Critical Care Guidelines
FOR CRITICAL CARE USE ONLY

Critical care guideline for the treatment of Status Epilepticus

Generalised, convulsive status epilepticus refers to five or more minutes of continuous seizures, or two or more discrete seizures between which there is incomplete recovery of consciousness[1]. For those patients admitted in status to Critical Care, it is likely they will be at stage 3 of the management pathway described below.

Evidence suggests that achieving seizure control quickly is a major determinant of good outcome[2]. **The priority in status epilepticus management is to achieve rapid termination of seizures, regardless of the agent used.**

Stage 1 - Early status epilepticus

Start high flow oxygen. Check glucose.

Administer benzodiazepine if seizure lasts ≥5 minutes.
If intravenous access is available:

- First choice: **lorazepam 4mg IV** over 2 minutes.
- OR **diazepam* 10mg IV** over 2 minutes.

If intravenous access is not available:

- First choice: **buccal midazolam 10mg.**
- OR **rectal diazepam 10mg**.

Benzodiazepine doses can be repeated once after 5-10 minutes if first administration does not terminate seizure. Beware of respiratory depression.
*Diazepam is rapidly redistributed and may accumulate with repeated dosing.
Prepare Stage 2 drugs during Stage 1. Gain IV access.

Stage 2 – Established status epilepticus

If seizures persist, administer loading dose of antiepileptic drug intravenously.
Notify intensive care.

First choice:

- **Levetiracetam 60mg/kg** (max dose 4500mg) over 10 minutes[3].

Second choice:

- **Phenytoin 20mg/kg** (max dose 2000mg) at max rate 50mg/minute[3].
  Infuse into a large vein with ECG and blood pressure monitoring due to risk of hypotension and bradycardia. Use with caution in elderly and patients with cardiac disease (may reduce rate to 25mg/min or lower).

OR

- **Sodium valproate 40mg/kg** (max dose 3000mg) over 10 minutes[3]. First choice in severe renal failure. Use alternative where possible in **pregnancy**, acute liver failure or if there are concerns about mitochondrial disease.

Stage 3 – Refractory status epilepticus

>30 minutes

Induce general anaesthesia. Intubate and ventilate with general supportive ICU care using the following drugs in a stepwise fashion:

- Propofol
- Midazolam
- Consider addition of second anticonvulsant drug from Stage 2.

Stage 4 – Super Refractory status epilepticus

>24 hours
Super refractory status epilepticus that has continued despite general anaesthesia. This requires complex specialist treatment involving a collaborative approach with neurology and neurophysiology and also continuous EEG monitoring. By this stage seizures are often non convulsive. Consider the following agents:

- Phenobarbital
- Ketamine
- Thiopental

1. **Investigation:**

- History and examination.
- Identify and treat the underlying causes of seizures.
- Blood glucose: identify and treat hypoglycaemia.
- Imaging: CT, MRI, CSF examination, metabolic screen, anti-NMDA receptor antibody assay.
- Patients in Critical Care in status epilepticus should have continuous EEG monitoring.

2. **Drug Treatment Guidelines:**

2.1 Levetiracetam

Intravenous loading dose administration for levetiracetam:
Administer 60mg/kg (max: 4500mg) with 100ml of 0.9% sodium chloride or 5% glucose over 10 minutes. Note: levetiracetam doses are based on the ESETT trial[3] and differ from those in NHS Lothian IV monographs.

Maintenance dose for levetiracetam:

- Levetiracetam: 1000-1500mg IV, oral or NG twice daily. For i.v. administration, dilute the required dose with at least 100ml sodium chloride 0.9% or glucose 5% and administer over 15 minutes.
- Start 10-12 hours after loading dose.
- Aim for reasonable dosing times 12 hours apart.[17]

Known severe renal failure:
Where eGFR is known to be less than 30 mL/min/1.73m^2, then sodium valproate should be used as first choice Stage 2 drug. No dose adjustment is required. Do not delay treatment to wait for blood results.
Levetiracetam is an appropriate second-line option. No dose adjustment is required for the loading dose, but the maintenance dose should be reduced, see Table 1.1 below.[17]

Creatinine Clearance	Dose
50-79ml/min	1000mg twice daily
30-49ml/min	750mg twice daily
<30ml/min	500mg twice daily
In CVVHD dialysis give 750mg once daily. For other forms of dialysis consult renal physician.	

Table 1.1 Maintenance doses of levetiracetam in renal impairment[6]

Patient already prescribed levetiracetam:
Levetiracetam can be used as the first choice anticonvulsant drug during Stage 2 at full dose, even if the patient was already prescribed levetiracetam prior to admission. Levetiracetam levels are not available acutely, and supratherapeutic doses of levetiracetam are unlikely to be harmful. If there is concern about administering levetiracetam in this context, sodium valproate or phenytoin can be given instead.[17]

Pregnancy
Levetiracetam is the preferred Stage 2 drug in pregnancy. Avoid sodium valproate where possible given the risk of teratogenicity.[17]

2.2 Phenytoin

Phenytoin Monograph

Loading dose administration for phenytoin:
Administer in 50-250ml of 0.9% sodium chloride (concentration not to exceed 10mg/ml) at a rate not exceeding 50mg/minute through an in-line filter (0.22-0.5 micron). Ensure working cannula in large vein prior to infusion due to risks associated with extravasation (see NHS Lothian IV guide).

Maintenance dose for phenytoin:

- Commenced 6-8 hours after the loading dose.
- If <80kg, 100mg IV three times per day (8 hourly).
- If ≥80kg, 100mg IV four times daily (6 hourly).
- Check phenytoin trough level 24 hours after starting maintenance dose. In general, level is checked on a daily basis prior to the first maintenance dose.

Phenytoin dosing in obesity: Obese patients have an increased volume of distribution. The dose for these patients is calculated using an adjusted "dosing weight" (DW) that is equal to the ideal body weight (IBW) plus the product of 1.33 times the excess over IBW. This accounts for the extra volume in distribution in this patient group.[18] In order to calculate the DW you must first determine the patient's 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)

DW = IBW + [1.33 x (total body weight – IBW)]

- **Loading dose** = 20mg/kg (using DW). Maximum dose = 2000mg.
- **Maintenance total daily dose** = 4mg/kg total daily dose (using DW). This figure is then given in 4 divided doses.

Interpreting serum concentrations:

- Aim for 15-20mg/litre, in many cases neurology may recommend aiming for higher levels of 20-25mg/litre. If in doubt, discuss with neurology.
- At target therapeutic concentrations of phenytoin, patients may experience minor central nervous depression and nystagmus, drowsiness or fatigue. Above the quoted therapeutic range (greater than 20 mg/L), ataxia, slurred speech and incoordination can occur. Seizures and coma can be induced by levels greater than 50 mg/litre.[18]
- Phenytoin levels are now automatically corrected for low albumin when reported on Trak. When interpreting levels always review the "adjusted phenytoin" result. This can also be calculated manually by using the following equation:

$$\text{Corrected level (mg/l)} = \frac{\text{observed phenytoin level (mg/l)}}{(0.9 \times \text{albumin} / 40) + 0.1}$$

- Correcting for renal impairment is required in patient with with a CrCl < 25mls/min or in patients requiring CVVHD as the free fraction of phenytoin increases in renal impairment. Use the following equation and discuss with pharmacy:

$$\text{Corrected level (mg/l)} = \frac{\text{observed phenytoin level (mg/l)}}{(0.01 \times \text{Albumin (g/l)}) + 0.1}$$

Top up Phenytoin dose: If the phenytoin level is subtherapeutic and the patient is not well controlled, a top up loading dose should be considered. Top up doses can be calculated using the following equation and Table 1.2 gives approximate increases in phenytoin concentration following doses of 250mg-750mg[19]:

Phenytoin top up dose (mg) = 20 – measured concentration (mg/l) x 0.7 x weight (kg).[18,19]

For example, a top up dose of 500mg administered to a 70kg patient with a serum concentration of 5mg/l should increase the concentration to 15mg/l.

Concentration increase with top-up dose				
Dose / Weight	50kg	60kg	70kg	80kg
250mg	7 mg/l	6 mg/l	5 mg/l	4.5 mg/l
500mg	14 mg/l	12 mg/l	10 mg/l	9 mg/l
750mg	21 mg/l	18 mg/l	15 mg/l	13.5 mg/l

Table 1.2: Increase in phenytoin concentration with 'top-up' doses. Note: In patients with hypoalbuminaemia, the measured phenytoin concentration must be corrected before using the above table (i.e. use the "adjusted level" on Trak results).

For patients who remain in status epilepticus with sub-therapeutic levels, consider a larger "top-up" dose or even reload, following discussion with the critical care consultant.

2.3 Sodium Valproate

Sodium valproate monograph

Loading dose administration for sodium valproate:
Administer 40mg/kg IV (Max: 3000mg) in 50ml of 0.9% sodium chloride or 5% glucose over 10 minutes. Note: sodium valproate doses are based on the ESETT trial[3] and differ from those in NHS Lothian IV monographs.

Where eGFR is known to be less than 30 mL/min/1.73m^2, then sodium valproate should be used as first choice Stage 2 drug, see below. No dose adjustment is required. Do not delay treatment to wait for blood results.

Maintenance dose for sodium valproate:

- 1000-1200mg IV, oral or NG twice daily. Start at least 6 hours after loading dose.

Maintenance doses of sodium valproate must not be started in women of childbearing age unless a Pregnancy Prevention Program is in place – contact neurology for advice.

Ammonia blood concentrations:

- Sodium valproate therapy can cause hyperammonaemia, especially in the early stages of treatment.
- 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 using Lithium Heparin tubes (avoiding any contamination with sweat, and place on ice immediately for transport). Inform the laboratory that the sample is arriving.

2.4 Propofol

- Initial bolus 100-200mg IV to induce anaesthesia.
- Maintenance intravenous infusion of up to 4mg/kg/hr.[4]
- Standard concentration- 1gram in 100mls, undiluted.

For patients on prolonged infusions, check serum Creatinine Kinase and triglycerides to exclude Propofol Related Infusion Syndrome (PRIS).

2.5 Midazolam

Midazolam monograph

- Loading dose: 0.1-0.2mg/kg IV bolus.[5]
- Maintenance IV infusion: 0.05-0.4mg/kg/hr. If breakthrough status epilepticus occurs, give a further bolus and increase the infusion every 3-4 hours by 0.05-0.1mg/kg/hr.[5]
- Continuous EEG monitoring is essential.
- Consider addition of second anticonvulsant drug from Stage 2.

2.6 Phenobarbital

Phenobarbital monograph

- Loading dose of 10mg/kg IV, up to a maximum of 1000mg.[5]
- Maintenance dose of 120mg IV daily.
- Once the patient is clinically stable and has satisfactory GI absorption, consider changing to 120mg daily orally or via NG tube.

2.7 Ketamine

Ketamine monograph

There is evidence on the use of ketamine as a safer alternative to thiopental, though it is mostly based on isolated case reports. From the information available:

- Loading dose: 3mg/kg IV bolus (using ideal body weight).
- Maintenance IV 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.[13] 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.

2.8 Thiopental

Thiopental Monograph

Intravenous loading dose regime (using ideal body weight):

First Hour	10 mg/kg/hr
Second Hour	7 mg/kg/hr
Third Hour	5 mg/kg/hr

Maintenance intravenous infusion: 4-7mg/kg/hr.[5,14,15,16]
See monograph for further dosing information. Titrate according to EEG. Once EEG is isoelectric, reduce the infusion rate to the lowest dose that will maintain burst suppression. Continue for 24-48 hours to achieve burst suppression.

Serum potassium and thiopental:
Serum potassium concentration may drop during thiopental sodium infusion. However, potassium replacement when infusing thiopental sodium can be dangerous. It can lead to serum potassium rebounding to dangerously high levels on stopping thiopental sodium. **Therefore, it is generally unnecessary to replace potassium unless it falls below 3.0mmol/l, or unless the patient is symptomatic of hypokalaemia, e.g. arrhythmias. On ceasing thiopental sodium infusion, check serum potassium levels every 2 hours for the first 24 hours.**

3. Other treatments

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

4. 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 thiopental or ketamine.

The evidence for this is not proven and it largely based on expert opinion such as that from Rossetti (20) 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.

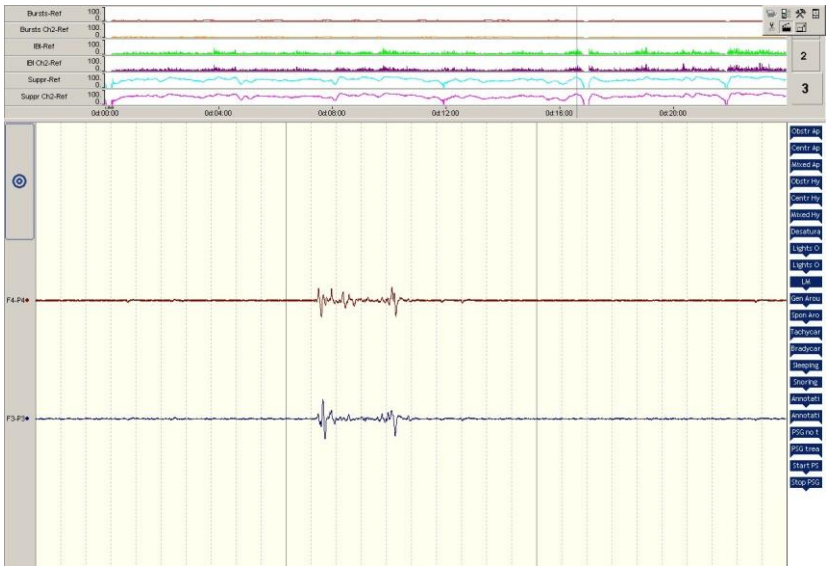


Fig 2.
This is not enough sedation, there are too many bursts per screen. Try a bolus and possibly increase the rate of infusion.

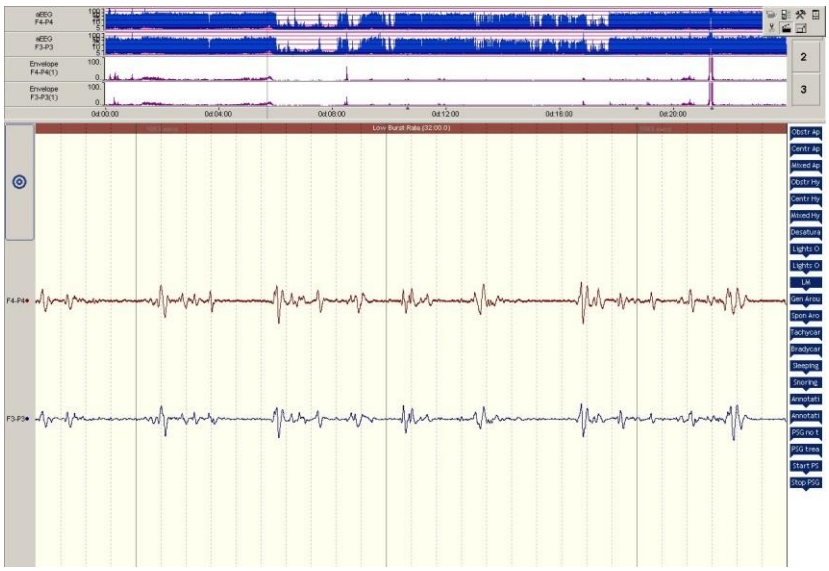


Fig 3.
This is too much sedation. The trace is iso-electric. Turn off the infusion for a while until bursts re-appear.

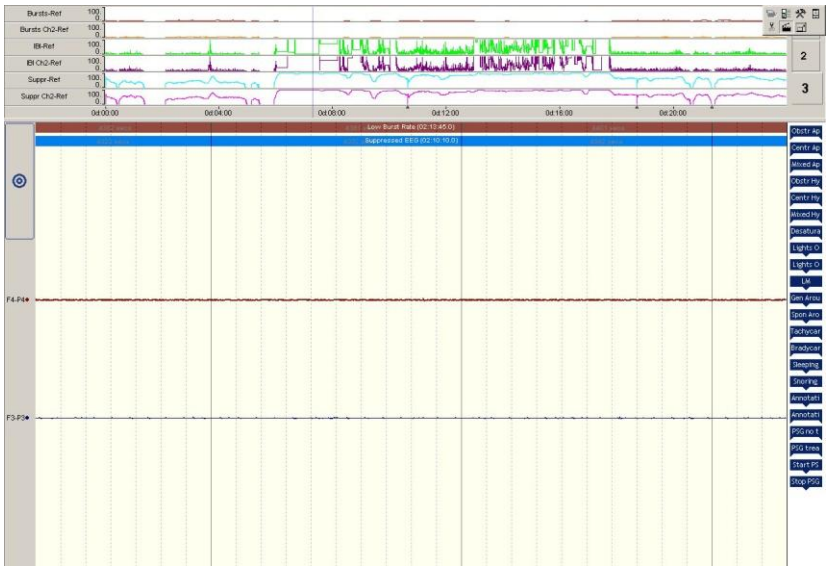
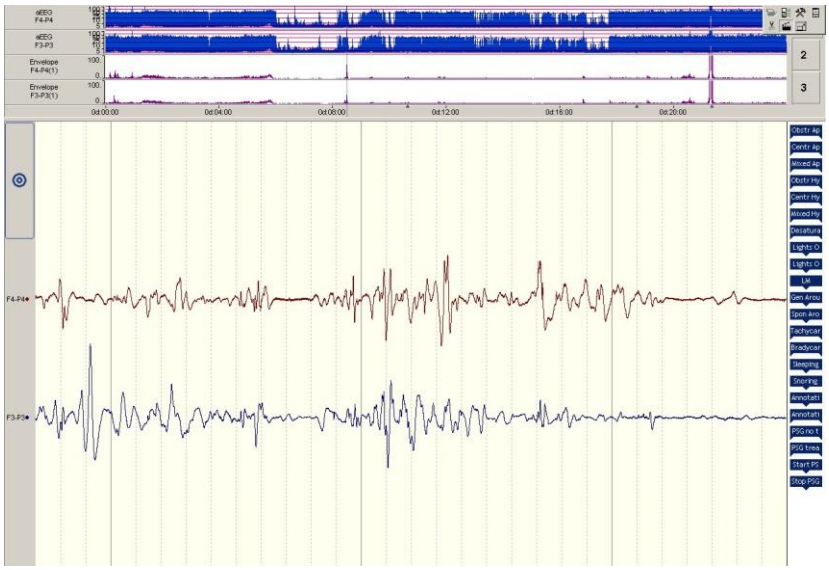


Fig 4 below
This may be fitting.
Needs additional treatment.



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