurrent seizures, and reduced use of additional anticonvulsants and reduced incidence of respiratory depression in those treated with lorazepam. [1]

A recent meta-analysis showed that compared to IV diazepam, IM midazolam results in more rapid cessation of seizures because of more rapid administration and may result in less apnea. [5] Both are > 90% successful in children with seizures of > 10 min duration.

Intranasal midazolam is also as effective as IV diazepam (80%) and results in a more rapid result than IV diazepam due to the delay caused by getting IV access in the latter. Excluding time to obtain access the onset in ½ - 1 minute longer: 3.5 vs. 2.9 min. [15]

In conclusion, initial treatment of status epilepticus should be IV lorazepam, midazolam or diazepam, IM midazolam, or IN midazolam. [15]

FIRST LINE TREATMENT[1]

- IV lorazepam 0.1 mg/kg, max 4 mg (PROBABLY BEST OPTION)
- IV diazepam 0.2 mg/kg, max 10 mg
- IV midazolam 0.15 mg/kg, max 5 mg
- IM midazolam 0.2 mg/kg, max 10 mg
- IN midazolam 0.2 mg/kg, max 10 mg
- RECTAL:
    - 2-5 years = 0.5 mg/kg max 20 mg
    - 6-11 years=0.3 mg/kg max 20 mg
    - >12 years= 0.2 mg/kg max 20 mg

Repeating x 1 is reasonable with 5-10 min between doses, provided airway and breathing and circulation are not unduly compromised. Treatment with more than 2 doses of lorazepam or diazepam is associated with increased risk of respiratory depression, but less so with buccal, intranasal or IM midazolam. [5, 16, 17]

SECOND LINE TREATMENT FOR ESTABLISHED STATUS EPILEPTICUS[2, 3]

If airway is *not* compromised, follow steps in order are:

A. IV levetiracetam (Keppra) 60 mg/kg (MAX 4500 mg) or IV valproic acid (Valproate) 20 mg/kg (MAX 3000 mg)

B. IV levetiracetam (Keppra) 20 mg/kg (MAX 4500 mg) or IV valproic acid (Valproate) 20 mg/kg (MAX 3000 mg) [18,19]

C. IV Fosphenytoin 15-20 PE/kg, MAX 1500 mg PE, admin at 2 mg PE/kg/minute up to maximum of 150 mg PE/minute [20] (same dose can be given undiluted IM)

D. IV phenobarbital 20 mg/kg, MAX 1000 mg, admin over 30 min

E. **IV Midazolam bolus of 0.1-0.2 mg/kg** (can give 0.5 mg/kg if airway protected) then continuous infusion starting at 0.06 - 1.2 mg/kg/hr increasing every 5-30 min by 0.05 -0.1 mg/kg/hr, preceded by a bolus of 0.1 mg/kg, up to 1 - 2 mg/kg/hr (some centers use up to 2.5 mg - 3 mg/kg/hr).

***Midazolam is less likely to cause cardiorespiratory depression than phenobarbital** and is successful in 95% of cases that have failed diazepam 0.3 mg/kg x 3, phenytoin 20 mg/kg and phenobarbital 20 mg/kg. [21, 22]

In another recent case series midazolam bolus and infusion and single phenytoin load controlled 89% of cases of pediatric status epilepticus. [21]

Goal of therapy is cessation of clinical and EEG seizures. *Note that burst suppression on EEG is not usually achieved with high dose midazolam alone.*

At any point if airway *is* compromised:

RSI (rapid sequence induction) with pre-oxygenation, ketamine or propofol 2-4 mg/kg (depending on CV status), succinylcholine 1-3 mg/kg (depending on age) or rocuronium 1 mg/kg and intubate with appropriately sized ETT.

THIRD LINE TREATMENT – SUPER REFRACTORY STATUS [7]

There is no known optimal regimen. The options are discussed below. The proposed APH regimen is as follows:

The ketamine dose ranges required to achieve status control was a loading dose of 0.5 - 2 mg/kg followed by a continuous infusion 0.5 - 3 mg/kg/hr. Some adult centers are using ketamine, instead of barbiturate therapy with good success, without the complications associated with barbiturates.

Traditionally, pentobarbital infusion was used 1-5 mg/kg load, then 1 - 5 mg/kg/hr, but has no known advantage over high-dose phenobarbital or pentobarbital therapy and may cause more side-effects.

The shorter acting barbiturate, pentobarbital (half-life 15-50 hrs.) is available, but is very expensive and confers no known advantage over phenobarbital, although many centers use it. Drug levels are available, but the turnaround time is > 24 hrs. [23]

Propofol infusion is not recommended due to the risk of 'propofol infusion syndrome' in children [24], however an effective combination of ketamine and propofol for effective control of super-refractory status has been reported. [25]

Lidocaine infusion is also an alternative, particularly in neonates. [26-28]

IV valproic acid (Valproate) 20 - 40 mg/kg bolus (MAX 3000 mg) and/or continuous infusion of 1 - 5 mg/kg/hr (20-100 mg/kg/day) has been found to be equally effective than levetiracetam and fosphenytoin in two randomized trials and its use should be considered early. [18, 19]

High dose NG topiramate (Starting dose 5-10 mg/kg/day in children, 150-750 mg BID in adults,) has been reported to be very successful in refractory status. [29, 30]

NG and IV levetiracetam (initial dose 60 mg/kg NG or IV, MAX 4500 mg) is now widely used, like IV valproic acid, especially as an alternative second line agent.

IV Lacosamide 5 - 10 mg/kg loading dose (MAX 400 mg) has emerged as an effective third lane agent including neonates. Maintenance 2-14 mg/kg/day divided BID, max 14 mg/kg/day. [31-33]

Isoflurane has been administered in status epilepticus achieving seizure control in 94.4% of cases. Hypotension was the only complication described. [34, 35] It can be used for very prolonged periods of time (> 1-2 months) in several case reports, though it may be neurotoxic. [36] Desired FIO% to achieve burst suppression is 1.5-2%.

In cases of anti-NDMA receptor-associated encephalitis or MOGAD associated status epilepticus early treatment with pulse steroids, IVIG and plasmapheresis should be implemented promptly. [37, 38]

In cases of FIRES and NORSE although the prognosis is poor [39], the anti-interleukin agent, anakinra has been successful. [40] [41, 42]

The urgent initiation of ketogenic diet and urgent epilepsy surgery have been also reported and can be relatively easy to implement in tertiary care facilities. [43, 44]

Magnesium sulfate 25-50 mg/kg IV (MAX 2000 mg) over 30 minutes should be considered for suspected POLG1 mutations cases. [45, 46]

GENERAL MANAGEMENT

Continuous VIDEO-EEG ideally with Trending Software (i.e., Persysts) monitoring is required for all patients on admission to PICU. The goal is cessation of all clinical and electrical seizure activity, which may require titration of therapy to EEG burst suppression***.***

Note that burst suppression on EEG is not usually achieved with high dose midazolam alone.

Clinical and electrical control of seizures in super-refractory status is usually maintained for 48-72 hrs., before stabilization on longer term therapy and 'awakening' from midazolam, barbiturate and/or ketamine 'coma'.

In any child on high dose anticonvulsant therapy may require dopamine or norepinephrine for blood pressure support. Check cardiac ECHO if inotropes required.

Maintain normothermia using heating or cooling blanket.

All cases of status epilepticus requiring intensive care admission require CT scanning and MRI once the patient is stable as the incidence of new findings that affect management is 20%.

Do not do a lumbar puncture initially, but take a blood culture if infection is suspected. Consider treating cases empirically for meningitis and encephalitis (i.e., consider empiric treatment with dexamethasone (meningitis PCR positive for *Haemophilus influenzae* only), vancomycin, ceftriaxone, and acyclovir).

Consider pyridoxine deficiency in younger children and infants – one initial treatment regimen is pyridoxine 100 mg IV, oral therapy can also be used. [47] Neonatal onset disease may respond best to pyridoxine phosphate [48-50] [51] initial dose is 40 mg/kg/day divided in 4 doses, followed by 50 mg/kg/day for 3 days). The response to parenteral pyridoxine (50-100 mg) is often dramatic, with normalization of the EEG pattern within minutes. Once the diagnosis is established, daily oral pyridoxine supplementation (5-10 mg/kg/day) is continued, adjuvant therapy with folinic acid 3 to 5 mg/kg/day has been suggested for infants with PDE.

Multiple studies indicate that the underlying pathology is the main determinate of the outcome of status epilepticus.

All children should have the following labs:

In blood:

1- MOG Antibodies
2- Autoimmune encephalopathy panel
3- GFAP antibodies
4- NMO antibodies

In CSF:

1. Autoimmune encephalopathy panel
2. GFAP antibodies

SUMMARY OF STATUS EPILEPTICUS MANAGEMENT PROTOCOL

The current regimen recommended for the APH ED or PICU is:

Lorazepam IV 0.1 mg/kg, MAX 4 mg

↓5 MIN

Lorazepam IV 0.1 mg/kg, MAX 4 mg

↓5 MIN

Levetiracetam IV 60 mg/kg, MAX 4500 mg or Valproic acid IV 20 mg/kg, MAX 3000 mg

***For Neonates LVT 40 mg/kg**

↓

Fosphenytoin IV 20 mg/kg, MAX 1500 mg PE admin at 2 mg PE/kg/minute up to maximum of 150 mg PE/minute

***Can be given undiluted IM and splitting sites**

↓15 MIN

PEDIATRIC NEUROLOGY NOTIFIED

↓

Phenobarbital IV 20 mg/kg, MAX 1000 mg

↓15 MIN

If Midazolam contraindicated – Valproic acid IV 20-40 mg/kg, infuse over 60 minutes

↓15 MIN

AIRWAY MANAGEMENT LIKELY NEEDED

↓

Midazolam 0.1-0.2 mg/kg bolus, start continuous infusion at 0.1 mg/kg/hr, then titrate every 5-30 min by 0.1 mg/kg/hr to seizure cessation or burst suppression. If seizure stops maintain dose.

If status continues: Titrate to 1-2 mg/kg/hr (some centers use up to 2.5 mg-3 mg/kg/hr)

*Consider adding another infusion agent if no response at 1 mg/kg/hr

↓ INOTROPES/PRESSORS MAY BE NEEDED

↓1 HR

Ketamine 0.5-2 mg/kg bolus, start continuous infusion at **0.5-1 mg/kg/hr,** then titrate every 15-30 minutes by 0.5 mg/kg/hr to seizure cessation or burst suppression. If seizure stops

maintain dose.

If status continues increase to **MAX dose 3 mg/kg/hr**

↓1 HR

Pentobarbital 1-5 mg/kg bolus, start continuous infusion of 0.5-1 mg/kg/hr, then titrate every 12 hours by 0.5-1 mg/kg/hr until burst suppression. If seizures stop maintain dose.

If status continues increase to **MAX dose 5 mg/kg/hr**
*Inotropes/pressors likely will be required

OR
Propofol 1-2 mg/kg bolus, start continuous infusion at 50 mcg/kg/min, titrate every 15-30 minutes by 25 mcg/kg/min to seizure cessation or burst suppression. If seizures stop maintain dose.

If status continues increase to **MAX dose 200 mcg/kg/min**
*Do not continue for > 67 mcg/kg/min for > 48 hours due to risk of PRIS

↓1 HR

Isoflurane – start at 0.5% and titrate up every 5 min by 0.1%, burst suppression % expired Isoflurane is usually 1.5 - 2%, STOP midazolam and ketamine

↓30 MIN
Maintain burst suppression for 48-72 hrs., maximize maintenance IV/NG therapy (Levetiracetam, valproic acid, topiramate or Lacosamide)

↓48-72 HRS
Wean continuous infusions

The goal is cessation of all clinical and electrical seizure activity, which may require titration of therapy to EEG burst suppression. Note that burst suppression on EEG is not usually achieved with high dose midazolam alone.

FURTHER INVESTIGATIONS

Further investigations of refractory status epilepticus can be pursued. Consider consulting Infectious diseases, Genetics, Metabolics and Rheumatology.

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STATUS EPILEPTICUS GUIDELINE FOR CHILDREN

INITIAL PRESENTATION OF A CHILD IN STATUS EPILEPTICUS

Lorazepam IV 0.1mg/kg, MAX 4mg

If IV access not available, may give Midazolam IM 0.2mg/kg (max 10mg)

5 mins

Lorazepam IV 0.1mg/kg, MAX 4mg

5 mins

Levetiracetam IV 60mg/kg, MAX 4500mg
(For Neonates, give LVT 40mg/kg)
Or
Valproic acid IV 20mg/kg, MAX 3000mg

Consider Pyridoxine deficiency early in neonates/infants; Administer pyridoxine 100mg IV

15 mins

Fosphenytoin IV 20mg/kg, MAX 1500mg PE admin at 2mg PE/kg/min up to a max of 150 mg PE/min
*can be given undiluted IM and splitting sites

15 mins

NOTIFY PEDIATRIC NEUROLOGY
Start Phenobarbital IV 20mg/kg
MAX 1000mg

15 mins

if Midazolam is contraindicated, start Valproic acid IV 20-40 mg/kg, infuse over 60 minutes

15 mins

If no contraindication to Midazolam, start infusion at 0.1-0.2 mg/kg bolus and proceed with continuous infusion at 0.1 mg/kg/hr; titrate every 5-30 minutes by 0.1mg/kg/hr to seizure cessation or burst suppression.
If seizure stops, maintain dose

If status continues, titrate Midazolam gtt to 1-2 mg/kg/hr
*Consider the addition of another infusion agent if no response at 1mg/kg/hr

60 mins

If after 1 hour and NO cessation of seizures, start Ketamine at 0.5-2 mg/kg bolus and then continuous infusion at 0.5-1mg/kg/hr; titrate gtt every 15-30 minutes by 0.5 mg/kg/hr to seizure cessation or burst suppression
If seizure stops, maintain dose

If status continues, increase to a MAX dose of 3mg/kg/hr

60 mins

Start Pentobarbital at 1-5mg/kg bolus and then continuous infusion at 0.5-1mg/kg/hr; titrate infusion every 12 hours by 0.5-1mg/kg/hr until burst suppression
If seizure stops, maintain dose
OR
Propofol 1-2mg/kg/ bolus and then continuous infusion at 50mcg/kg/min; titrate every 15-30 mins by 25mcg/kg/min to seizure cessation or burst suppression
If seizure stops, maintain dose

If status continues, increase to a MAX dose of 5mg/kg/hr

If status continues, increase to a MAX dose of 200mcg/kg/min

60 mins

Start Isoflurane at 0.5% and titrate up every 5 min by 0.1%, burst suppression % expired Isoflurane is usually 1.5-2%, STOP Midazolam and Ketamine

Maintain burst suppression for 48-72 hours, maximize maintenance IV/NG therapy; begin weaning infusions after 48-72 hours

Check for important treatable causes:
Hyponatremia – seizures due to hyponatremia (usually NA < 125 mmol/L): give 5 mL/kg of 3% Saline bolus (1 cc raises ~ Na 1 meq), repeat if required [9].
Hypoglycemia:
•Dextrose 10% 5 mL/kg (max 250 mL)
•Dextrose 25% 2 mL/kg (max 100 mL)
•Neonates: Dextrose 10% 2 mL/kg (max 250 mL)
Hypocalcemia – give calcium gluconate: 50 mg/kg (MAX 2000 mg) slow IV.
Hypertensive encephalopathy (usually due to acute nephritis, main treatment is to use antihypertensive agents with furosemide if needed).

These are points in the algorithm where respiratory and hemodynamic status should be monitored closely and intervention should occur swiftly

Rapid Sequence Intubation
Pre-oxygenation
Ketamine or Propofol
Rocuronium

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