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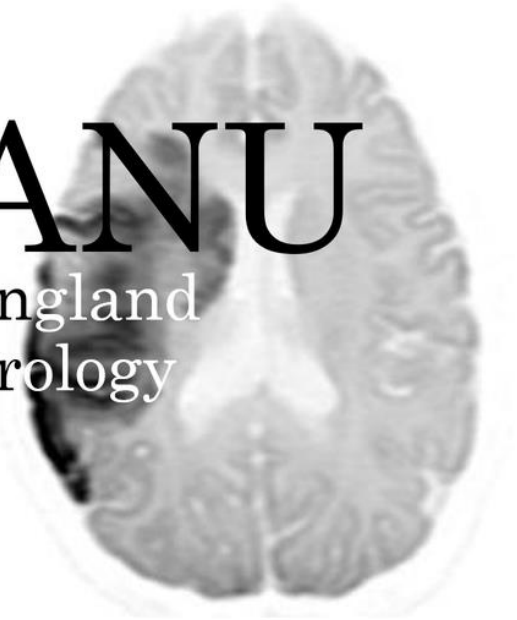
Update



Diagnosis and management of

Status epilepticus

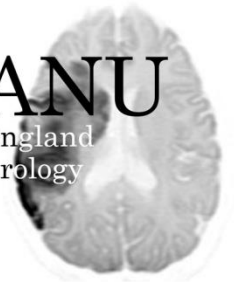
Rajiv Mohanraj

MANCHESTER 1824
The University of Manchester

Manchester Centre for Clinical Neurosciences

Salford Royal NHS
NHS Foundation Trust

What is status epilepticus?



"Status epilepticus occurs when a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition"
Gastaut 1970

"Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to >=5 min of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness"

Lowenstein et al 1999

"Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1). It …can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures"

ILAE Task Force on Status Epilepticus, 2015

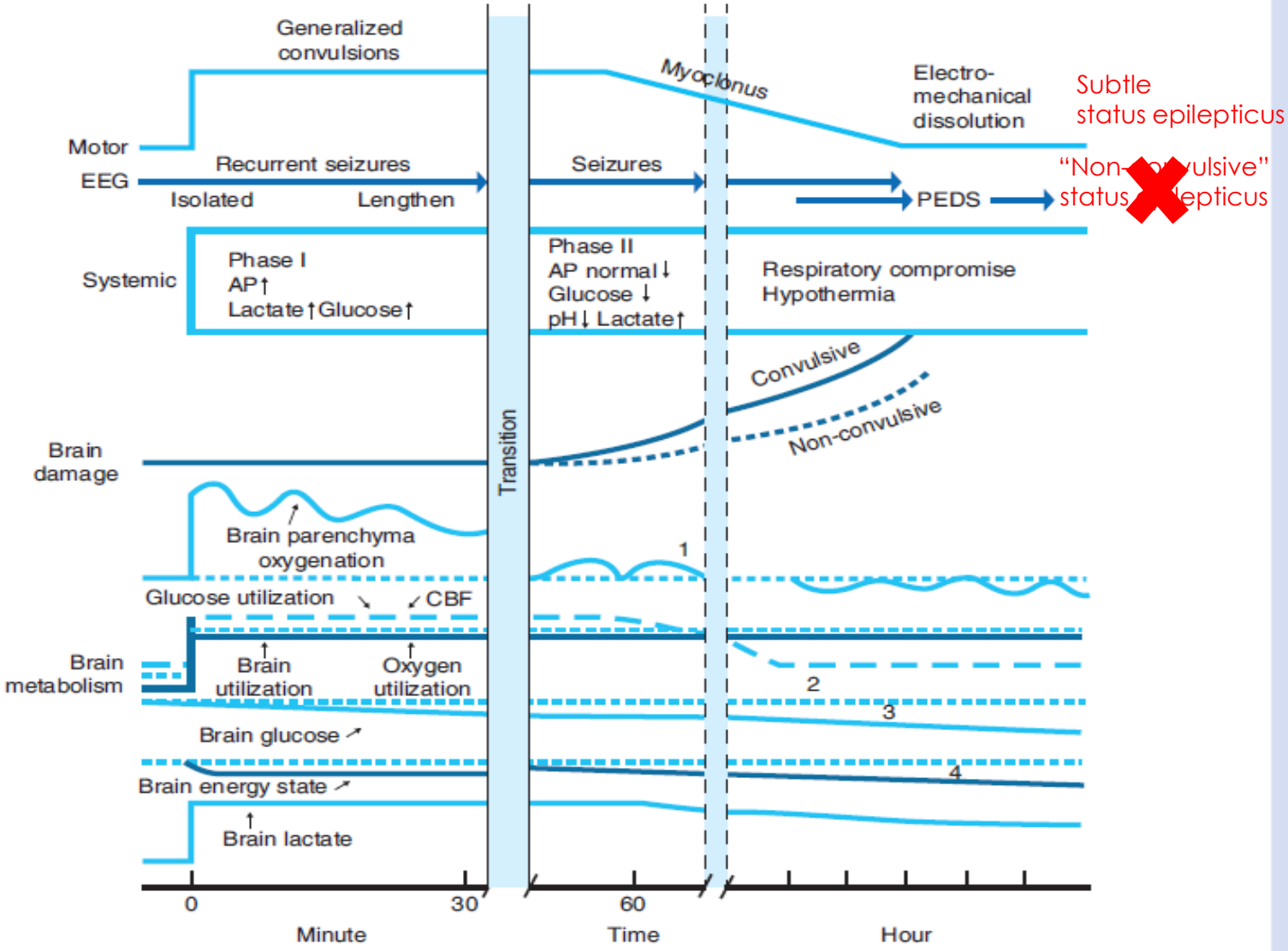


Fig 1 Physiological changes occurring during prolonged status epilepticus. Adapted from Shorvon.[106] PED, periodic epileptic discharge; CBF, cerebral blood flow. 1, Loss of reactivity of brain oxygen tension; 2, mismatch between the sustained increase in oxygen and glucose utilization and a decrease in cerebral blood flow; 3, a depletion of cerebral glucose and glycogen concentrations; 4, a decline in cerebral energy state.

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Status Epilepticus and Prolonged Seizures Guideline for Management in Adults

Lead Author:	Rajiv Mohanraj, Consultant Neurologist
Additional author(s)	Varduhi Cahill, Consultant Neurologist Matt Jones, Consultant Neurologist Katherine Harwood, Neurology Specialist Pharmacist
Division/ Department::	Neurosciences
Applies to: (Please delete)	Salford Royal Care Organisation
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Drug treatment of convulsive status epilepticus

- First line
  - IV lorazepam / diazepam
  - IM / buccal midazolam
- Second line
  - Valproate / levetiracetam
  - Phenytoin
- Third line
  - Propofol, Midazolam
  - Thiopentone

(not opioids – alfentanil, remifentanil)

Landmark RCTs of benzodiazepines in SE

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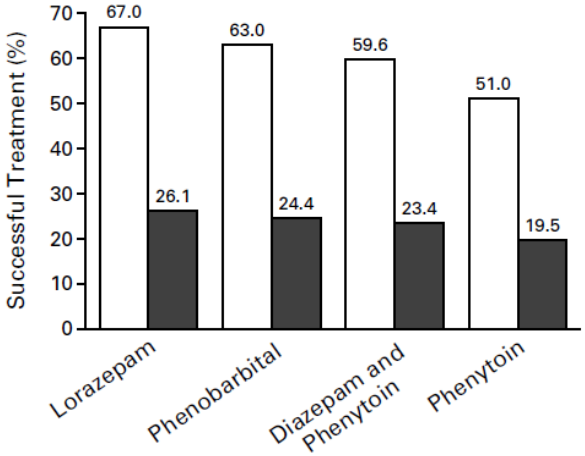
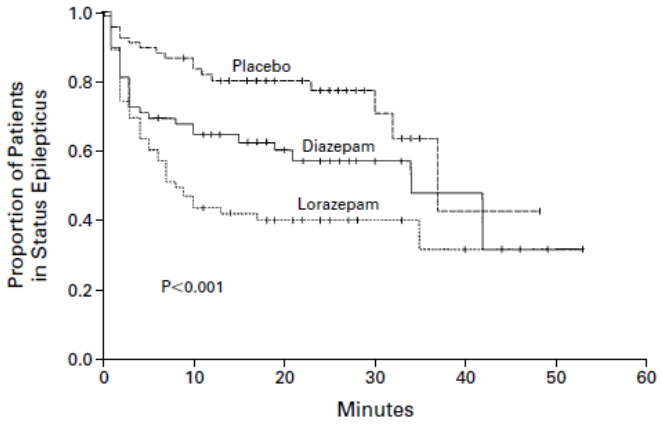


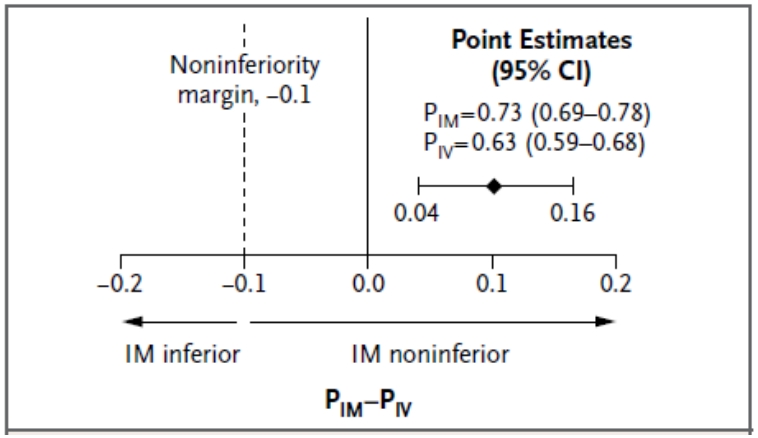
No. of Patients				
Overt	100	92	99	104
Subtle	46	41	47	41

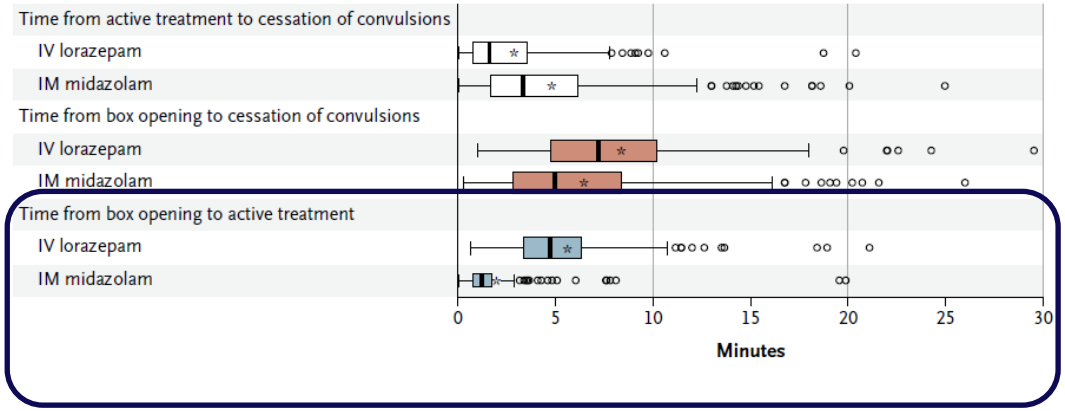
Treiman D et al. N Engl J Med 1998; 339: 792-798



No. at Risk						
Diazepam	68	41	21	8	2	1
Lorazepam	65	29	15	6	2	0
Placebo	67	53	26	10	1	0

Alldredge et al. N Engl J Med 2001; 345: 631-637





Silbergleit et al. N Engl J Med 2012;366:591-600

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First line treatment of convulsive SE

- Patient with IV access
  - Lorazepam 4 mg IV
  - Diazemules 10 mg IV (current shortage)
  - If unavailable, IM / IV/ buccal/ nasal midazolam 10 mg
- Patient without IV access
  - Midazolam 10 mg (buccal or IM)
  - Rectal diazepam not to be used routinely

Second line treatment

Established **S**tatus **E**pilepticus **T**reatment **T**rial (ESETT)

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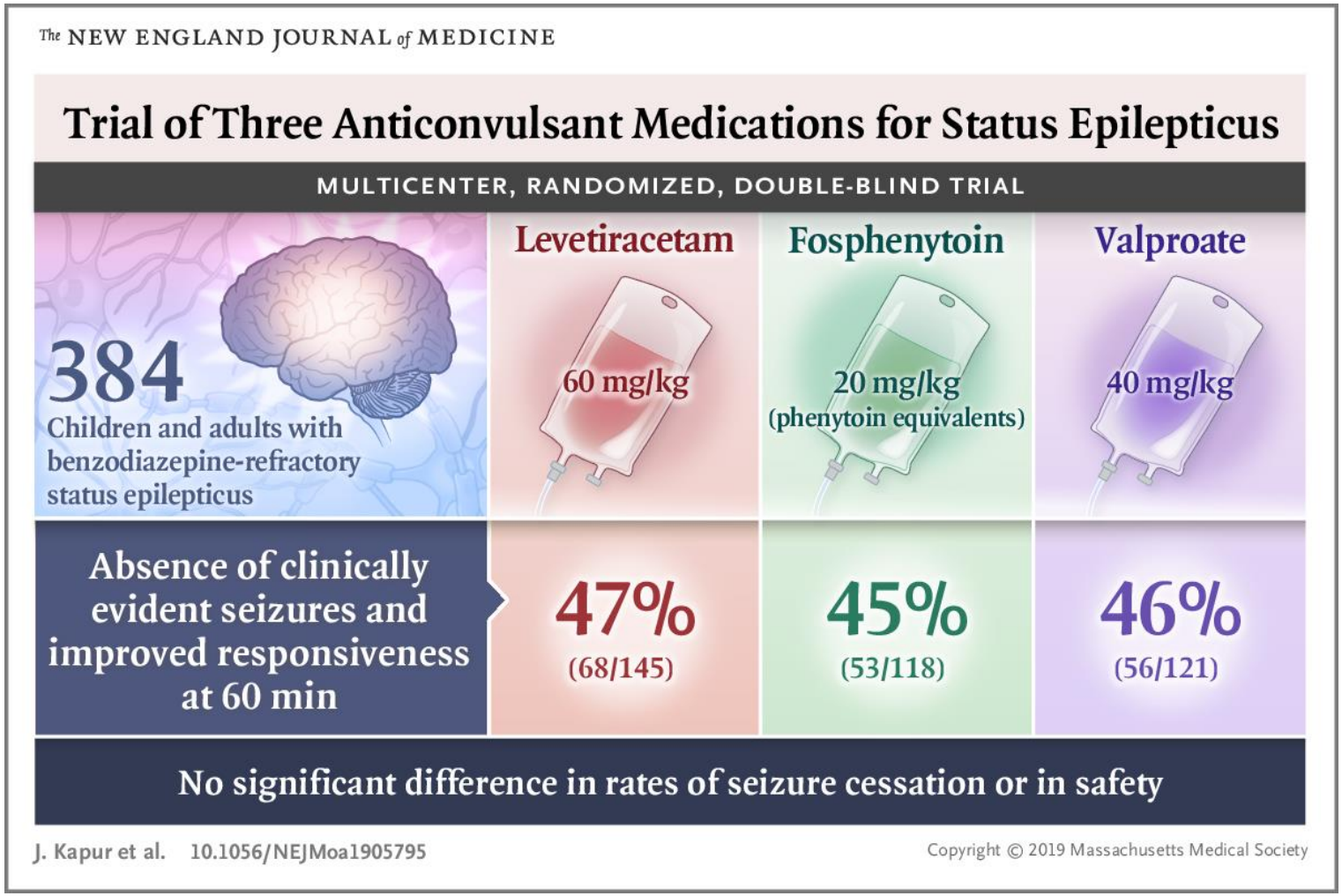

N Engl J Med 2019;381:2103-13.

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Second line treatment of convulsive status epilepticus

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- IV levetiracetam 60mg /kg (max 4500mg, ≥75kg) over 10 minutes
- Maintenance dose 1.5g BD

- IV sodium valproate 40 mg/kg (max 3000 mg, ≥75kg) over 10 minutes
- Maintenance dose 600mg TDS

Phenytoin

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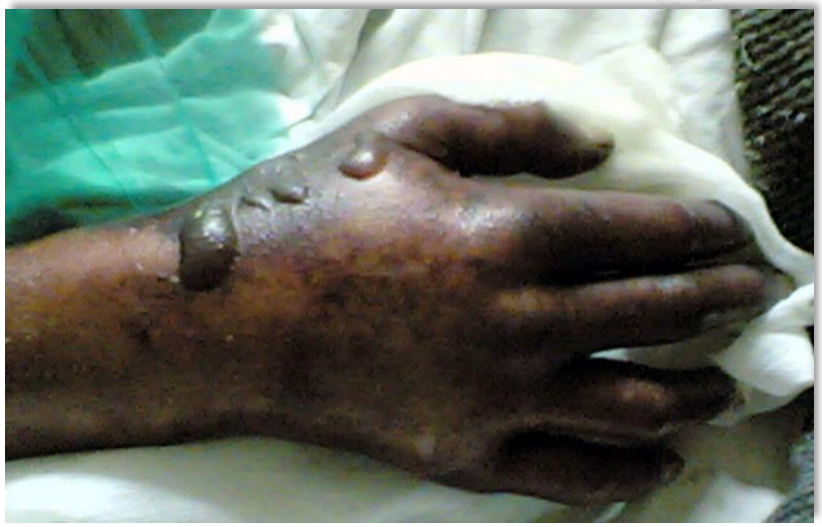
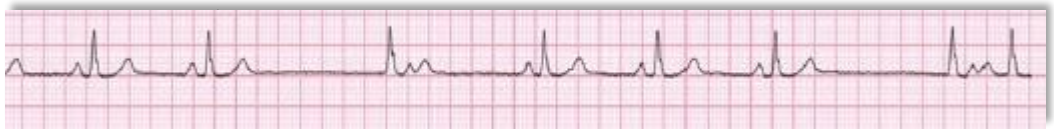
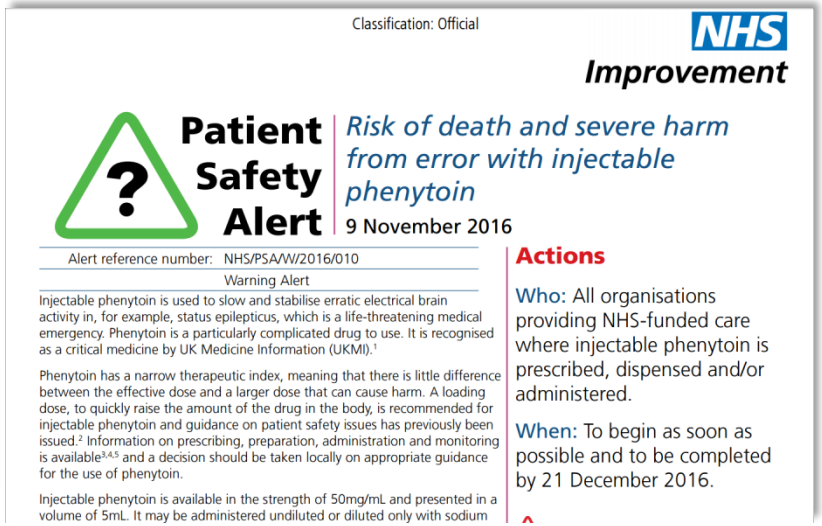
- IV Phenytoin 20mg/kg (2g max)
- Infusion rate
  - 25-50mg/min (max 50mg/min)
  - 10-25mg/min for elderly, cardiac disease
- Serum concentration 2 hours after loading
  - Further loading if required





See appendix of SE policy for safe administration of phenytoin on wards



Classification: Official

NHS Improvement

Patient Safety Alert

Risk of death and severe harm from error with injectable phenytoin

9 November 2016

Alert reference number: NHS/PSA/W/2016/010

Warning Alert

Injectable phenytoin is used to slow and stabilise erratic electrical brain activity in, for example, status epilepticus, which is a life-threatening medical emergency. Phenytoin is a particularly complicated drug to use. It is recognised as a critical medicine by UK Medicine Information (UKMI).[1]

Phenytoin has a narrow therapeutic index, meaning that there is little difference between the effective dose and a larger dose that can cause harm. A loading dose, to quickly raise the amount of the drug in the body, is recommended for injectable phenytoin and guidance on patient safety issues has previously been issued.[2] Information on prescribing, preparation, administration and monitoring is available[3,4,5] and a decision should be taken locally on appropriate guidance for the use of phenytoin.

Injectable phenytoin is available in the strength of 50mg/mL and presented in a volume of 5mL. It may be administered undiluted or diluted only with sodium

Actions

Who: All organisations providing NHS-funded care where injectable phenytoin is prescribed, dispensed and/or administered.

When: To begin as soon as possible and to be completed by 21 December 2016.

Other second line options

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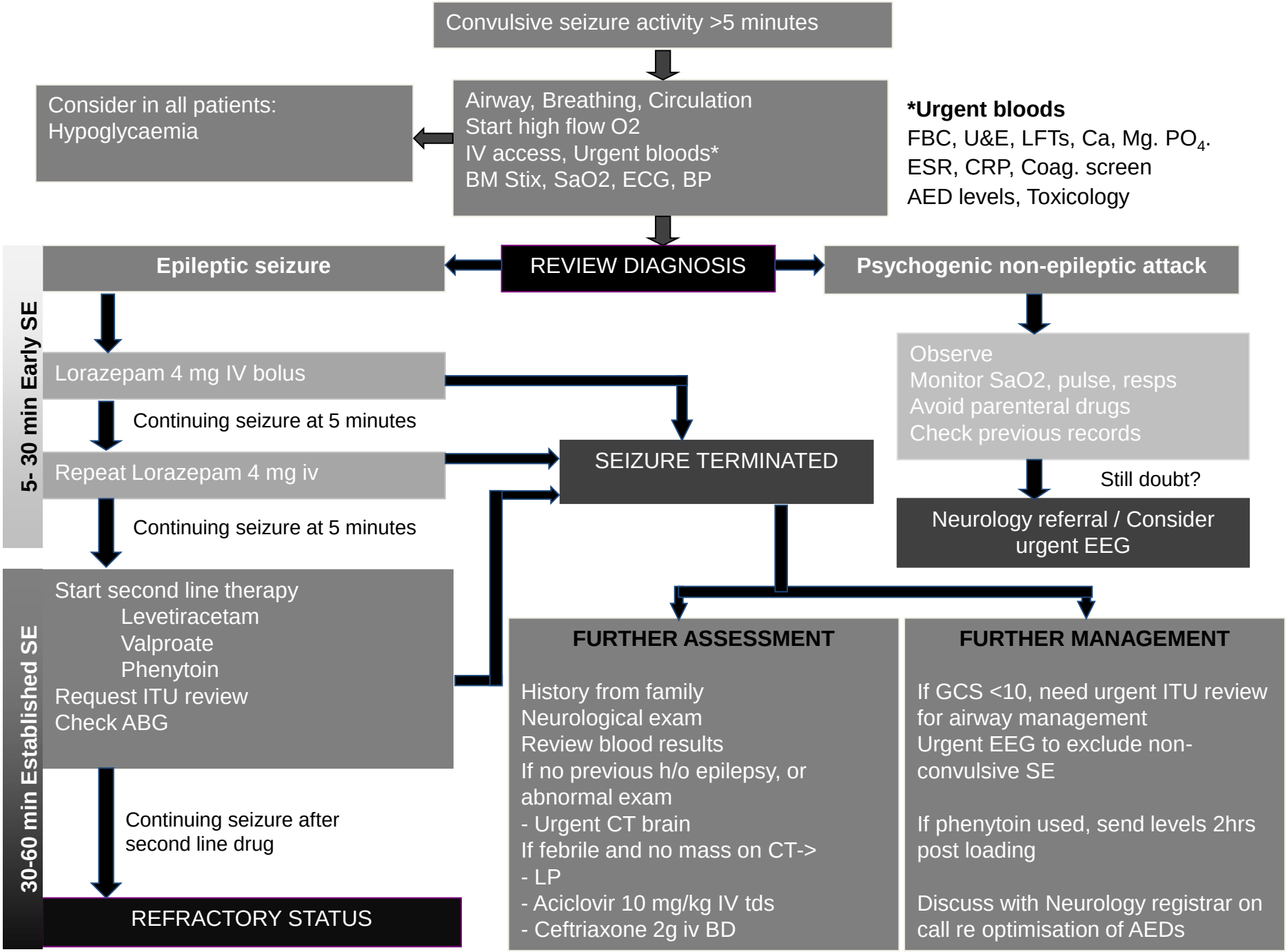
- Phenobarbitone
  - Usual IV loading dose 10 mg/kg @100 mg/min
    - Recent meta-analysis found 20mg/kg superior to VPA, LEV, PHT as second line
  - Risk of sedation / respiratory depression when used after benzo
    - Meta-analysis showed no significant increase in AEs
- Lacosamide
  - Meta-analysis of second line treatments found 66% response rate
    - 400 mg IV loading, followed by 200 mg BD
    - Cardiac monitoring

Brigo F, et al. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: A systematic review and network meta-analysis. Epilepsy Behav. 2019; 101: 106466


Convulsive seizure activity >5 minutes
Airway, Breathing, Circulation
Start high flow O2
IV access, Urgent bloods*
BM Stix, SaO2, ECG, BP
Consider in all patients:
Hypoglycaemia
*Urgent bloods
FBC, U&E, LFTs, Ca, Mg. PO4.
ESR, CRP, Coag. screen
AED levels, Toxicology
REVIEW DIAGNOSIS
Epileptic seizure
Psychogenic non-epileptic attack
5- 30 min Early SE
Lorazepam 4 mg IV bolus
Continuing seizure at 5 minutes
Repeat Lorazepam 4 mg iv
Continuing seizure at 5 minutes
SEIZURE TERMINATED
Observe
Monitor SaO2, pulse, resps
Avoid parenteral drugs
Check previous records
Still doubt?
Neurology referral / Consider urgent EEG
30-60 min Established SE
Start second line therapy
Levetiracetam
Valproate
Phenytoin
Request ITU review
Check ABG
Continuing seizure after second line drug
REFRACTORY STATUS
FURTHER ASSESSMENT
History from family
Neurological exam
Review blood results
If no previous h/o epilepsy, or abnormal exam
- Urgent CT brain
If febrile and no mass on CT->
- LP
- Aciclovir 10 mg/kg IV tds
- Ceftriaxone 2g iv BD
FURTHER MANAGEMENT
If GCS <10, need urgent ITU review for airway management
Urgent EEG to exclude non-convulsive SE
If phenytoin used, send levels 2hrs post loading
Discuss with Neurology registrar on call re optimisation of AEDs

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ICU management of refractory status epilepticus

Maintain burst suppression with no breakthrough seizures for 24 - 48 hours

Convulsive seizure activity for 40 – 60 minutes, not terminated by IV lorazepam x 2 and second line agent (eg: IV valproate / levetiracetam)

General anaesthesia with
Propofol bolus, then continuous infusion
Midazolam then continuous infusion

Intubate, ventilate, arterial line, central access
Admit to ITU
Observe for subtle convulsive activity
Neurology review

Obtain urgent EEG to ensure electrographic seizures abolished and burst suppression achieved

If ongoing seizure activity - Thiopentone 3-5 mg/ kg bolus, and continuous infusion (with monitoring)

Daily EEG recordings or continuous EEG monitoring
Correct any metabolic derangement
Ensure on adequate antiepileptic medication
If on phenytoin, check level – consider further IV loading dose

Daily Bloods
FBC, U&E, LFT, CRP, CK, Coagulation screen
Phenytoin levels

Super refractory SE (SRSE)

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- SE that recurs after 24 hours of general anaesthesia
- NORSE syndrome, FIRES, DESC
- High mortality (up to 50%)
  - 3rd line anaesthetic agents (ketamine, isoflurane)
  - Phenobarbitone, Magnesium, Topiramate
  - Immunotherapy (steroids, IVIg, PLEX, rituximab/tocilizumab)
  - Non pharmacological treatments (VNS, TMS, ketogenic diet)

Cases

Case 1

- 58 year old lady, cryptogenic left MCA stroke in 2018
- Witnessed by husband to suddenly become unresponsive, with a staring expression
- Brought in on the stroke pathway
- Seen in A&E 30min later – ongoing twitching of hand and face, reduced responsiveness, intermittent vocalisation only

Q1. What is your diagnosis and management plan?

1. This is not status epilepticus; no intervention is required
2. This may be status epilepticus, EEG is needed for confirmation
3. This is status epilepticus, and **should be** treated as per status policy
4. This is status epilepticus, but **should not be** treated as per status policy

Table 2. Axis 1: Classification of status epilepticus (SE)

(A) With prominent motor symptoms

A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.c. Unknown whether focal or generalized

A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
- A.2.a. With coma
- A.2.b. Without coma

A.3 Focal motor
- A.3.a. Repeated focal motor seizures (Jacksonian)
- A.3.b. Epilepsia partialis continua (EPC)
- A.3.c. Adversive status
- A.3.d. Oculoclonic status
- A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 Tonic status

A.5 Hyperkinetic SE

(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)

B.1 NCSE with coma (including so-called "subtle" SE)

B.2 NCSE without coma
- B.2.a. Generalized
  - B.2.a.a Typical absence status
  - B.2.a.b Atypical absence status
  - B.2.a.c Myoclonic absence status
- B.2.b. Focal
  - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
  - B.2.b.b Aphasic status
  - B.2.b.c With impaired consciousness
- B.2.c Unknown whether focal or generalized
  - B.2.c.a Autonomic SE

Table 3. Currently indeterminate conditions (or "boundary syndromes")

Epileptic encephalopathies
Coma with non evolving epileptiform EEG pattern[a]
Behavioral disturbance (e.g., psychosis) in patients with epilepsy
Acute confusional states, (e.g., delirium) with epileptiform EEG patterns

[a]Lateralized and generalized periodic discharges with monotonous appearance are not considered as evolving EEG patterns.[26,27]

Trinka E et al ILAE Task Force on Classification of Status Epilepticus, Epilepsia 56 (2015) 1515–1523

Conceptual and pathophysiological definition of SE

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Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

Trinka E et al ILAE Task Force on Classification of Status Epilepticus, Epilepsia 56 (2015) 1515–1523

Q2. How will you treat this patient?

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1. IV lorazepam 4 mg
2. IV lorazepam 1 mg
3. Buccal midazolam 10 mg
4. Oral clobazam 10 mg
5. IV levetiracetam 4.5 gm

Classification by treatment approach

Supported by class 1 evidence (Status policy)

A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.c. Unknown whether focal or generalized

A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
- A.2.a. With coma
- A.2.b. Without coma

Started as GCSE

Treat as per SE policy

A.3.b. Epilepsia partialis continua (EPC)

No history of GCSE

Probably treat as per SE policy

- A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 Tonic status

A.5 Hyperkinetic SE

No class I evidence to guide treatment

B.1 NCSE with coma (including so-called "subtle" SE)

B.2 NCSE without coma
- B.2.a. Generalized
  - B.2.a.a Typical absence status
  - B.2.a.b Atypical absence status
  - B.2.a.c Myoclonic absence status
- B.2.b. Focal
  - B.2.b.a Without impairment of consciousness (aura continua, with
  - B.2.b.b Aphasic status

Lower risk of neuronal damage from prolonged episodes than GCSE

Risks of aggressive treatment may not be justifiable

Table 3. Currently indeterminate conditions (or "boundary syndromes")

Epileptic encephalopathies
Coma with non evolving epileptiform EEG pattern[a]
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[a]Lateralized and generalized periodic discharges with monotonous appearance are not considered as evolving EEG patterns.[26,27]

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'Non-convulsive status epilepticus'

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- Describes a wide variety of clinical states
  - 'True' non convulsive status (absence, focal aware / unaware)
  - Advanced convulsive status
  - Boundary syndromes
- True NCSE (absence SE, focal SE)
  - No class 1 evidence to guide treatment
  - No evidence that absence SE leads to neuronal damage
  - Focal (aware/ unaware) SE in patients with epilepsy probably associated with low risk of neurological decline
    - Aggressive treatment, particularly in the elderly, may be associated with worse outcomes
  - Focal SE in patients with acute brain insults associated with worse outcomes
    - Unclear if aggressive treatment of seizures improves outcomes

General anaesthesia and outcomes of SE

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Anesthetic Drugs in Status Epilepticus: Risk or Rescue? A 6-Year Cohort Study.

Sutter R, Marsch S, Fuhr P, Kaplan PW, Rüegg S. *Neurology* 2014 Feb 25;82:656–664.

OBJECTIVE: To evaluate the risks of continuously administered IV anesthetic drugs (IVADs) on the outcome of adult patients with status epilepticus (SE). METHODS: All intensive care unit patients with SE from 2005 to 2011 at a tertiary academic medical care center were included. Relative risks were calculated for the primary outcome measures of seizure control, Glasgow Outcome Scale score at discharge, and death. Poisson regression models were used to control for possible confounders and to assess effect modification. RESULTS: Of 171 patients, 37% were treated with IVADs. Mortality was 18%. Patients with anesthetic drugs had more infections during SE (43% vs 11%; $p < 0.0001$) and a 2.9-fold relative risk for death (2.88; 95% confidence interval 1.45–5.73), independent of possible confounders (i.e., duration and severity of SE, nonan
effect modification by di
drugs failed, there was a
results regarding the risk
ings heighten awareness
the association of IVADs
evidence that patients w
compared to patients no

Status Epilepticus: Impact of Therapeutic Coma on Outcome.

Marchi NA, Novy J, Faouzi M, Stähli C, Burnand B, Rossetti AO. *Crit Care Med* 2015;43:1003–1009.

OBJECTIVES: Therapeutic coma is advocated in guidelines for management of refractory status epilepticus; this is, however, based on weak evidence. We here address the specific impact of therapeutic coma on status epilepticus outcome. DESIGN: Retrospective assessment of a prospectively collected cohort. SETTING: Academic hospital. PATIENTS: Consecutive adults with incident status epilepticus lasting greater than or equal to 30 minutes, admitted between 2006 and 2013. MEASUREMENTS AND MAIN RESULTS: We recorded prospectively demographics, clinical status epilepticus features, treatment, and outcome at discharge and retrospectively medical comorbidities, hospital stay, and infectious complications. Associations between potential predictors and clinical outcome were analyzed using multinomial logistic regressions. Of 467 patients with incident status epilepticus, 238 returned to baseline (51.1%), 162 had new disability (34.6%), and 67 died (14.3%); 50 subjects (10.7%) were managed with therapeutic coma. Therapeutic coma was associated with poorer outcome in the whole cohort (relative risk ratio for new disability, 6.86; 95% CI, 2.84–16.56; for mortality, 9.10; 95% CI, 3.17–26.16); the effect was more important in patients with complex partial compared with generalized convulsive or nonconvulsive status epilepticus in coma. Prevalence of infections was higher (odds ratio, 3.81; 95% CI, 1.66–8.75), and median hospital stay in patients discharged alive was longer (16 d [range, 2–240 d] vs 9 d [range, 1–57 d]; $p < 0.001$) in subjects managed with therapeutic coma. CONCLUSIONS: This study provides class III evidence that therapeutic coma is associated with poorer outcome after status epilepticus; furthermore, it portends higher infection rates and longer hospitalizations. These data suggest caution in the straightforward use of this approach, especially in patients with complex partial status epilepticus.

Treatment of non-convulsive status epilepticus

A proposed protocol

EEG confirmation mandatory in all situations apart from focal motor status (EPC)

ongoing seizure

Focal status epilepticus +/- impairment of awareness

First line line

10 min — Oral BZD
IV LEV / VPA)

Second line

45-60 min — Oral/ IV BZD
IV LEV / VPA (if benzo 1st line)

Seek neurology advice

Absence status epilepticus

First line line

15 min — Oral / IV (in young) BZD
IV VPA (?LEV)

Second line

1 hr + — Oral / IV (in young) BZD
IV VPA (if benzo 1st line)

Seek neurology advice

Coma Evolved from GCSE (subtle CSE)

Coma with no previous CSE

Should be managed as per status epilepticus policy with GA to achieve burst suppression

Where possible, avoid IV BDZ in older adults.
In general, risks of general anaesthesia outweigh risks of potential neuronal damage in focal and absence SE

Treat underlying cause

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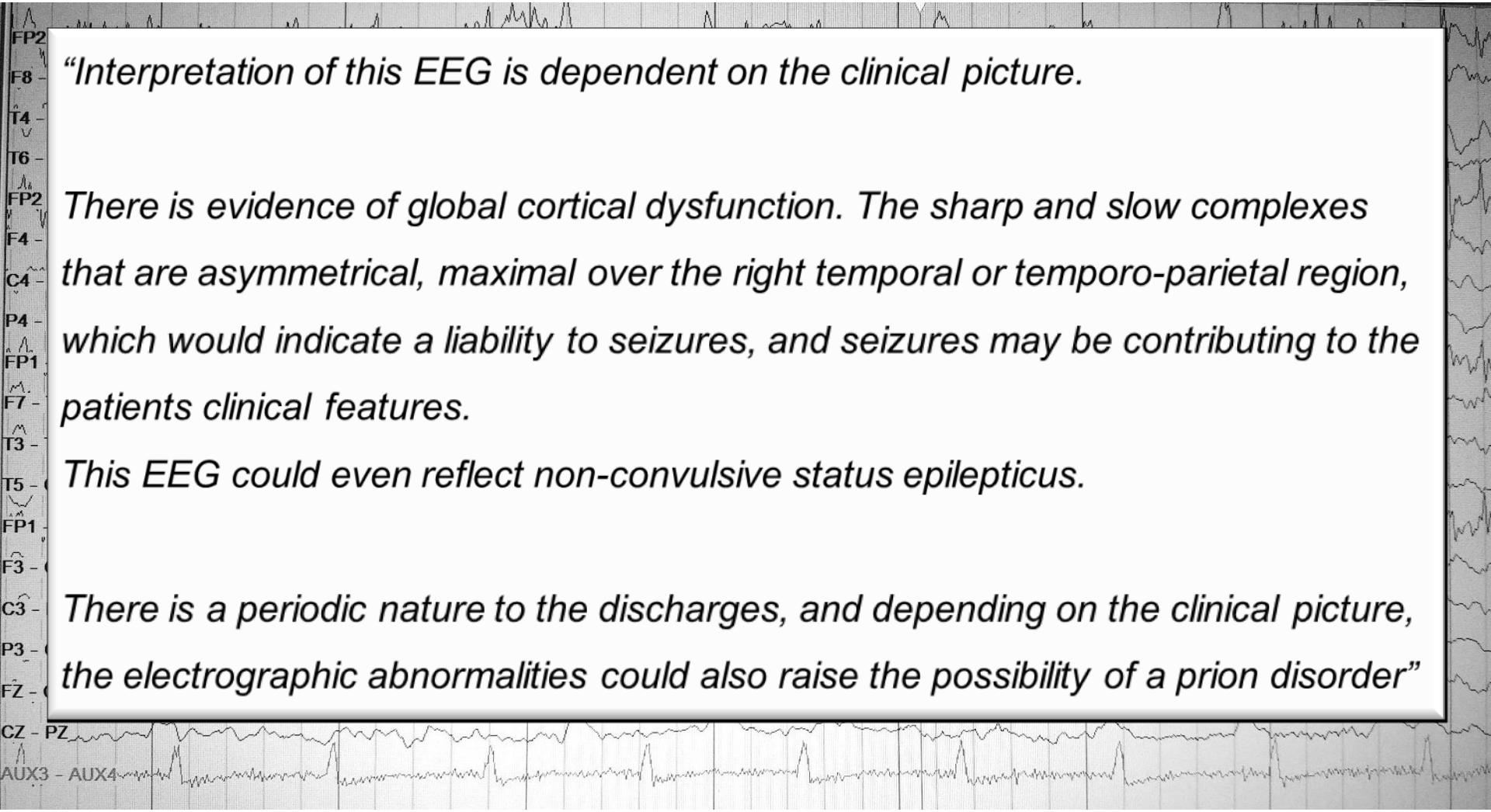
Case 2

- A 90 year old lady, nursing home resident, was admitted with suspected respiratory infection
- At admission she was febrile, confused and had a CRP of 25
- She was started on antibiotics, but the following day was still febrile and more drowsy. CT brain and LP were unremarkable
- Your colleague requests an EEG



"Interpretation of this EEG is dependent on the clinical picture.

There is evidence of global cortical dysfunction. The sharp and slow complexes that are asymmetrical, maximal over the right temporal or temporo-parietal region, which would indicate a liability to seizures, and seizures may be contributing to the patients clinical features.

This EEG could even reflect non-convulsive status epilepticus.

There is a periodic nature to the discharges, and depending on the clinical picture, the electrographic abnormalities could also raise the possibility of a prion disorder"

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Q3. What management will you advise?

1. "Load with IV Valproate"
2. "Try and give some oral Clobazam"
3. "Get an MRI to look for DWI changes of CJD"
4. "Ignore the EEG?"

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CRP 326

Diagnosis: Sepsis Associated Encephalopathy

What is a seizure?

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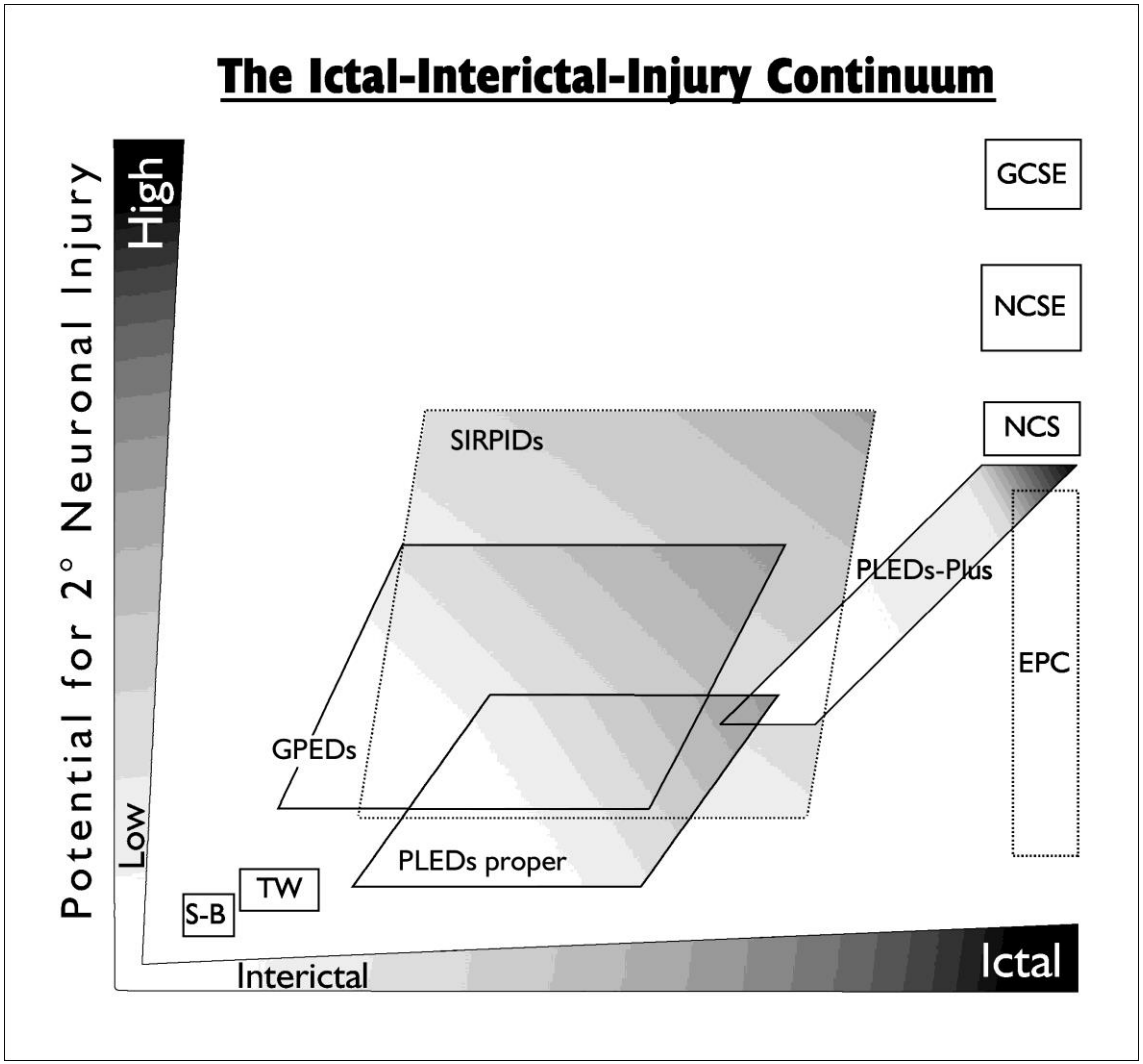
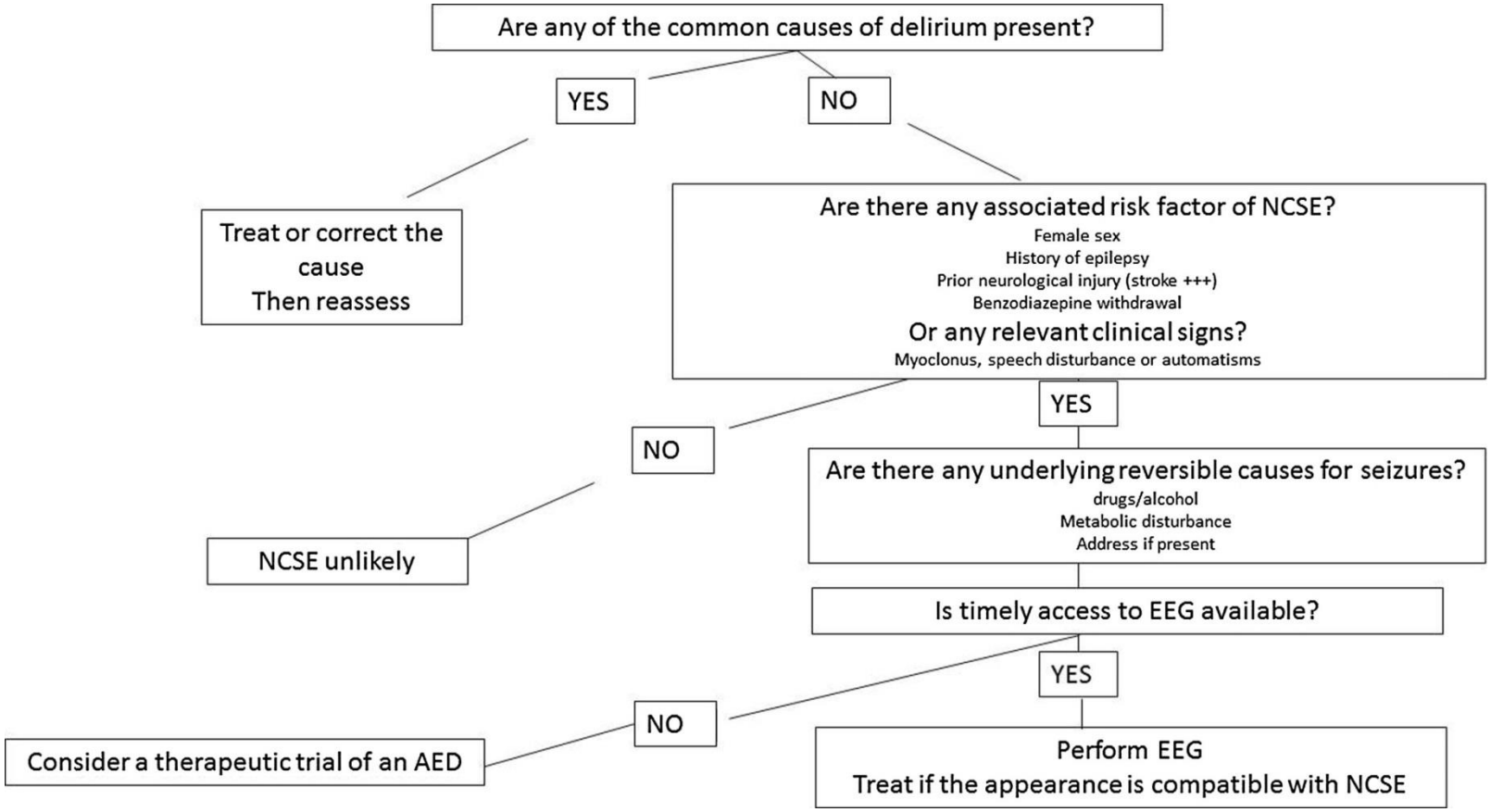
Acute Neurology
Update

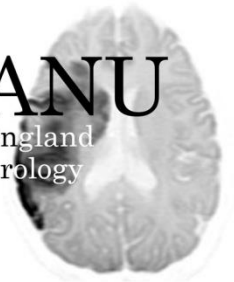


Elderly with encephalopathy
Approach to ?NCSE



Woodford HJ, George J, Jackson M. Non-convulsive status epilepticus: a practical approach to diagnosis in confused older people. Postgrad Med J 2015;91:655–61

Conclusions



- There is an evidence based policy for management of convulsive SE
- 'Non convulsive SE' is a non specific term that needs to be interpreted in the correct context
  - It is over-diagnosed, mainly due to misinterpretation of EEG reports
  - Neurologists have a key role in interpreting EEG findings in clinical context
  - Aggressive treatment of focal / absence SE may be associated with worse outcomes