Critical Care guideline for the treatment of Status Epilepticus

Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to >**5 min of (a)** continuous seizures **or (b) two or more discrete seizures** between which there is incomplete recovery of consciousness.[1] This is based on the concept that by 5 minutes the seizure is prolonged, but that by 30 minutes neuronal damage may occur, so treatment should commence early.

Management of status epilepticus is conveniently described by a stepwise approach. Critical Care is usually involved from stage 2 or 3 onwards or where intubation and ventilation are required.

Stage 1
0-5 mins
Early status epilepticus
Treat with benzodiazepines, midazolam, diazepam or lorazepam

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Stage 2
>5 mins
Established status epilepticus
Treat with IV anti epileptic drugs eg. Phenytoin

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Stage 3
>30 mins
Refractory status epilepticus
Treat with general anaesthesia eg propofol and intubation, ventilation and propofol +/- midazolam with addition of sodium valproate and/or levetiracetam

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Stage 4
>24 hrs.
Super refractory status epilepticus
Complex specialist treatment requiring neurologist/neurophysiology and EEG input. Drug therapies include the above plus barbiturates and ketamine.

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Investigation

History and examination.
Identify and treat the underlying causes of seizures.
Blood glucose: identify and treat hypoglycaemia.
Imaging: CT, MRI, EEG. CSF examination, metabolic screen, anti-NMDA receptor antibody assay.

Drug Treatment Guidelines

The general stepwise addition of drug treatment is outlined below. Preparation information for all drugs can be found in appendix 1.

Stage 1.

Early status epilepticus 0-5minutes.
Initial treatment is with **diazepam** emulsion (Diazemuls®).

- 2mg increments IV initially up to 10mg over 5 minutes.
- Alternative is IV lorazepam 4mg slow IV into a large vein.
- Repeat diazepam once 15 minutes later up to total 20mg if required.
- Repeat lorazepam once 15mins later up to a total of 8mg, if required.[1]

Stage 2.

>5 minutes
Established status epilepticus

- Load with **phenytoin** and commence maintenance dose.
- Loading dose 20mg/kg (see appendix 2 for dosing in obesity). Caution in frail and elderly as may cause significant hypotension. Consider loading in two divided doses.
- Maintenance dose 100mg IV 8 hourly if <80kg, 6 hourly if >80kg .
- Check level morning following loading to check adequate loaded. See appendix 2 for details of levels. [2]

Stage 3.

>30 minutes
Refractory status epilepticus.
Induce general anaesthesia. Intubate and ventilate with general supportive ICU care. Use drugs as follows in a stepwise fashion.

Propofol

Initial bolus to induce anaesthesia
Maintenance infusion of up to 4mg/kg/hr[4,5]

Midazolam

Loading dose bolus: 0.1-0.2mg/kg
Maintenance infusion 0.05-0.4mg/kg/hr. If breakthrough SE give a further bolus and increase the infusion every 3-4hours by 0.05-0.1mg/kg/hr. [4,5,6]

Sodium Valproate
Loading dose of 30mg/kg i.e. 2100mg if 70kg. If obese use ideal body weight. Maintenance infusion of 2400mg over 24 hours. Ammonia levels should be performed for patients started on valproate approximately two days after starting valproate. See appendix 3. [3,4,5] Please note that sodium valproate should only be used after careful consideration in women of childbearing potential due to the high risk of fetal anomalies and cognitive impairments when given during pregnancy.

Levetiracetam (Keppra). Typical doses 1g IV twice daily.
This drug is well tolerated and widely used by neurologists, although its use in status epilepticus is unlicensed. The evidence base for status is still developing and the Established Status Epilepticus Trial comparing fosphenytoin, levetiracetam and sodium valproate is still to report. Discuss with neurology if any concerns regarding dosing.

Stage 4
>24 hrs.
Super refractory status epilepticus. Status epilepticus that has continued despite general anaesthesia. This requires complex specialist treatment involving a collaborative approach with neurology and neurophysiology, EEG input and continuous EEG monitoring. By this stage the seizures are often non convulsive.

Phenobarbitone
Loading dose of 10mg/kg IV up to a maximum of 1000mg.
Maintenance dose of 120mg once daily IV. [2,3]

Ketamine
There is evidence on the use of ketamine as a safer alternative to thiopentone,though it is mostly based on isolated case reports. From the information available:
Loading dose of 50mg
Maintenance infusion of 1-5mg/kg/hr.[7,8,9,10,11,12]
It is recommended that increased intracranial pressure should be excluded before ketamine is administered.[9] There are few published data on the theoretical risk of neurotoxic effects when the drug is used for prolonged periods and its safety in prolonged use is largely untested.

Thiopentone
Using a 25mg/ml solution for a 70kg adult infuse approximately:
40mls per hour for 1 hour
24mls per hour for 2 hours
12-20mls per hour thereafter [14]

Other treatments
Inhalational anaesthetic agents
Magnesium infusion
Hypothermia
Ketogenic diet
For auto-immune encephalitis: high dose steroids, immunoglobulin and plasma exchange, in consultation with a neurologist.

Burst suppression

"Burst suppression" may be requested by a neurologist. This is where a bedside EEG is used to titrate the drug against suppression of bursts of EEG activity. We use the Nicolet ™ Monitor to observe this at the bedside. The drug will usually be thiopentone or ketamine.

The evidence for this is not proven and it largely based on expert opinion such as that from Rossetti (15) who says *"In view of present knowledge, an initial course of midazolam anaesthesia targeting EEG burst-suppression patterns with an interburst interval of about 10 s for 24 h, followed by progressive tapering over 6–12 h under EEG control, seems to be a reasonable option. Propofol and, subsequently, barbiturates can be used thereafter"*

In practice, a period of burst suppression followed by lightening of sedation does seem to result in recovery for some patients, perhaps by "resetting" the brain.

What to look for on the Nicolet. The screen sweep on the Nicolet is about 12 seconds. So the target is one burst of activity (of say 2 seconds), followed by a flat line on every screen. This would be consistent with an interburst interval of about 10 seconds as suggested above. The aim is to achieve near maximal suppression of brain metabolism short of an isoelectric EEG (flatline) because that could result in overdose and systemic problems.

Fig 1.
This is about right. There is one burst per screen.

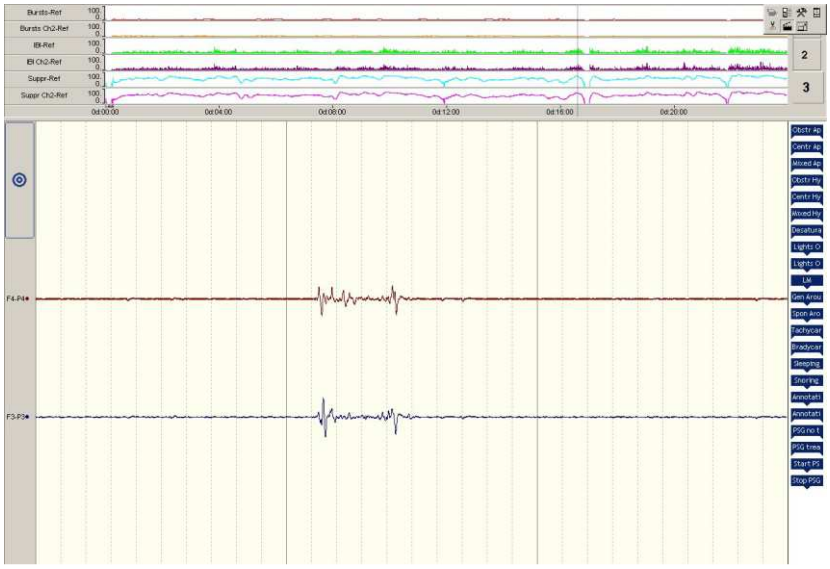


Fig 2.
This is not enough sedation, there are too many bursts per screen. Try a bolus and possibly increase the rate of infusion.

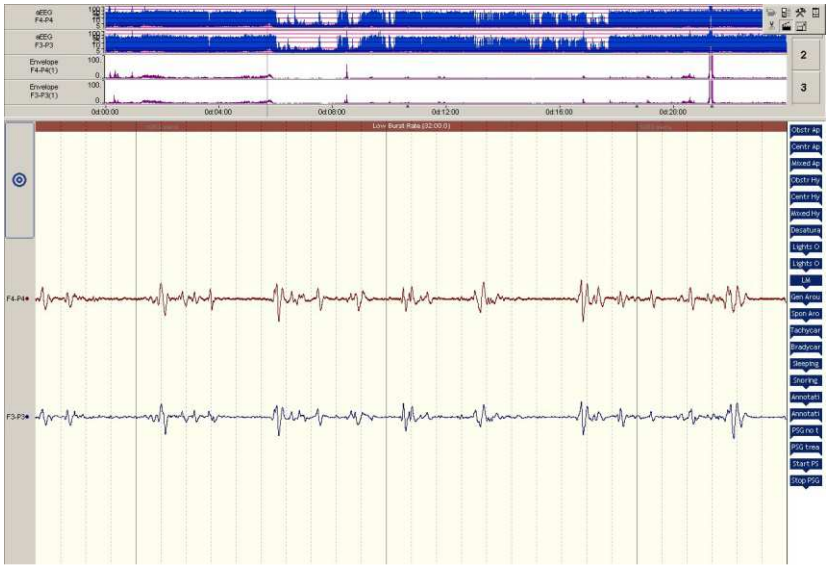


Fig 3.
This is too much sedation. The trace is iso-electric. Turn off the infusion for a while until bursts re-appear.

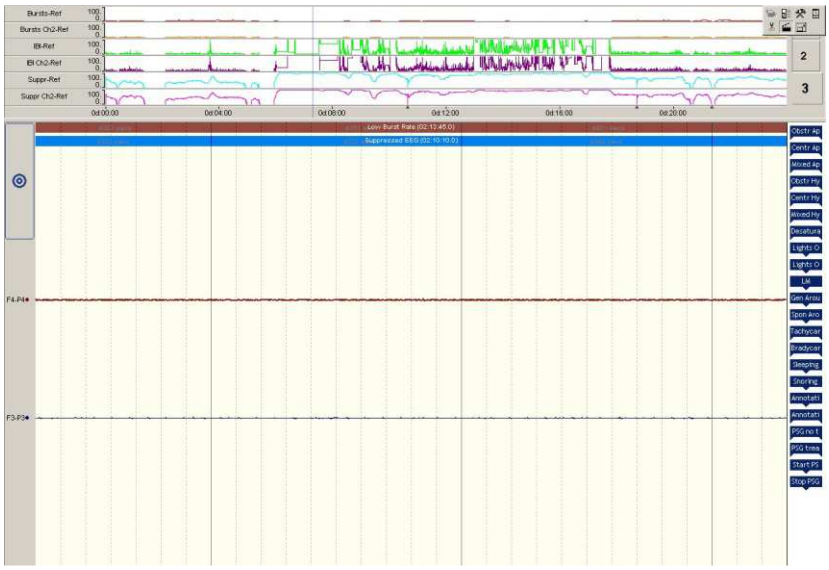
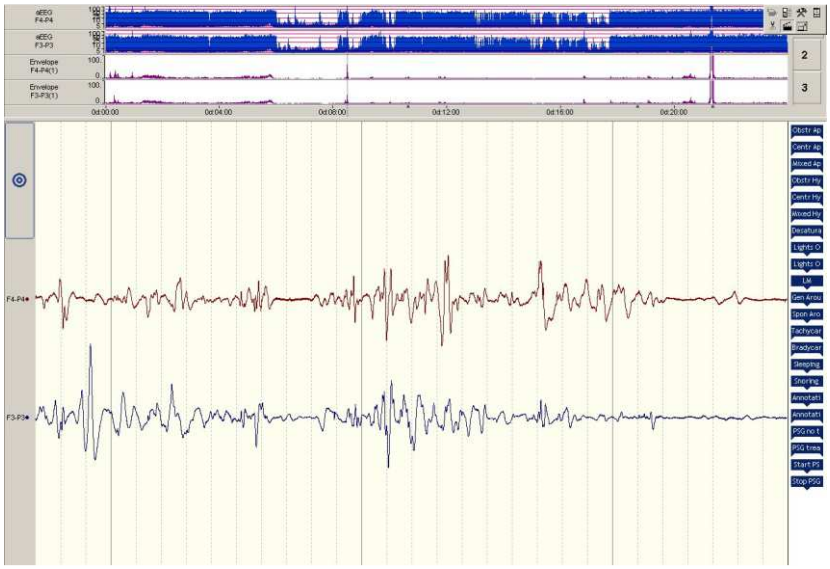


Fig 4
This may be fitting.
Needs additional treatment



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Appendix 1

Drug	Preparation and administration details
Diazemuls	Undiluted at max rate of 5mg per minute
Lorazepam	Undiluted as slow IV into a large vein
Phenytoin	Undiluted if given centrally or up to 10mg/ml if diluted i.e up to 1g in 100ml sodium chloride 0.9%, >1g <2.5g in 250ml sodium chloride 0.9%. Incompatible in glucose 5% Phenytoin may be administered centrally without dilution at a maximum rate of 50mg/minute but it is preferable to administer more slowly to minimise the hypotensive effects e.g. 100mg over 3- 5minutes, 1000mg over 60 minutes. If diluted as per the standard infusion the solution can be administered over 60 minutes (but no greater than 60 minutes due to physical incompatibility of the infusion). If there is concern over hypotensive effects of large doses the loading dose can be split into 2 infusions, each given over one hour.
Levetiracetam	1g BD . Dilute in 100mls sodium chloride and infuse IV over 15 minutes
Propofol	1g in 100ml NEAT
Midazolam	60mg in 60ml glucose 5% Boluses over 3-5 minutes, maintenance by continuous infusion
Sodium Valproate	Sodium valproate injection may be given undiluted by slow intravenous injection over 3-5 minutes, by an intermittent infusion or by a continuous infusion. Dilute the required dose of sodium valproate injection, whether for intermittent or continuous infusions, in 100ml glucose 5% infusion. Sodium valproate infusion is usually administered as an intravenous infusion over 60 minutes at a rate that does not exceed 20mg/minute i.e. maximum of 1200mg over 60 minutes.
Phenobarbitone	Loading dose and maintenance dose: One ml phenobarbitone injection should be diluted with 10ml water for injections and given at a max rate of 100mg/min. So for maintenance dose if using 60mg/ml injection, 2ml (120mg) should be diluted in 20ml water for injections (final volume 22ml) and given over at least two minutes.
Ketamine	Loading dose: if using 100mg/ml solution dilute with equal volume of sodium chloride 0.9%. 50mg/ml solution can be give undiluted. Give over at least one minute. maintenance infusion**:** 2000mg ketamine in 40mL UNDILUTED. i.e 50mg/ml . Reference for this is ketamine monograph in Renal Drug Handbook in administration section. Ketamine does not need to be administered in a locked syringe.
Thiopentone	1500mg in 60ml water for injections

Appendix 2

Phenytoin

Dosing in obesity

The dose is calculated using an "adjusted body weight" (ABW) that is equal to the ideal body weight (IBW) plus the product of 1.33 times the excess over IBW.

IBW is calculated as follows:

IBW females= 45.5kg + (2.3kg per inch over 5 feet)
IBW males= 50kg + (2.3kg per inch over 5 feet)

ABW (obese) = IBW + (1.33 x (actual weight – IBW))

Loading dose = 20mg/kg (using ABW)
Maintenance dose = 4mg/kg (using ABW)

Interpreting serum concentrations

Aim for 15-20microgram/ml. Toxicity between 20-30 microgram/ml is ataxia

Correcting for low albumin

$$\text{Factor} = 0.9 \times \frac{\text{albumin}}{40} + 0.1$$

$$\text{Actual level} = \frac{\text{measured level}}{\text{Factor}}$$

Correcting for renal impairment

Use this equation in patient's with a CrCl <25mls/min or if being haemofiltered. The free fraction of phenytoin increases in renal impairment.

$$\text{Factor} = 0.48 \times \frac{\text{albumin}}{40} + 0.1$$

$$\text{Actual level} = \frac{\text{measured level}}{\text{Factor}}$$

Appendix 3

Ammonia blood concentrations

Sodium valproate therapy can cause hyperammonaemia, especially in the early stages of therapy.

An ammonia concentration should be measured at approximately two days after starting sodium valproate. Consider rechecking while on sodium valproate particularly if the patient's conscious level does not improve despite control of the seizures or if the patient shows signs of encephalopathy.

Take samples of blood into Lithium Heparin tubes (avoiding any contamination with sweat) and place on ice immediately for transport.

Call the RIE duty biochemist on 26879.