Management of Convulsive Status Epilepticus in Adults: A Brief Overview

Lawrence Tucker MBChB FCP(SA) PhD
Division of Neurology
Groote Schuur Hospital
University of Cape Town

Convulsive Status Epilepticus:
Requires Emergency Intervention

Status epilepticus is associated with multiple complications, including death.

- **Neurological Emergency**
- **Medical Emergency**

Overall mortality has been estimated at 9.4%, of whom 93% have persisting seizure activity 60 minutes after initiating treatment.
(SENSE Registry 2019)

Intervene early and aggressively

Therapeutic delay and under-treatment are recognised as significant factors influencing both morbidity & mortality

Ann Neurol. 2019;85:421-43

Status Epilepticus:
Neuro-molecular Changes

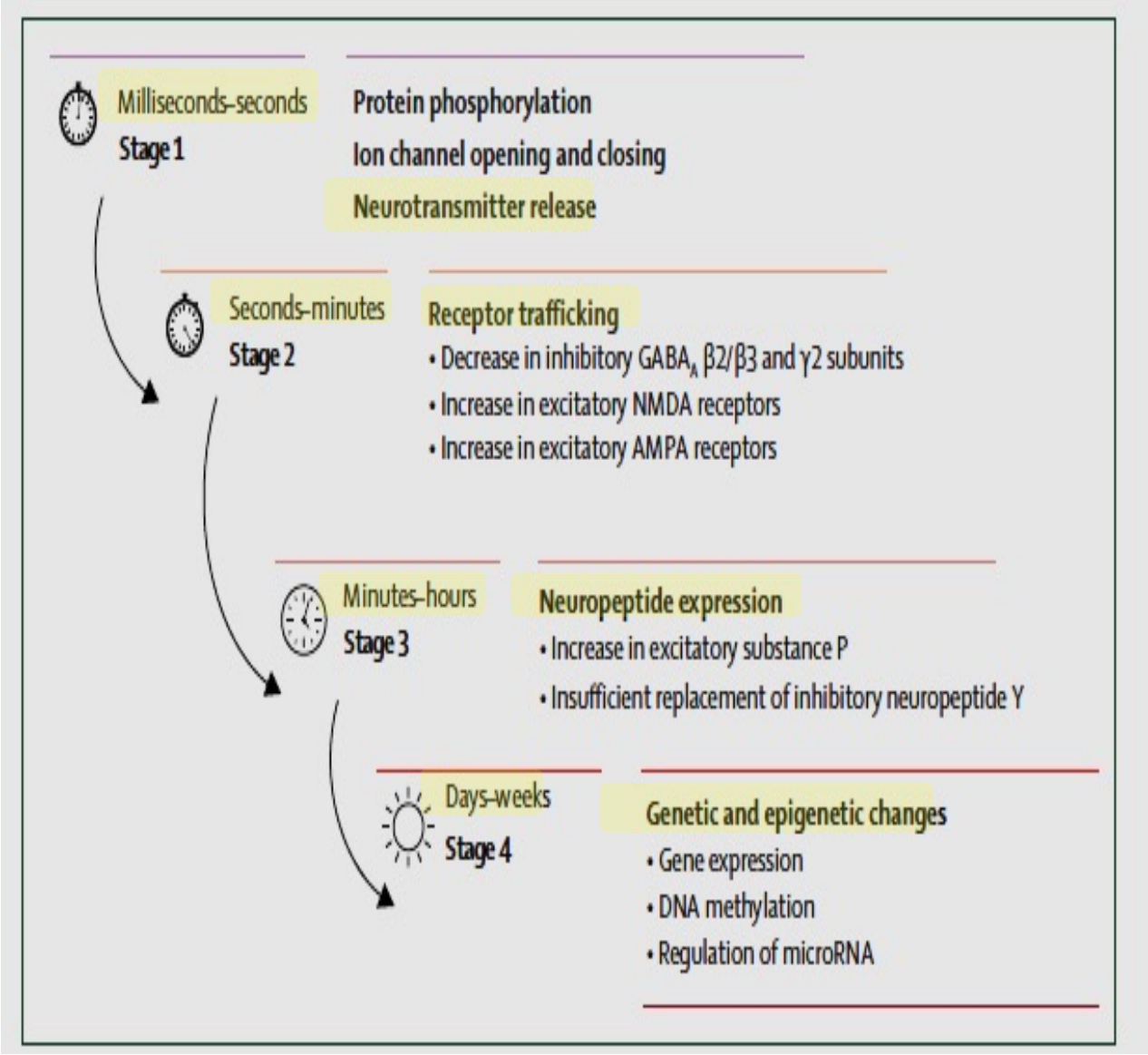
Prolonged status results in failure of endogenous mechanisms which normally terminate seizure activity.

These involve both:

- **Loss of endogenous inhibitory mechanisms**
- **Excessive, abnormal neuronal excitation**

These processes, in turn, mean that many ***anti-seizure medications become less effective as the duration of the seizure persists***

Status Epilepticus:
Some Neuro-molecular Mechanisms



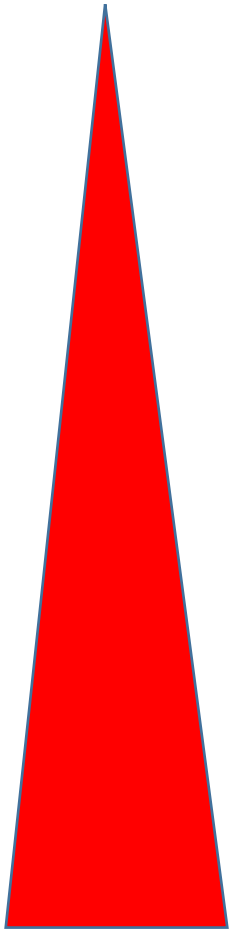
Hyper-excitability

Pharmaco-resistance

Neuronal Injury

Poor prognosis

Mortality



Lancet Neurology 2007; 6:329-39

Consequences of Persisting SE

In short, with persisting status, there is a progressive increase in:

- **Excitotoxic neuronal injury**
- **Pharmaco-resistance**

These negatively affect functional outcome and increase mortality

Ann Neurol. 2019. 85:421-432

Status Epilepticus:
Systemic Consequences

In addition to these molecular mechanisms, there are more overt pathological processes associated with prolonged SE which may have to deal with which include:

- **Hypoxia**
- **Acidosis**
- **Haemodynamic instability**
- **Hyper -> hypoglycaemia**
- **Rhabdomyolysis and hyperkalaemia**

Status Epilepticus:
Definitions

The definition of Status epilepticus remains constantly under review with an eye to improving its clinical usefulness

Status Epilepticus

Operational Definition:

SE is now defined as ***5 minutes*** or more of:

- ***Continuous clinical and/or electrographic seizure activity***

or

- ***Recurrent seizure activity without recovery between seizures***.

ILAE: Epilepsia 2015. 56(10):1515-1523
Neuro Critical Care Society (2012);
American Epilepsy Society (2016)

Status Epilepticus Guidelines

Most Neurologists and Neuro-intensivists use Guidelines drawn up by:

American Epilepsy Society

Neuro-critical Care Society

National Institute for Health & Care Excellence (NICE)

These guidelines are similar and advise:

- **Stabilisation** of the patient, and then
- A **stepwise approach to the administration of AEDs**

Epilepsy Curr 2016;16(1):48–61.
Neurocrit Care 2012;17(1):3–23.
NICE Guideline CG 137

After Stabilisation:
A Staged Approach to AEDs

First-line therapy :

Typically **Benzodiazepine** administration:

midazolam/lorazepam/diazepam/clonazepam

Second-line therapy: **(Benzodiazepine-resistant SE)**

Typically **Anti-Seizure Drug** loading:

phenytoin/fospenatoin/valproate/levetiracetam/phenobarbital

Third-line Therapy: **(Refractory SE)**

RSI and **General anaesthesia**:

Propofol, midazolam, ketamine

Forth-line Therapy: **(Super-refractory SE)**

Typically **unproven interventions**

Hypothermia, vagal nerve stimulation, repetitive transcranial magnetic stim, ketogenic diet, etc.

Definitions:
Refractory and Super-refractory SE

Refractory SE is defined as continuous seizure activity not controlled by 1st and 2nd line anti-seizure drugs (Benzo's & AED).

Super-refractory SE is defined as status epilepticus not controlled by third-line agents (i.e. anaesthetic).

Of all patients with status epilepticus:

- 12% to 43% progress to refractory SE, and
- 10% to 15% progress to super-refractory SE

Lancet Neurol 2011;10(10):922–930.
J Clin Med 2016;5(5).
Epilepsy Behav 2015;49:131–134

Guidelines:
1st and 2nd line AEDs are evidence-based

There is now good evidence regarding the choice and dosage of:

1st line benzodiazepines

2nd line anti seizure drugs (AEDs)

But, evidence guiding 3rd line anaesthetic treatment remains scarce

We will discuss this in more detail later

SE Guidelines: Poor Adherence

Despite the progressive introduction of evidence-based SE guidelines, a recent study has shown that there has been no significant improvement in mortality or functional outcomes after SE over the past 30 years

JAMA. Neurol. 2019;76:897-905

Why?

- Poor adherence to these guidelines
- 1st and 2nd line drugs are administered too late, and in inadequate dosage

Ann Neurol 2019; 85:421–432

An Overview of Practical Status Epilepticus Management

Is this Status Epilepticus?

1. Is this Status Epilepticus or a seizure which will terminate spontaneously within 5 minutes

2. Is this Status Epilepticus or a mimic?

    - Functional Non-Epileptic Seizure
    - Dissociative seizure
    - Encephalopathy
    - Metabolic derangements
    - etc.

EEG may be very helpful

Convulsive SE Management:
Stabilisation Phase

The diagnosis of convulsive status epilepticus is typically straightforward

Remember, time is brain

You need as many hands as you can get because assessment, investigations and management must occur in parallel

(ideally, 2 doctors and three nurses and any interns who may be standing around)

Convulsive SE Management:
Stabilisation Phase

ABC

- **Secure airway, decubitus position**.
- O_2 Sats monitor, **Face mask O_2** / nasal prongs
- Send an **urgent blood gas** with electrolytes
- **Two IV lines** with fluid running
- **Finger prick blood glucose (? Rx Thiamine & glucose)**
- **Blood pressure** (hyper/hypotension)
- **ECG**

Stabilisation Phase:
Focussed Examination

Always keep in mind potentially reversible systemic and intracranial provoking factors

- **Fever, rash, signs of head trauma**
- **Meningism**
- Hyper salivation
- Smell (alcohol/liver failure?)
- GCS
- Myosis / midriasis
- **Lateralising or localising neurological signs**

Stabilisation Phase:
Focused History

From witness / family member

Keep in mind any reversible provoking factors!

Known epilepsy?

Seizure onset and duration

Comorbidities (diabetes, liver/renal/cardiac)

Medications

Psychiatric history (depression, ? para-suicide)

Recreational drug use (? overdose)

Recent or distant **head injury**

Preceding febrile or other illnesses (meningitis/encephalitis?)

Prodromal psychiatric / behavioural changes (auto-immune?)

Stabilisation Phase:
Urgent Lab's

- Arterial blood gas
- Na K Ca Mg PO
- Acid-base & lactic acid
- FBC, CRP, ESR
- Renal & liver function (ammonia?)
- Toxicology screen
- AED drug level
- Cardiac Markers

(If you suspect bacterial meningitis: blood culture & start IV antibiotics – remember some are epileptogenic)

- **Etiologic Investigation**
  - Glucose
  - Antiepileptic drug levels
  - Acid-base disturbances
  - Arterial blood gas
  - Basic metabolic panel
  - Lactic acid
  - Acute organ failure
  - Creatinine
  - Blood urea nitrogen
  - Transaminases (aspartate and alanine aminotransferase)
  - Ammonia
  - Electrolyte imbalances
  - Calcium
  - Magnesium
  - Phosphorus
  - Intoxications
  - Alcohol level
  - Adulterant survey
- **Systemic Injury Screening**
  - Creatine kinase
  - Troponin

Continuum 2015;21(5):1362–1383

Convulsive SE Management:
Stabilisation Phase

Don’t forget chest auscultation and request a mobile chest radiograph

? aspiration pneumonia

Convulsive SE Management:
Stabilisation Phase

Contact ICU

Contact CT scanner

Lumbar puncture after CTB (contrasted if N renal function)

CSF: Chemistry
Microscopy
Herpes PCR
IgG index
(TB gene expert)
(auto-immune encephalitis abs)
(syphilis)
(etc.)

Multi-task!

Stabilisation of the patient and early termination of the SE are the first two priorities

Evaluation, stabilisation and management of SE must occur simultaneously.

Early treatment has been shown to be much more effective than late treatment

Use of a **treatment protocol** has been shown to result in better seizure control and shorter admission to ICU and ward

N Engl J Med 1998;339(12): 792-798.

Epilepsia 2010;51(10):2159-2167

First Line Therapy (Adults)

Medical News Today

First Line Therapy:
The Evidence

Treatment	Class, Level of Evidence[b]
First-line therapy	
Lorazepam	Class I, Level A
Midazolam	Class I, Level A
Diazepam	Class IIa, Level A
Phenytoin/fosphenytoin	Class IIb, Level A
Phenobarbital	Class IIb, Level A
Valproate sodium	Class IIb, Level A
Levetiracetam	Class IIb, Level C

First Line Therapy:
The Evidence

Veterans Affairs Status Epilepticus Cooperative Study Group Trial (1998)

In terminating Statue Epilepticus:

- **Benzodiazepines were more effective than phenytoin**
- **Lorazepam, diazepam or phenobarbital were equally effective**

N Engl J Med 1998;339(12):792-798

First Line Therapy:
The Evidence

RAMPART study (2012)

Efficacy pre-hospital administration of IM Lorazepam vs IV Lorazepam for terminating SE

IM midazolam (10mg for adults) **is as effective as IV lorazepam** (4mg for adults) **in terminating SE.**

N Engl J Med 2012;366(7):591-600

First Line Therapy:
The Evidence

What about Diazepam?

- A **meta-analysis of 5 RCTs** showed **no statistically significant differences between IV LZP and IV DZP for clinical seizure cessation, ventilator support or clinically relevant hypotension**

Epilepsy & Behav 2016;64 29-36

- A comprehensive **meta-analysis of 19 studies** identified **no difference in the efficacy of seizure cessation or adverse effects of non-intravenous MDZ vs. rectal or IV DZP in adults and children**

Epilepsy & Behavior, 2015; 49, 325-336

First Line Therapy:
So, Which Benzo?

My personal order of preference is:

- **Lorazepam IV 4mg** (repeat after 5 min x 1 if required)
- **Midazolam IV/IM 10 mg** (typically I do not repeat)
- **Diazepam 10mg IV** (repeat after 5 minutes if required)

Rule of thumb:

- ***Use the benzo' you know and have at hand***
- ***But give it early***
- ***Use the appropriate dose***

N Engl J Med 2001;345(9):631–7.
Engl J Med 2012;366 591–600
N Engl J Med 1998;339(12):792–8

First Line Therapy:
The Evidence

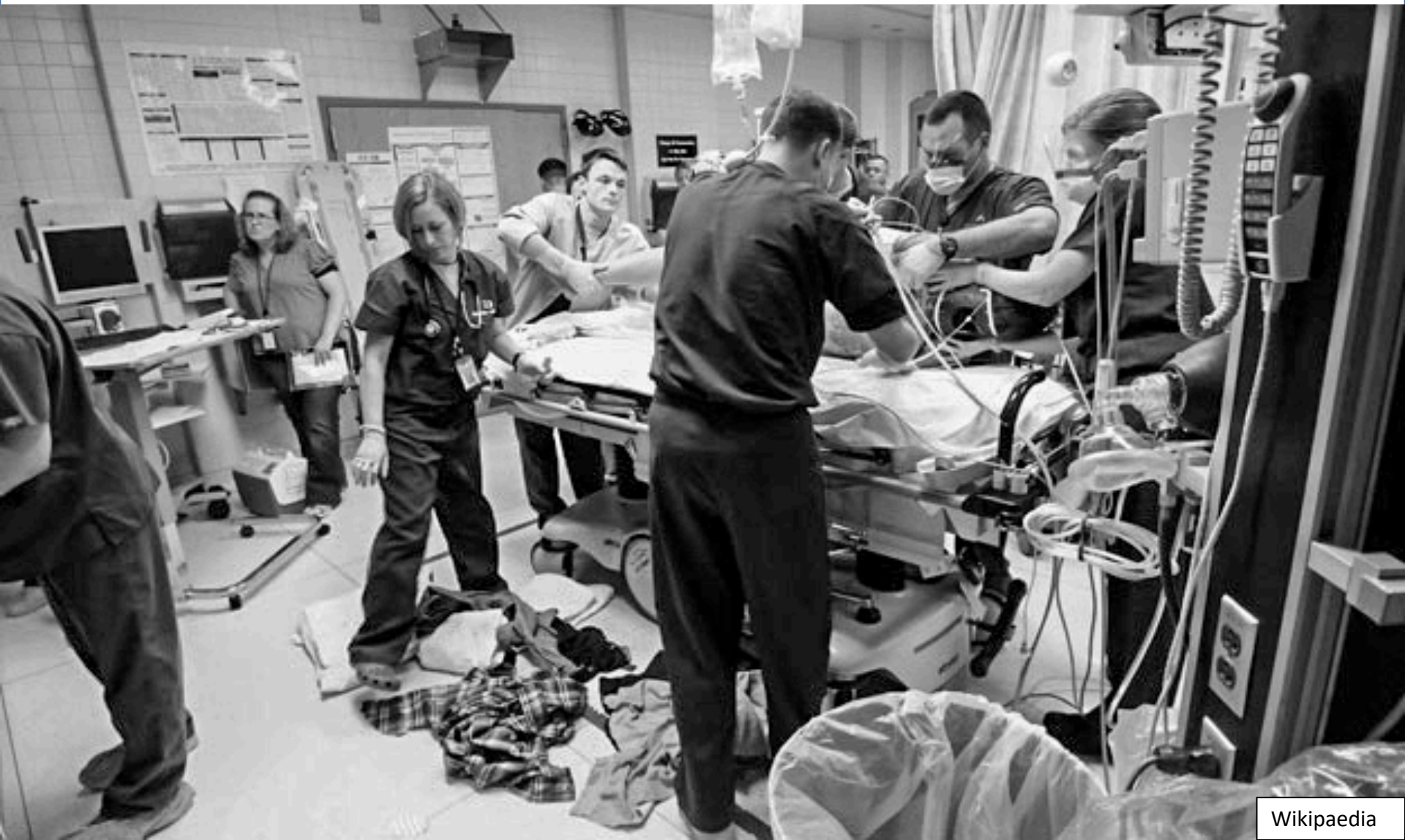
Keep in mind:

Up to **70% of patients in SE are under-dosed with a first-line benzo'.**

The risk of respiratory depression and hypotension with aggressive benzo' use is less than that from ongoing convulsive status epilepticus

N Engl J Med. 2019;381:2103-2113
N Engl J Med 2001;345(9):631–7.
Engl J Med 2012;366 591–600
N Engl J Med 1998;339(12):792–8

SE Management:
2nd Line Anti-Epileptic Drug (AED)



Wikipaedia

SE Management:
2nd Line AED

Typically:

All patients with convulsive SE should be loaded with a second-line AED immediately after the first-line benzodiazepine, whether or not status epilepticus has been aborted by benzodiazepines.

N Engl J Med 2001;345(9):631–7.
Engl J Med 2012;366 591–600
N Engl J Med 1998;339(12):792–8.

SE Management:
2nd Line AED

But which AED is best?

- Phenytoin / Phosphenytoin
- Valproate
- Levetiracetam
- Phenobarbital

Second Line Therapy:
The Evidence

2019 ESETT Trial (adults & children)

Levetiracetam, fosphenytoin and sodium valproate are equally effective in the management of benzo'-resistant SE

Termination of SE was only approximately 50% in all arms

- ? Under-dosing of 1st line benzo', and
- ? Delay in initiating 2nd line AED

N Engl J Med. 2019;381:2103-2113.

Second Line Therapy:
The Evidence

2019 ConSEPT Trial (children)

Levetiracetam and phenytoin were equally effective in inducing SE cessation in children

Lancet. 2019;393:2125-2134

Second Line Therapy:
The Evidence

2019 EcLiPSE Trial (children)

Successive use of phenytoin and levetiracetam was effective in terminating benzodiazepine-resistant SE and associated with extremely low morbidity and mortality.

Lancet. 2019;393:2135-2145

Second Line Therapy:
Phenobarbital?

Old drug with significant haemodynamic and respiratory depressive **side effects** and has fallen out of favour

Has **excellent seizure terminating properties**, at least equal to those of Phenytoin, valproate and Levetiracetam

Although it is seldom used in adults, there is a large body of evidence of its efficacy in Paediatric literature

Second Line Therapy:
Phenobarbital?

Phenobarbital vs. Phenytoin

Single-center randomized parallel clinical trial
144 episodes of SE in 111 children

Termination of benzodiazepine-resistant SE:

Phenobarbital (20mg/kg) :	**87%**	**(NNT = 2.5)**
Phenytoin arm (20mg/kg):	**46%**	

Respiratory depression was more common in the Phenytoin!

Burman *et al.* **Frontiers in Neurology 2019 10: article 106**

Second Line Therapy:
Phenytoin

Disadvantages:

- hypotension and cardiotoxicity
- Requires slow administration with cardiac monitoring

Best avoided in:

- TCA / cocaine overdose and toxidromes
- Liver failure
- Cardiac history
- Already therapeutic on Phenytoin
  - Unlikely to be effective
  - Risk of cardiac toxicity

Second Line Therapy:
Phosphenytoin

Phosphenytoin vs Phenytoin

- Water soluble
- Fewer cardiovascular side effects

  (Does not contain propenyl gluconate)
- Fewer drip-site reactions
- May be infused more quickly

Second Line Therapy:
Valproate

- May be infused more rapidly than phenytoin/phosphenytoin
- Better side effect profile
- Avoid in women of child bearing potential

Always exclude eclampsia as a cause for SE in women, which is best treated with magnesium sulphate!

Second Line Therapy:
Levetiracetam

ESETT, ConSEPT and EcLiPSE have all demonstrated that levetiracetam is a viable alternative to phenytoin

Advantages:

- Speed of administration
- Absence of adverse cardiovascular effects
- Low drug-drug interactions
- Simpler pharmacokinetics

In future, levetiracetam will probably supersede phenytoin as the default treatment in benzo'-resistant SE.

BRAIN 2021: 144; 1336–1341

Second Line Therapy:
Which AED at What Dose?

In short, all of the following agents are acceptable as 2nd-line AED in convulsive SE:

Levetiracetam	**40-60mg/kg**
Valproate	**20-40mg/kg**
Phenytoin / Phosphenytoin	**20mg/kg**
Phenobarbital	**15-20mg/kg**

Load early and do not under-dose!

Second Line Therapy:
Which AED?

The choice of 2nd-line AED depends on:

- Availability
- Familiarity with the drug
- Patient-related factors
- Side effect profile

Third Line Therapy:
Super-refractory SE: Intubation & Anaesthesia

https://www.irvinedentalcare.com/blog/intubation

Third Line Therapy:
Rapid Sequence Intubation (RSI) & Anaesthesia

When to intubate?

- Ongoing clinical or electrographic seizure activity after 1st and 2nd line AED loading

- Intubate earlier if:
  - Respiratory depression
  - Haemodynamic instability
  - Very ill patients

Third Line Therapy:
Intubation & Anaesthesia

Remember:

Risk of respiratory depression, cardiovascular collapse and brain injury is increased in patients with ongoing seizures

Some even suggest going straight to intubation and anaesthesia before loading with second-line AEDs
But this is a minority opinion

Third Line Therapy:
Intubation & Anaesthesia

Also keep in mind:

Just because a patient is not clinically convulsing after 1st and 2nd line treatment, this does not exclude ongoing subclinical ("subtle") status epilepticus

Identifying
Non-Convulsive / “Subtle Status Epilepticus

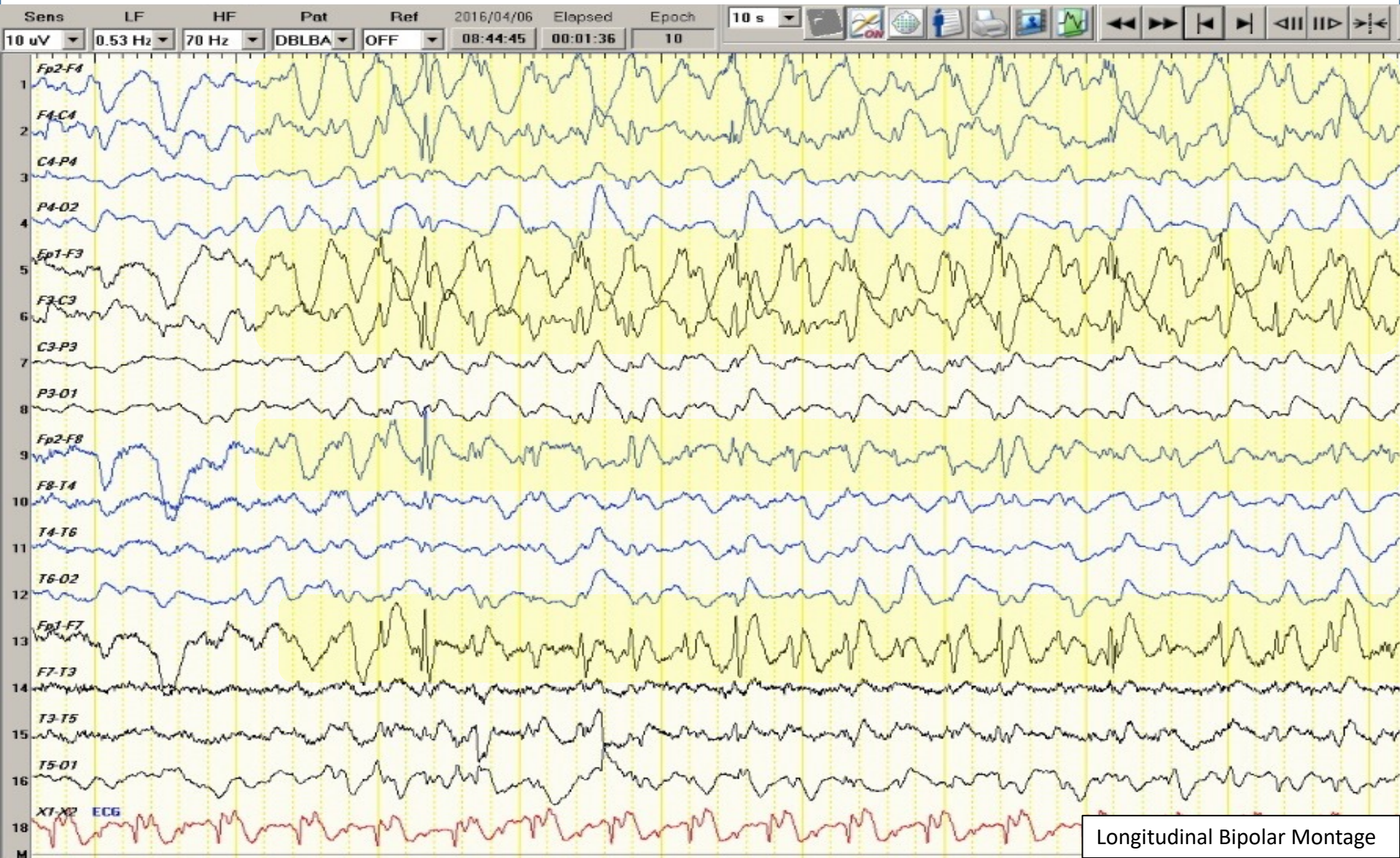
Suspect if the patent remains persistently unresponsive despite no overt clinical signs of seizure activity

Clinical

- Gaze deviation,
- nystagmus,
- subtle conic movements face/fingers,
- lip smacking,
- subtle hippus of a pupil

EEG is extremely helpful if available

EEG:
Subclinical Electrographic SE



Longitudinal Bipolar Montage

Routine vs. Continuous EEG for Subclinical SE

- A 30 minute **routine EEG** will identify approximately 25% of sub-clinical SE

- 24 hours of **continuous video-EEG** monitoring will identify 90% of subclinical SE

Third Line Therapy (Super-Refractory SE):
Rapid Sequence Intubation (RSI) & Anaesthesia

It is important to know a little about the paralytic and anaesthetic agents which the anaesthetist / intensivist may administer to your patient to your patient

RSI:
Paralysing Agents for Intubation

- **Succinylcholine** (depolarising)
  - Disadvantages:
    - **Hyperkalaemia** after prolonged seizures (rhabdomyolysis)
    - Avoid in renal failure, neuromuscular disorders
  - Advantages:
    - Rapid onset & **short duration (10 min)**

- **Rocuronium** (non-depolarising)
  - Disadvantages:
    - slow onset & **long duration (60-90 min)**
    - Clinical assessment not possible
    - Requires EEG confirmation of seizure control
  - Advantages:
    - Reversible using sugammadex (expensive)

Third Line Therapy (Super-Refractory SE): Anaesthesia

Which Anaesthetic Agent?

- **Midazolam**
- **Propofol**
- **Pentobarbital**
- **Ketamine**

All have pro's and cons

No good evidence for which is best

Midazolam and Propofol are the most widely used

Which Anaesthetic Agent: Induction & Post-Induction Sedation

- **Midazolam**
  - Safe and less vasoactive than Propofol
- **Propofol**
  - Hypotension in high doses
  - More likely to require vasopressor support
- **Ketamine** (Little evidence)
  - Seems to be good agent in hypotensive patients
  - ? Neuroprotective anti-NMDA activity?
- **Etomodate** (used for induction)
  - Associated with myoclonic jerks in up to 30%
  - ? Reduced seizure threshold

Third Line Therapy:
Anaesthesia

Bear in mind:

- **Almost all seizures should be suppressible on adequate doses of anaesthetic agents**

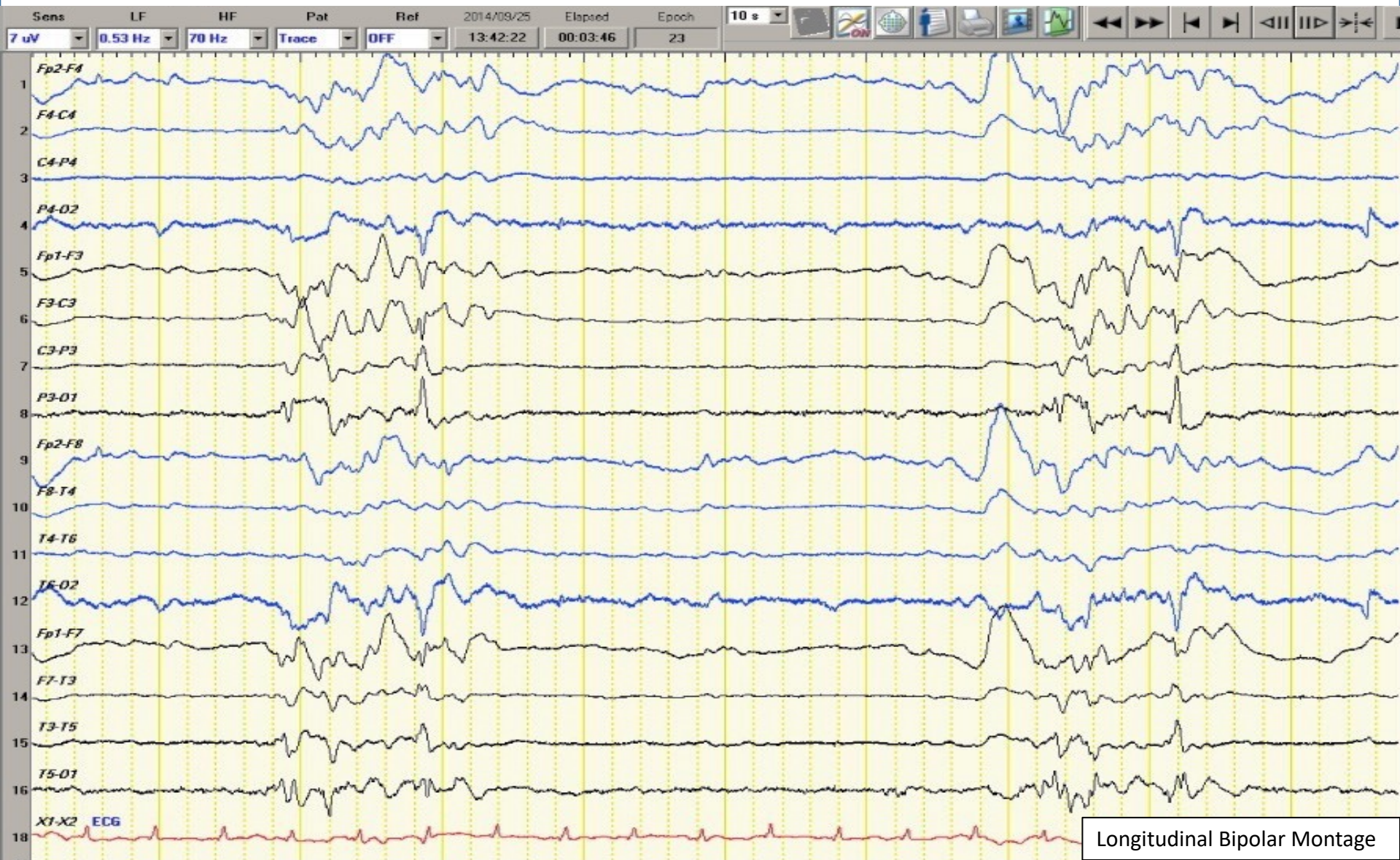
- Anaesthetic doses required for the management of status epilepticus are typically much higher than those used for sedation in most other conditions

Anaesthesia:
EEG Confirmation of Seizure Suppression

After anaesthesia has been initiated, and there is no longer clinical evidence of seizure activity, another EEG should be performed to confirm either:

- Cessation of electrographic seizure activity
- A burst-suppression pattern

EEG Confirmation of Seizure Suppression:
Burst-Suppression Pattern



Anaesthesia:
How Long and When to Wean?

General anaesthesia is typically continued for 24 - 48 hours before weaning

There little good evidence for this

Anaesthesia:
After Weaning

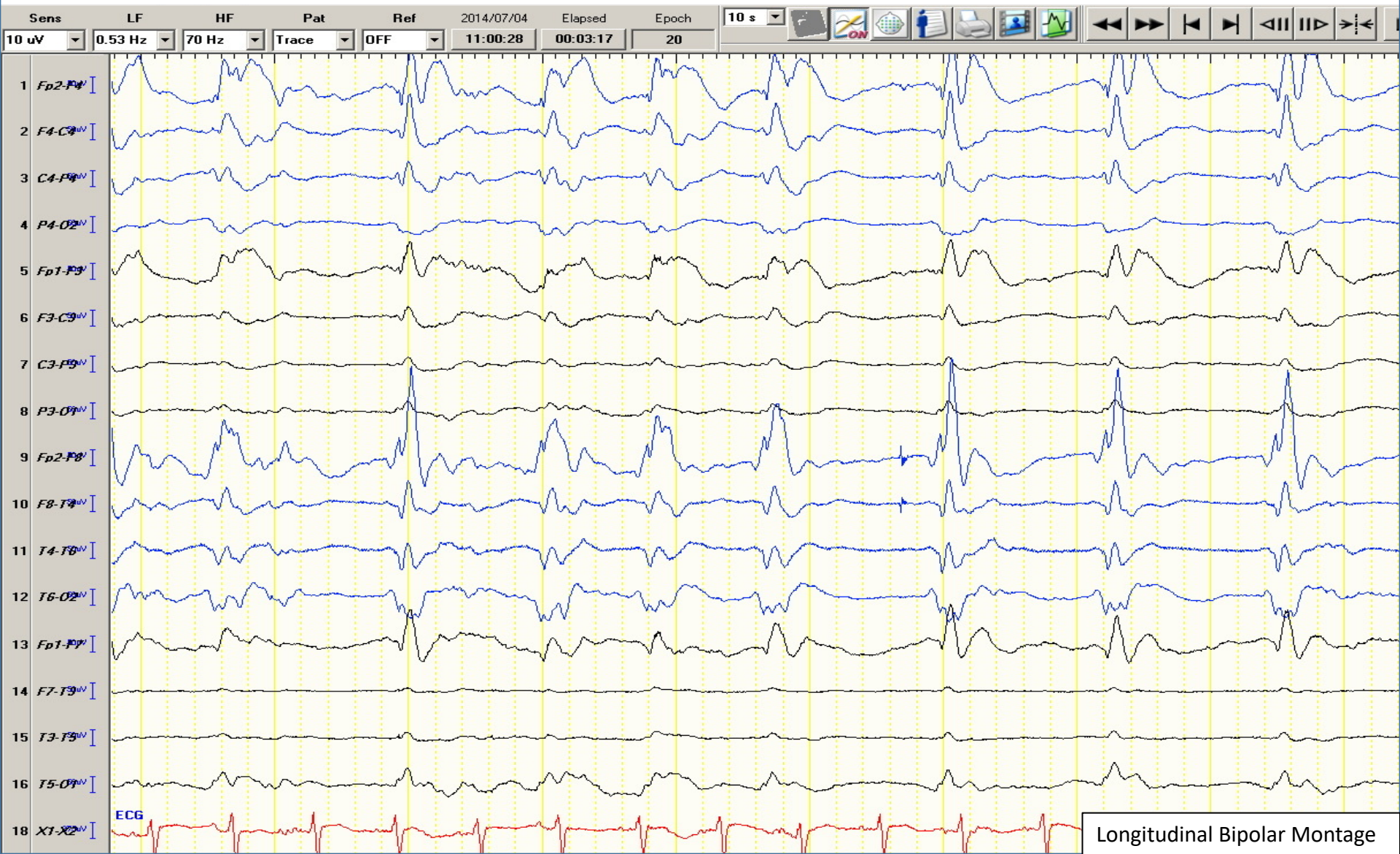
After weaning:

If clinical and/or electrographic seizure activity persists, the patient is typically re-anaesthetised for another 24 – 48 hours

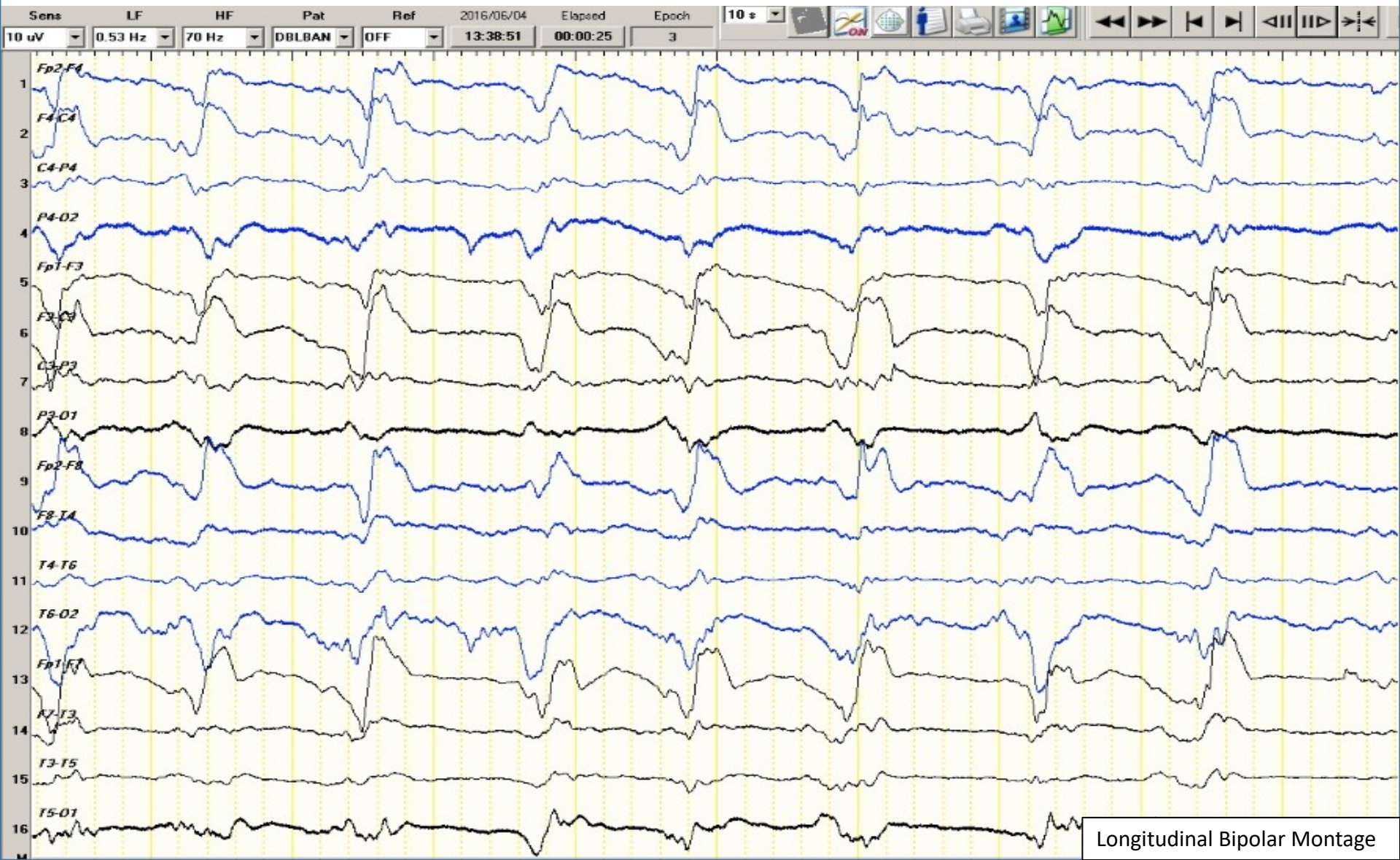
However, there is debate about what to do in the case of many abnormal EEG patterns which fall in the **ictal-interictal continuum…**

Does one continue to wean or re-anaesthetise?

Ictal-Interictal Continuum:
Lateralised Periodic Discharges

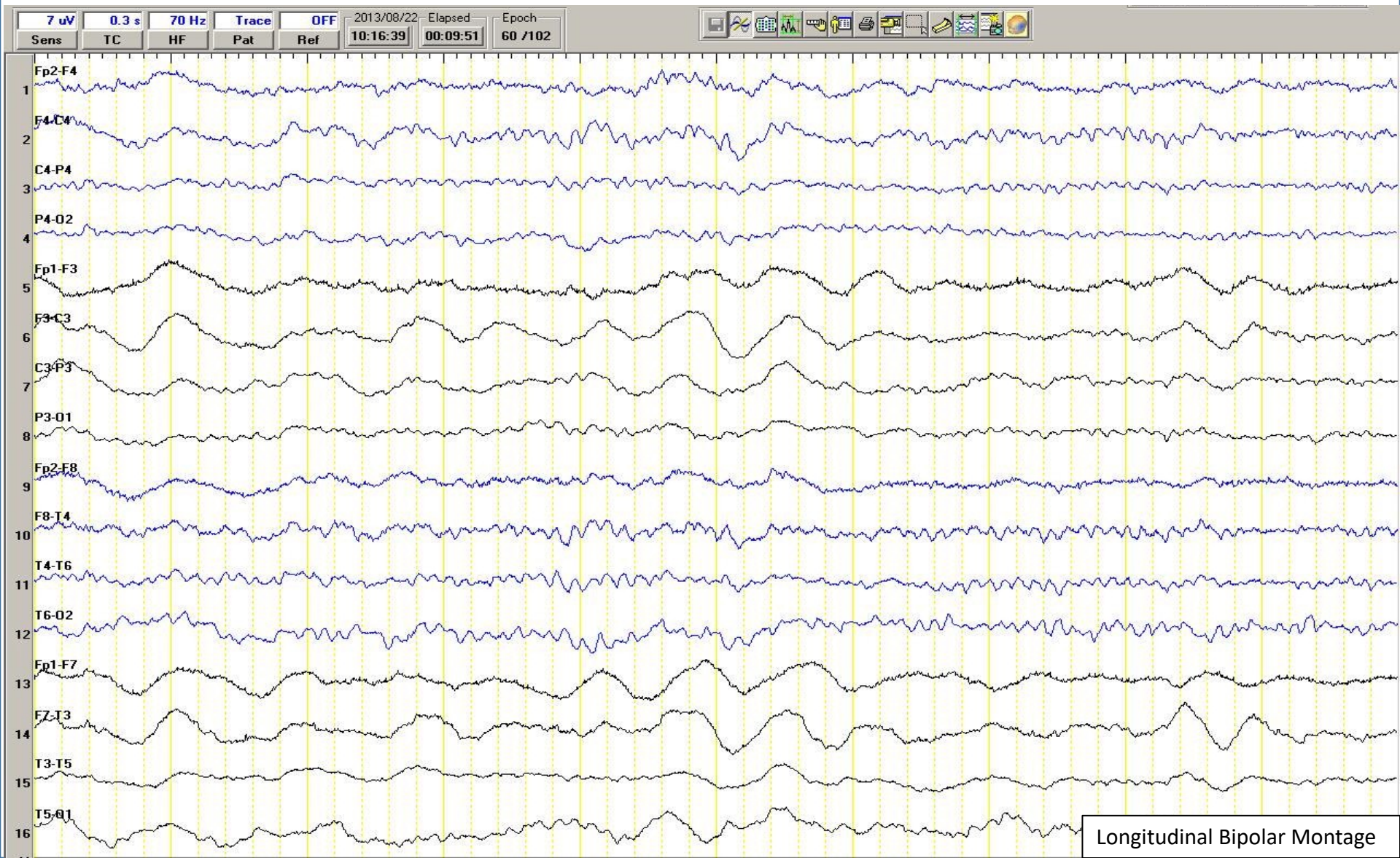


Ictal-Interictal Continuum:
Generalised Periodic Discharges



Longitudinal Bipolar Montage

Ictal-Interictal Continuum:
Lateralised Delta Slowing



Longitudinal Bipolar Montage

Status Epilepticus
The Role of Brain imaging

Siemens

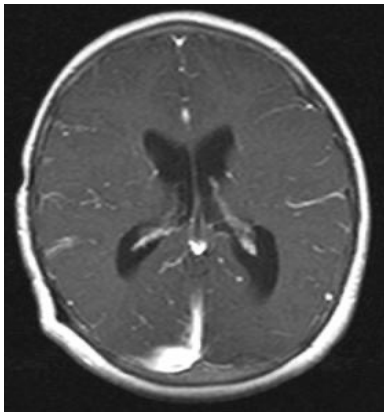
Brain Imaging
CT

Once seizures are controlled, virtually all stabilised patients will require brain imaging to exclude structural or inflammatory intracranial pathology.

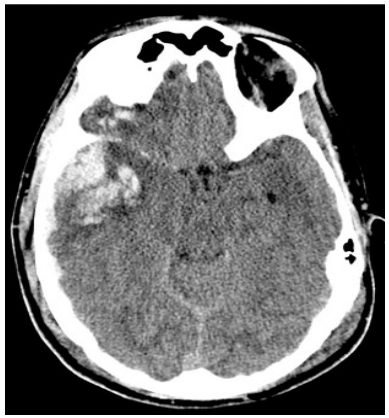
Contrasted CTB Scan (if normal renal function)

Brain Imaging
CT

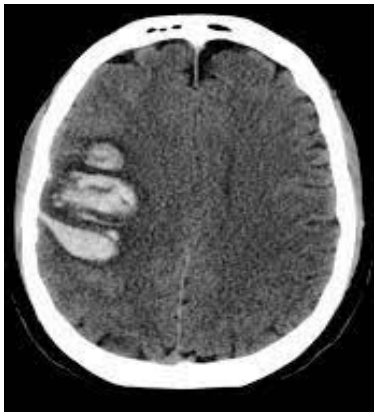
Source: Radiopedia



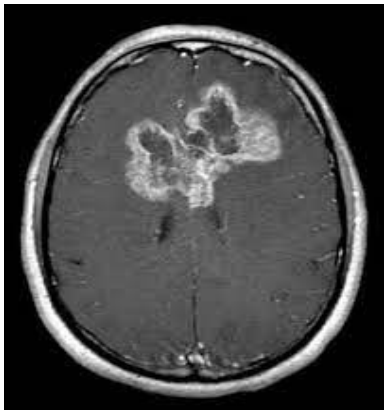
Meningitis



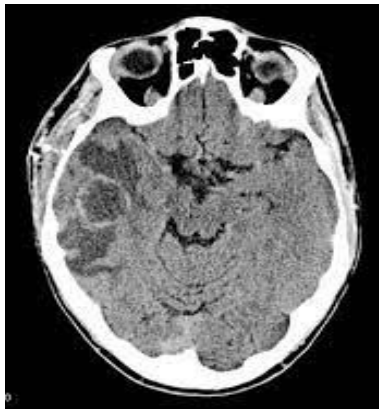
Traumatic Brain Injury



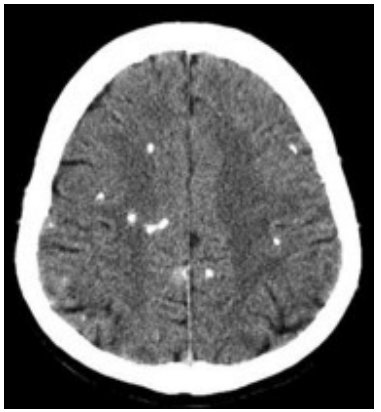
Intracerebral Haemorrhage



Metastasis



Glioma



Neurocisticercosis

Brain Imaging
CT

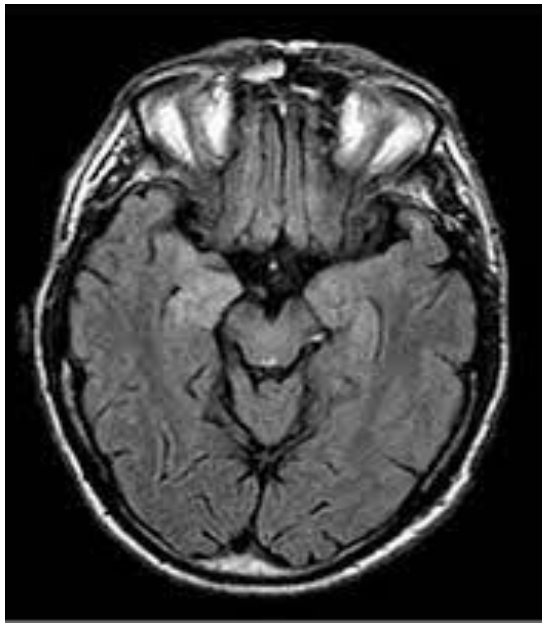
Keep in mind that changes related to prolonged SE may be seen on CT, and mistaken for other pathology:

These include

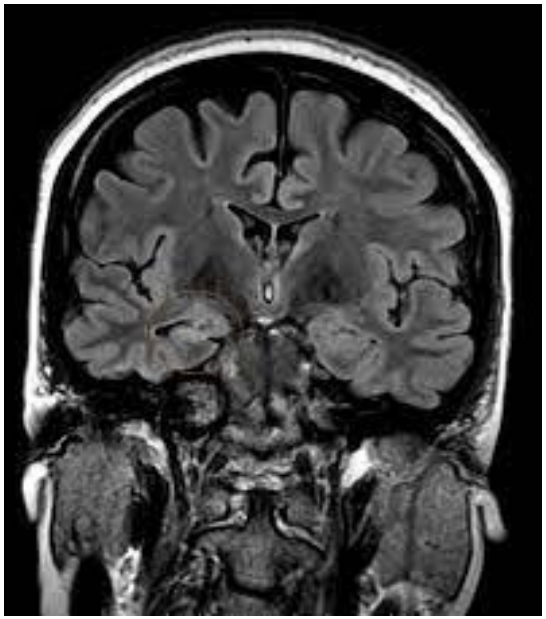
- Oedema
- Loss of grey–white matter differentiation
- Sulcal effacement
- Gyriform enhancement

Brain Imaging:
MRI

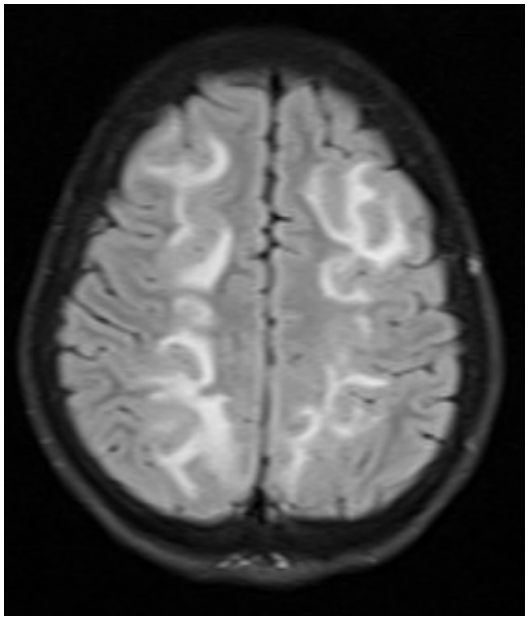
If CT is “normal”, MRI may be performed exclude more subtle structural intracranial abnormalities



Auto-immune (NMDA) Encephalitis

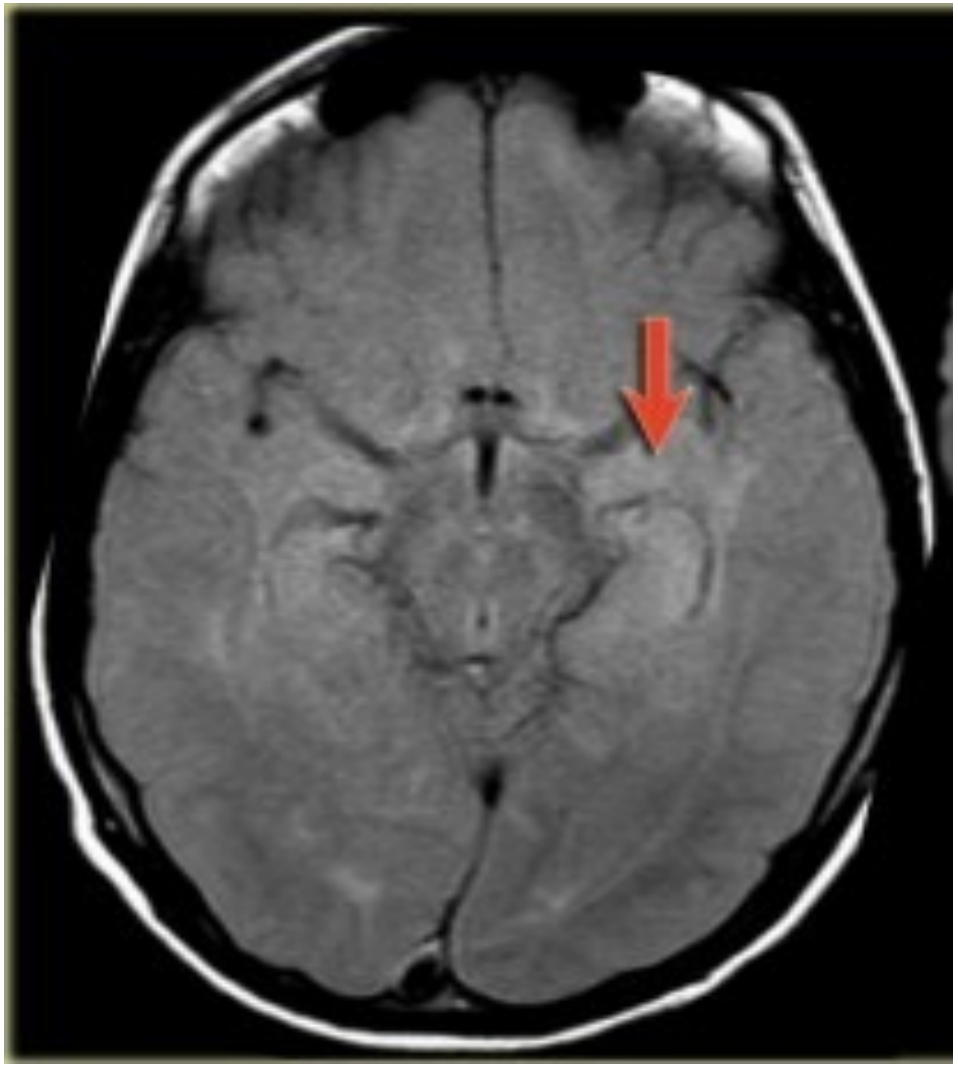


Mesial Temporal Sclerosis



MILAS

Source: Radiopedia



Status Epilepticus-related hippocampal changes (Flair sequence)

http://www.radiologyassistant.nl

Brain Imaging:
MRI

In prolonged SE, restricted diffusion sequences may closely resemble an ischaemic infarction

These changes are typically seen in the ***cortex*** and ***hippocampi***

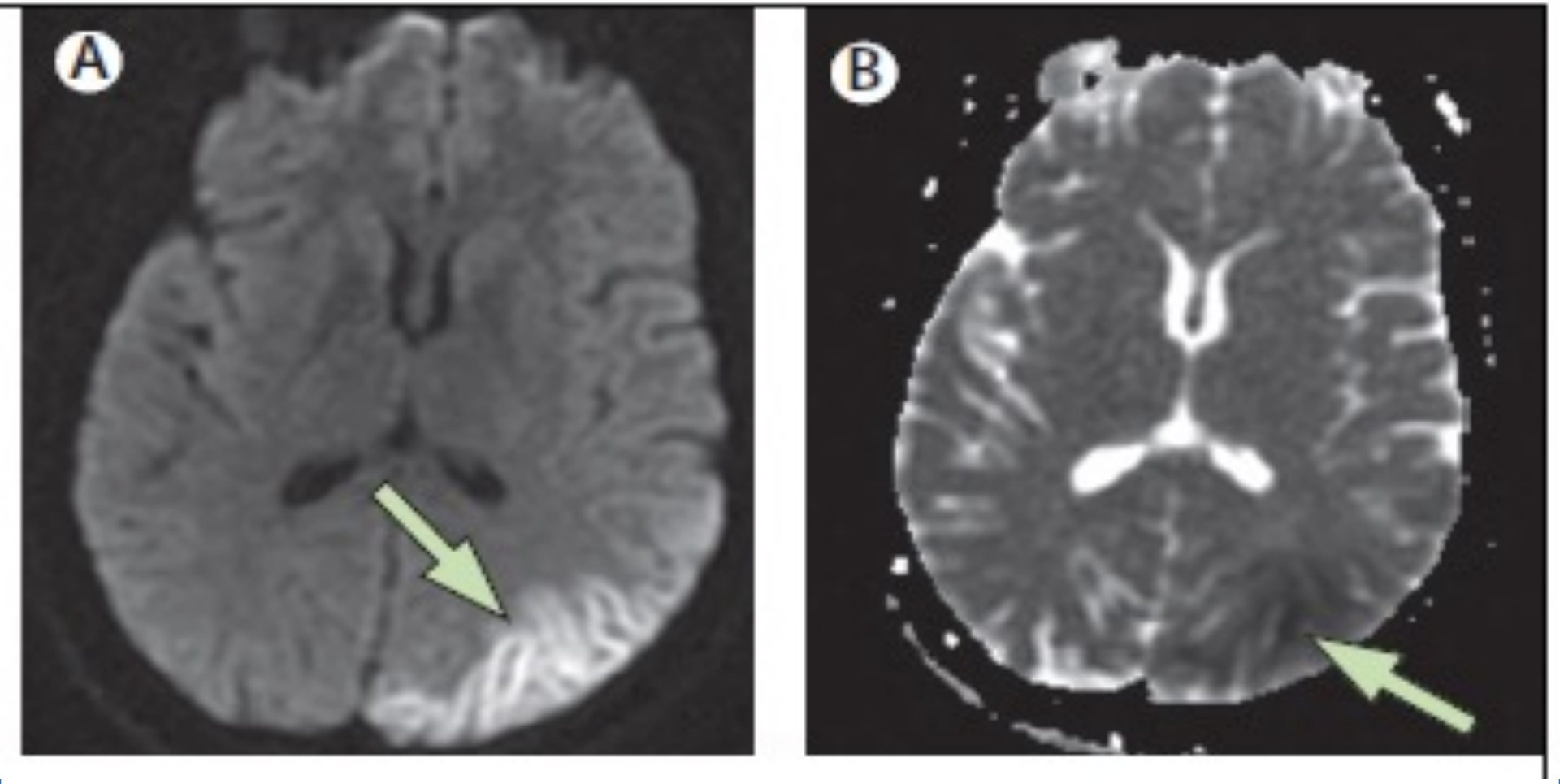
But other structures can also be affected:

- basal ganglia
- corpus callosum
- thalami

Neurology **1999; 52: 1021–27;** ***Epilepsy Behav*** **2014; 33: 24–30**

SE-related changes resembling cerebral infarction

MRI



Diffusion weighted imaging (A) and restricted diffusion (B)

Lancet Neurol 2015:14:615-24

Convulsive Status Epilepticus:
In Short…

- Convulsive status is a **neurological and medical emergency**
- Your first priorities are **stabilisation** of the patient and early **termination of the status**.
- As well as the identification of any underlying **provoking factors**

Convulsive Status Epilepticus:
In Short…

- **Therapeutic delay and under-treatment** are recognised as significant factors influencing both morbidity & mortality
- There is **good evidence regarding the choice and dosage of: 1st line benzodiazepines, and 2nd line AEDs** but little evidence guiding 3rd line anaesthetic management
- **Use a recognized treatment protocol**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Thank you