**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)\(^1\) or buccal midazolam\(^2\) 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.\(^3\)

**Initial Presentation to Hospital**

Check for important treatable causes:

- **Hyponatraemia** - seizures due to hyponatraemia (usually Na < 125 mmol/L): give 5 mls/kg of 3% Saline bolus (raises ~ Na 4 mmol/L), repeat if required.\(^4\)
- **Hypoglycaemia** – give 0.5 ml/kg 50% dextrose or 2.5 ml/kg of 10% dextrose IV
- **Hypocalcaemia** – give calcium gluconate (0.22 mmol/L Ca) 50 mg/kg or 0.5 ml/kg (MAX 3 grams) slow IV
- **Hypertensive encephalopathy** (usually due to acute nephritis, mainstay of treatment is diuresis with frusemide)

There is evidence that lorazepam is more effective than phenobarbitone, phenytoin, and diazepam/phenytoin combined in adult subtle and overt status epilepticus (>10 min). Seizure recurrence and side effects were no different between the drugs.\(^5\) A Cochrane review supported this conclusion and added that lorazepam was more effective than diazepam alone.\(^6\) At least one study has reported reduced seizure recurrence with lorazepam.\(^7\)
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).8

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.9 A more recent pediatric study from India demonstrated than lorazepam alone was as effective as a combination of diazepam and phenytoin (100% success rate in both groups).10

Compared to IV diazepam, IM midazolam results in more rapid cessation of seizures because of more rapid administration11 and may result in less apnoea.12 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.13 Excluding time to obtain access the onset in ½ - 1 minute longer: 3.5 vs. 2.9 min.14

In conclusion, initial treatment of status epilepticus should be IV lorazepam, midazolam or diazepam, IM midazolam, or IN midazolam. Experience with buccal/oral midazolam is limited at present. Optimal initial or maximal dosages have not been clearly identified.

**First Line Treatment**

- IV lorazepam 0.1 mg/kg, max 4 mg (PROBABLY BEST OPTION)
- IV midazolam 0.15 mg/kg, max 5 mg
- IM midazolam 0.2 mg/kg, max 5 mg
- IN midazolam 0.2 mg/kg, max 10 mg
- IV diazepam 0.2 mg/kg, max 10 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 benzodiazepines is associated with increased risk of respiratory depression.15

**Second Line Treatment**

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

A. IV Fosphenytoin 15-20 mg/kg, MAX 2000 mg, over 15 min or max rate 50 mg/min
B. IV Phenobarbital[one] 20 mg/kg, MAX 1000 mg load over 30 min.
C. IV Midazolam bolus of 0.1-0.2 mg/kg (some centres use 0.5 mg/kg if airway protected) then infusion starting at 60-120 mcg/kg/HR increased every 5-30 min by 50-240 mcg/kg/HR
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preceded by a bolus of 0.1 mg/kg, up to 1000-1500 mcg/kg/HR (some centres use up to 2000-3000 mcg/kg/HR).16

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 phenobarbitone 20 mg/kg.17

In another recent case series midazolam bolus and infusion and single phenytoin load controlled 89% of cases of paediatric status epilepticus.18

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 appropriate sized ETT.

Third Line Treatment – Super Refractory Status

There is no known optimal regime. The options are discussed below. The proposed ACH Regime is described in the next section.

Traditionally thiopentone infusion was used 5 mg/kg load, then 1-5 mg/kg/HR, but has no known advantage over high-dose phenobarbitone or pentobarbital therapy and may cause more side-effects. Thiopentone is now unavailable in Canada.

The shorter acting barbiturate, pentobarbital (half life 15-50 hrs) is available, but is very expensive and also confers no known advantage over phenobarbitone, although many centres use it.19 Drug levels are available, but the turnaround time is > 24 hrs.

Phenobarbitone (half life in adults mean 80 hrs, children 110 hrs) can be given in increments of 5-10 mg/kg every 5-30 min to achieve EEG burst suppression. Up to 100 mg/kg/day (serum levels may be > 1000 μmmol/L) may be required. Hemodynamic compromise is a frequent problem, as well as a prolonged wake-up time.

Propofol infusion is not recommended due to the risk of ‘propofol infusion syndrome’ in children.20

Lidocaine infusion is an alternative,21 as is ketamine.22 23

The ketamine dose ranges required to achieve seizure control was 300-3600 mcg/kg/HR, after a loading dose of 0.5-2 mg/kg. Some adult centres are using ketamine, instead of barbiturate therapy with good success, without the complications associated with barbituates.
IV valproate (25 mg/kg bolus and/or continuous infusion of 20-100 mg/kg/day) is currently under investigation as a treatment option and many centres are now using it early in their treatment algorithms.\textsuperscript{24}

High dose NG topiramate (150-750 mg bd in adults, starting dose 5-10 mg/kg/day in children\textsuperscript{25}) has recently been reported to be very successful in refractory status.

NG and IV Keppra (levetiracetam, initial dose 20-50 mg/kg NG or IV) is also gaining in popularity. IV Keppra is currently not available in Canada.\textsuperscript{26 27 28}

IV lacosamide is also promising.\textsuperscript{29}

Therapeutic hypothermia has been reported to be effective in febrile infection-related epilepsy syndrome (FIRES).\textsuperscript{30}

New onset refractory status epilepticus or NORSE syndrome is reported to respond well to IV IgG,\textsuperscript{31} as does anti-NDMA receptor-associated encephalitis. Plasmapheresis is also used in the latter condition.\textsuperscript{32} There are other forms of encephalitis e.g. Rasmussen encephalitis, that may respond to immune-modulating therapies.

Isoflurane has been administered in status epilepticus for very prolonged periods of time (> 1-2 months) in several case reports, though it may be neurotoxic.\textsuperscript{33} Desired MAC to achieve burst suppression is 1.5-2%.

The urgent instigation of a ketogenic diet and urgent epilepsy surgery have been reported also.\textsuperscript{34 35}

**General Management**

Continuous EEG 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 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 (or ideally MRI) once the patient is stable as the incidence of new findings that affect management is 20%.\textsuperscript{36}
Do not do a lumbar puncture initially\textsuperscript{37}, but take a blood culture if infection is suspected. Consider treating cases imperically for meningitis and encephalitis (i.e. consider empiric treatment with dexamethasone, vancomycin, cefotaxime and aciclovir).

Consider pyridoxine deficiency in younger children and infants – one initial treatment regime is pyridoxine 100 mg IV, oral therapy can also be used\textsuperscript{38 39}. Neonatal onset disease may respond best to pyridoxine phosphate\textsuperscript{40}.

Multiple studies indicate that the underlying pathology is the main determinate of the outcome of status epilepticus.\textsuperscript{41}

**ACH Regime**

The current regime recommended for the ACH PICU is:

- Lorazepam IV 0.1 mg/kg, MAX 4 mg
  \(\downarrow\) 5 MIN
- Lorazepam IV 0.1 mg/kg, MAX 4 mg
  \(\downarrow\) 5 MIN
- Fosphenytoin IV 20 mg/kg, MAX 2000 mg over 15 min or 50mg/min
  \(\downarrow\) 15 MIN
- PICU & NEUROLOGY NOTIFIED
- Phenobarbitone IV 20 mg/kg, MAX 1000 mg
  \(\downarrow\) 15 MIN
- If Midazolam contraindicated - Valproate IV 20-40 mg/kg, MAX rate 1 mg/kg/min
  \(\downarrow\) 15 MIN
- AIRWAY MANAGEMENT LIKELY NEEDED
- Midazolam IV infusion\textsuperscript{42} - load 0.1-0.5 mg/kg, constant infusion 120 mcg/kg/hr, every 5 min repeat bolus dose of 0.1 mg/kg and increase infusion by 120 mcg/kg/HR x 2, thereafter increase by 240 mcg/kg/HR if required, MAX dose 2000 mcg/kg/hr
  \(\downarrow\)
- INOTROPES/PRESSORS MAY BE NEEDED
  \(\downarrow\) 1 HR
- Ketamine IV infusion – load 2 mg/kg, start infusion at 300 mcg/kg/hr, every 5 min repeat load of 0.5 mg/kg and increase infusion by 400 mcg/kg/HR, MAX dose 3600 mcg/kg/HR
  \(\downarrow\) 1 HR
- Isoflurane – start at 0.5% and titrate up every 5 min by 0.1%, burst suppression MAC is usually 1.5 - 2%, STOP midazolam and ketamine
  \(\downarrow\) 30 MIN
- Maintain burst suppression for 24-48 hrs, maximize oral therapy (Keppra, Topiramate, Valproate)
  \(\downarrow\) 24-48 HRS
- Wean
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

A HSC protocol for the investigation of refractory status epilepticus is available. Consider consulting Metabolic Medicine, Genetics and Rheumatology.

References


2 McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier J, Smith S, Choonara I. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet. 2005 Jul 16-22;366(9481):205-10. Therapeutic success was 57% vs. 27% (lower than most individual drug series). Respiratory depression occurred in 5.5%, equally in both groups. The dose of midazolam and diazepam was ~ 0.5 mg/kg, max 10 mg, higher than our recommended dose: 2.5 mg 6-12/12, 5 mg 1-4 yrs, 7.5 mg 5-9 yrs and 10 mg ≥ 10 yrs.

3 Harbord MG, Kyrkou NE, Kyrkou MR, Kay D, Coulthard KP. Use of intranasal midazolam to treat acute seizures in paediatric community settings. J Paediatr Child Health. 2004 Sep-Oct;40(9-10):556-8 – dose was 0.2-0.3 mg/kg, max 10 mg, successful in 89%.


7 Cock HR, Schapira AH. A comparison of lorazepam and diazepam as initial therapy in convulsive status epilepticus. QJM. 2002 Apr;95(4):225-31.


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41 See reference 32.