Management of Convulsive and Non-Convulsive Status Epilepticus

1. Purpose of Document

To guide management of patients with status epilepticus admitted to the Department Of Critical Care Medicine (DCCM) within the Auckland District Health Board (ADHB).

2. Responsibility

All medical and nursing staff providing care and treatment for patients admitted to the DCCM with status epilepticus.

3. Document Principles and Goals

Status epilepticus is a neurological and medical emergency, which manifests as prolonged seizure activity or multiple seizures without return to neurological baseline. It is associated with significant morbidity and mortality, therefore appropriate investigation and timely medical therapy are essential.

Seizure subtypes can be classified by semiology, etiology or EEG pattern. However, for the purposes of emergent management seizures are best classified as either *non-convulsive, focal* or *generalised convulsive* and further characterised by duration and response to therapy, where *status epilepticus* is seizure activity lasting longer than 5 minutes; *refractory status epilepticus* is seizure activity persisting despite treatment with a benzodiazepine and a second line anti-epileptic; and *super-refractory status epilepticus* is seizure activity that persists or recurs 24hrs after the initiation of general anesthesia.

This document primarily addresses the management of convulsive status epilepticus. There is considerable controversy about whether to treat non-convulsive status epilepticus (NCSE) as aggressively as convulsive status epilepticus. We recommend diagnosing and treating NCSE as quickly as possible and in accordance with this document but with minimal sedation so as to avoid prolonging coma and intubation since these risks are likely higher than the risk of neuronal damage from NCSE itself.

In order to provide a practical reference for the physician caring for these patients during their course from admission to discharge from the intensive care unit, management is divided into two phases. The first is initial (often ward based) management and the second is intensive care management. Pharmacotherapy is described using a staged approach, where each stage represents not only an increase in the burden of therapy but also an increase in the incidence of morbidity and mortality.

The management of focal seizures without a change in level of consciousness is beyond the scope of this document, and the neurology service should be consulted for management advice.

4. Inclusion Criteria

All patients admitted to the DCCM with status epilepticus.

5. Exclusion Criteria

Patients may not receive this treatment if:

- The duty intensivist (usually in consensus with the neurology consultant) determines a clinical or other indication for deviation from this document.
- The patient has been admitted as a potential organ donor or for palliative care.

6. Process of Treatment

Initial Management

Most seizures stop spontaneously within two minutes and rapid administration of a benzodiazepine is not required. However, seizure activity lasting longer than five minutes or recurrent seizures without return to a normal neurological baseline should be assessed and treated emergently.

Assessment and Management (see also Algorithm 1)

Assessment and management should take place concurrently and are usually performed by the DCCM registrar alongside the ED or MET team.

A. **Attend to airway breathing and circulation**.
B. **Initiate monitoring** of blood pressure, temperature, pulse oximetry and ECG.
C. **Perform a rapid focused neurological examination**.

- Ascertain the GCS (motor score most important), pupillary size and reactivity, evidence of gaze deviation and any overt focal neurological deficit.
- Pupillary dilation and gaze deviation (usually contralateral to the side of the epileptogenic focus) are common features of seizures and generally resolve with effective therapy.

D. **Attain a finger-prick blood glucose** – Administer 50mls of 50% glucose if low (this can be administered by a peripheral line in an emergency). Consider co-administration of 100mg of IV thiamine in malnourished patients or those with a history of heavy alcohol use.
E. **Attain IV access and send blood** for: FBC, coagulation studies, electrolytes (including calcium, magnesium and phosphate), liver function tests and anti-epileptic drug levels if appropriate.
F. **Attain a serum B-HCG –** Consider eclampsia and TTP.
G. **Attain an ABG** - lactate will generally be elevated.
H. **Attain neuro-imaging** – usually CT brain (with contrast if intra-parenchymal mass lesion is suspected).

I. **Consider lumbar puncture** or empiric treatment for meningitis or infectious encephalitis if clinically appropriate (caution if suspected increased intracranial pressure)
J. **Consider toxidromes** – seizures should be treated as per this document but consideration will need to be given to enhanced elimination, decontamination, specific antidotes and the omission of Phenytoin from the treatment regime.
e.g. Tricyclic's (Sodium bicarbonate), Isoniazid (5g IV pyridoxine) and Theophylline (dialysis).
K. **Send urinary toxicology screen**. (the mainstay for the treatment of this is benzodiazepines)

Stage 1 Pharmacotherapy

Benzodiazepines are the first line therapy for convulsive status epilepticus because they control seizures rapidly. They should generally be combined with a non-benzodiazepine anti-seizure medication (which should be administered concurrently) to prevent seizure recurrence. Lorazepam is the preferred IV agent, Midazolam is the preferred IM agent and Diazepam is preferred for rectal administration but any benzodiazepine, provided it is administered in appropriate doses, may be used.

A. **Administer one of:**

Consider requirement for intubation and ventilation

Lorazepam IV – 4mg (or 0.1mg/Kg) IV followed by repeated doses of 4mg IV every 5mins if still seizing.
Or
Midazolam IV - 5mg (or 0.1mg/Kg) IV followed by repeated doses of 5mg IV every 5mins if still seizing.
Or
Diazepam IV – 10mg (or 0.15mg/Kg) IV followed by repeated doses of 5mg IV every 5mins if still seizing.

(Rarely – Midazolam 10mg IM or Diazepam 10mg PR)

There is no definite maximum dose of benzodiazepines but therapy should cease ***when seizures cease, side effects limit further administration or a decision is made*** *to progress to stage 2 pharmacotherapy.*

Plus one of:

Levetiracetam IV – 30 to 60mg/kg up to 4500mg infused over 15mins
Or
Sodium Valproate IV – 30mg/kg injected slowly over 3-5 minutes .
Or
Phenytoin IV – 20mg/kg (with additional 5 to10mg/kg if required) at no more than 50mg/min. Requires continuous cardiac monitoring and regular blood pressure monitoring for duration of infusion.

There is limited evidence to suggest superiority of any one non-benzodiazepine anti-epileptic over another. Sodium Valproate and Leviteracetam offer the advantage of rapid IV administration and a more desirable short-term side effect profile when compared to Phenytoin, and for this reason are preferred agents in the ward setting.

Patients who respond to stage 1 pharmacotherapy rarely require admission to the intensive care unit and this only occurs if the side effects of medications or concomitant pathology require ICU specific therapies.

Stage 2 Pharmacotherapy – Refractory Status Epilepticus

Status epilepticus that fails to respond to the administration of adequate doses of benzodiazepines and a first-line non-benzodiazepine anti-epileptic is termed refractory status epilepticus. Recent evidence, expert opinion and society guidelines support early progression to the induction of anaesthesia and intensive care treatment for these patients (if not already undertaken), in order to minimise irreversible neurological injury.

A. **Induce general anaesthesia.**

   Propofol or Ketamine are the induction agents of choice. Muscle relaxant for induction but avoid ongoing administration to aid clinical assessment of seizures

B. **Administer alternative second non-benzodiazepine anti-epileptic from the previous list.**

C. **±Transfer to the Intensive Care Unit.**

<u>Ongoing management in the Intensive Care Unit</u>
The general principles for intensive care management are to terminate seizures, achieve therapeutic levels of at least 2 non-benzodiazepine anti-epileptic medications and identify and treat underlying causative pathology.
This will usually be undertaken in concert with the neurology service and all patients should be referred for assessment.

D. **Initiate standard physiological targets –** BOIC (brain orientated intensive care) is not indicated.
E. **Propofol infusion at 2-4mg/kg/hr and opiate for tube tolerance.**
F. **Attain an EEG** and consider continuous EEG monitoring or repeat EEGs.
G. **Attain therapeutic levels of at least two non-benzodiazepine anti-epileptic agents** – consult neurology for assistance with selection of the appropriate agent.
H. **Titrate intravenous Propofol infusion rate to a maximum of 5 to 10mg/kg/hr –** initiate monitoring for PRIS (propofol infusion syndrome) (daily CK, ECG and lipids) and limit duration to <48hours.
   or
   Initiate intravenous Midazolam infusion at 0.1 to 2mg/kg/hour.

or

Administer Phenobarbitone intravenous 15 mg/kg (maximum 1g) at a rate not exceeding 60 mg/minor
Thiopentone 1-3 mg/kg (up to 5 mg/kg in haemodynamically stable patients) and consider infusion of 1-5mg/kg/hr (maximum dose of 100 mg/kg/day) (1).

Therapy should be targeted to either burst-suppression (with inter-burst intervals of 2 to 30secs) or the termination of seizures on EEG. If EEG unavailable out of hours then aim for clinical seizure control

Therapy should be continued for 12 to 24hours from the point of seizure cessation or burst-suppression on EEG and therapeutic levels of non-benzodiazepine anti-epileptics attained. At this point de-escalation in therapy should be initiated while monitoring for seizure re-crudescence.

Stage 3 Pharmacotherapy – Super Refractory Status Epilepticus
Seizure activity that persists or recurs 24hrs after the initiation of general anesthesia is termed super-refractory status epilepticus. There are no established effective therapeutic modalities. It is associated with very high rates of morbidity and mortality.
Options that may be considered for treatment are(1)(2):

1) **Further barbiturate loading, increased infusion rate or second agent.**
2) **Ketamine infusion** – 2mg/kg loading dose followed by 1 to 5mg/kg/hr infusion.
3) **Ketogenic diet –** 3 to 4 grams of fat to each gram of carbohydrate. Serum BHB (beta hydroxybutyrate) levels can be monitored to determine ketosis(3). A protocol and practical advice can be attained in the referenced article. Administered in conjunction with dietetics service

Other therapies used rarely and in consultation with the neurology service:

4) **Intravenous magnesium infusion -** titrated to attain serum levels of 3.5mmol/L.
5) **Intravenous Lidocaine infusion.**
6) **Electroconvulsive therapy.**
7) ? Cannabis oil ?Lacosamide ?Topiramate

Appendix One :Assessment of Patients Admitted to the Intensive care unit

Most cases of status epilepticus in adults are the result of a structural brain abnormality or toxic metabolic disturbance.
The neurology service should be consulted for assistance with diagnostic workup.
Investigations should always be tailored to the clinical scenario. A suggested approach follows.

All Patients:

1) **Medical, social and medication history**.
   Withdrawal seizures may occur with cessation of alcohol or benzodiazepines.
   A number of medications may lower the seizure threshold.
   Posterior reversible encephalopathy syndrome (PRES) is an increasingly recognized cause of seizures, this can be precipitated by medications and is often associated with severe systemic hypertension.
2) **Blood glucose and electrolytes** including liver function tests, calcium, magnesium, phosphate and urea.
3) **Full blood count and coagulation studies –** consider TTP and confirm safe for lumbar puncture (Platelets >40, INR <1.5 and APTT <40s).
4) **Neuroimaging** – CT and/or MRI depending on clinical scenario.
5) **Lumbar puncture** – Volume of CSF depends on assay required – see lab link.
   Bacterial and viral PCR panel if the WCC:RBC is elevated.
   Cryptococcus antigen if immunosuppressed or HIV positive.
   TB PCR and culture if lymphocytic predominant, sub-acute presentation, immunosuppressed or clinical concern.
   Flow cytometry if CNS lymphoma considered.
   Cytology if leptomenigeal malignancy considered.
   Auto-immune encephalitis panel requires neurologist endorsement (see later).
   Consider empiric anti-microbial and anti-viral therapy as per ADHB protocol or Dexamethasone 10mg IV Q6H, Ceftriaxone 2g IV Q12H, Benzyl Penicillin 2.4g IV Q4H, Vancomycin as per vanculator and Aciclovir 10mg/kg IV Q8H.
6) **Urine toxicology screen**.
7) **Serum B-HCG.**
8) **Thyroid function tests.**

Selected Patients:

1) **Syphilis and HIV serology**.
2) **Anti-Thyroid Peroxidase and anti-Thyroglobulin antibody**.
3) **CSF cytology and flow cytometry** – leptomeningial metastases or lymphoma.
4) **ANA/ENA and ANCA –** CNS vasculitis.
5) **Brain biopsy.**
6) **Urine porphobilinogen -** Acute intermittent Porphyria.

In the absence of a diagnosis following the preceding investigations consideration is often given to an autoimmune encephalitis with antibodies to extracellular antigens, cell surface or synaptic proteins.

Clinical features common to these syndromes are a history of a viral prodrome, neuro-psychiatric symptoms, autonomic dysfunction and facial dyskinesias (the Antibody Prevalence in Epilepsy Score may help to identify these patients).
Investigation includes:

1) **Standard CSF analysis** – high protein common.
2) **MRI brain** – commonly shows changes consistent with limbic encephalitis (medial temporal lobe hyper-intensity on T2/FLAIR).
3) **CSF and serum "Autoimmune encephalitis panel"** – requires neurologist endorsement.
4) **CT scan of chest abdomen and pelvis** – May be associated with underlying malignancy. This may be undertaken prior to return of the auto-immune panel.

In the absence of identifiable underlying pathology despite investigation a diagnosis of new-onset refractory status epilepticus (NORSE) may be provided.
Under these circumstances or when autoimmune encephalitis is suspected empiric immunosuppressive therapy may be initiated. It is essential to exclude active infection and to attain hepatitis B serology prior to initiation.

1. References

1. Hocker S, Tatum WO, LaRoche S, Freeman WD. Refractory and Super-Refractory Status Epilepticus—an Update. Curr Neurol Neurosci Rep. 2014 Jun;14(6):452.

2. Lionel K. Seizures - just the tip of the iceberg: Critical care management of super-refractory status epilepticus. Indian J Crit Care Med. 2016 Oct;20(10):587–92.

3. Thakur KT, Probasco JC, Hocker SE, Roehl K, Henry B, Kossoff EH, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology. 2014 Feb 25;82(8):665–70.

2. Disclaimer

No document can cover all variations required for specific circumstances. It is the responsibility of the health-care practitioners using this ADHB document to adapt it for safe use within their own institution, recognise the need for specialist help and call for it without delay, when an individual patient falls outside of the boundaries of this document.