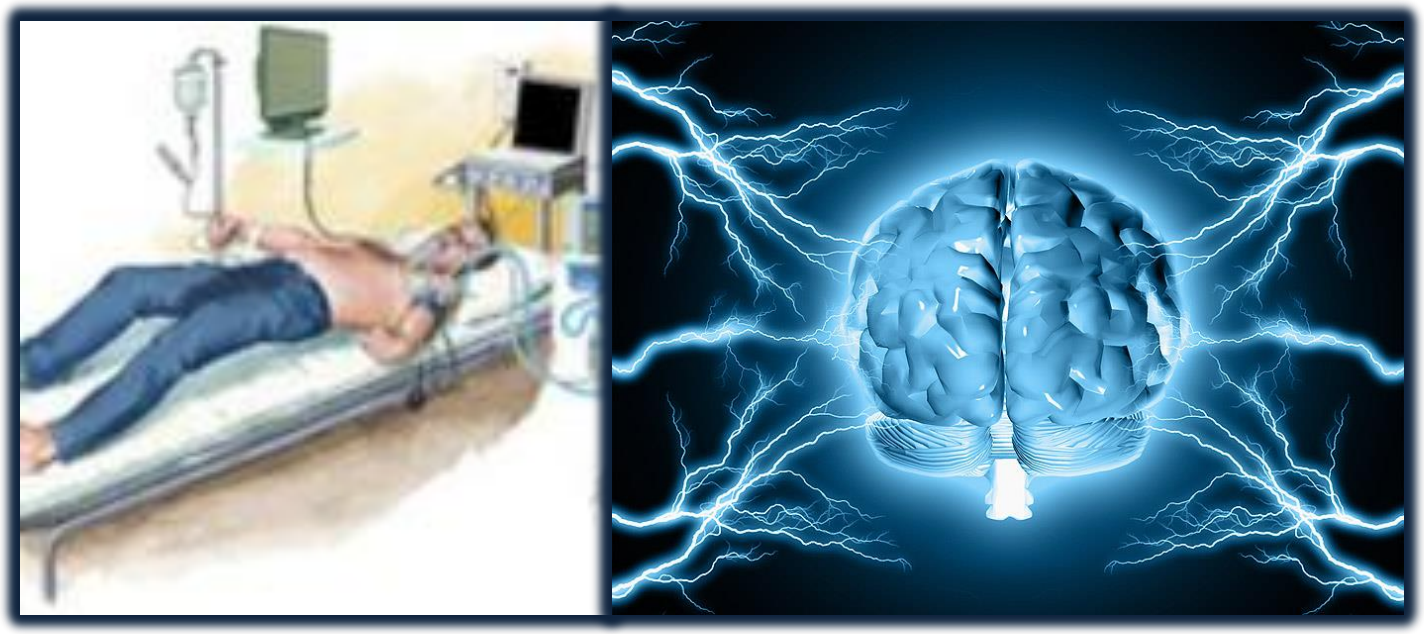
12th Regional Teaching Course in Sub-Saharan Africa

STATUS EPILEPTICUS



A.O. CHARWAY-FELLI

37 MILITARY HOSPITAL, ACCRA,GHANA

Status Epilepticus

Definitions

- A single seizure or back-to-back seizures without return of consciousness lasting
  - > 45 minutes (primate studies)
  - >30 minutes (WHO definition)
  - >10 minutes (working definition)

In 2015, ILAE task force defined the time periods for SE as:

- **5 minutes for generalized tonic-clonic seizures**
- **10 minutes for focal seizures**
- **10 to 15 minutes for absence seizures**

- When an adult has a seizure or seizures lasting more than a defined time period -→SE.
- SE -estimated incidence of 15 to 20 cases per 100,000 people, most common neurological emergency
- 20% of cases are fatal; long-term mortality rates up to 22% in children and 57% in adults.

Aetiology of Status Epilepticus

- **Unknown - 50%**
- Prolonged febrile seizure
  - Most common cause (in children)
- Idiopathic status epilepticus
  - Non-compliance to anti-convulsants
  - Sudden withdrawal of anticonvulsants
  - Sleep deprivation
  - Intercurrent infection

Causes of Status Epilepticus

1. Low AED levels	-	35%
2. Stroke, including haemorrhagic	-	20%
3. Alcohol withdrawal	-	15%
4. Anoxic brain injury	-	15%
5. Metabolic disturbances	-	15%
6. Remote brain injury/ cong. malformations	-	20%
7. Infections	-	5%
8. Brain neoplasms	-	5%
9. Idiopathic	-	5%

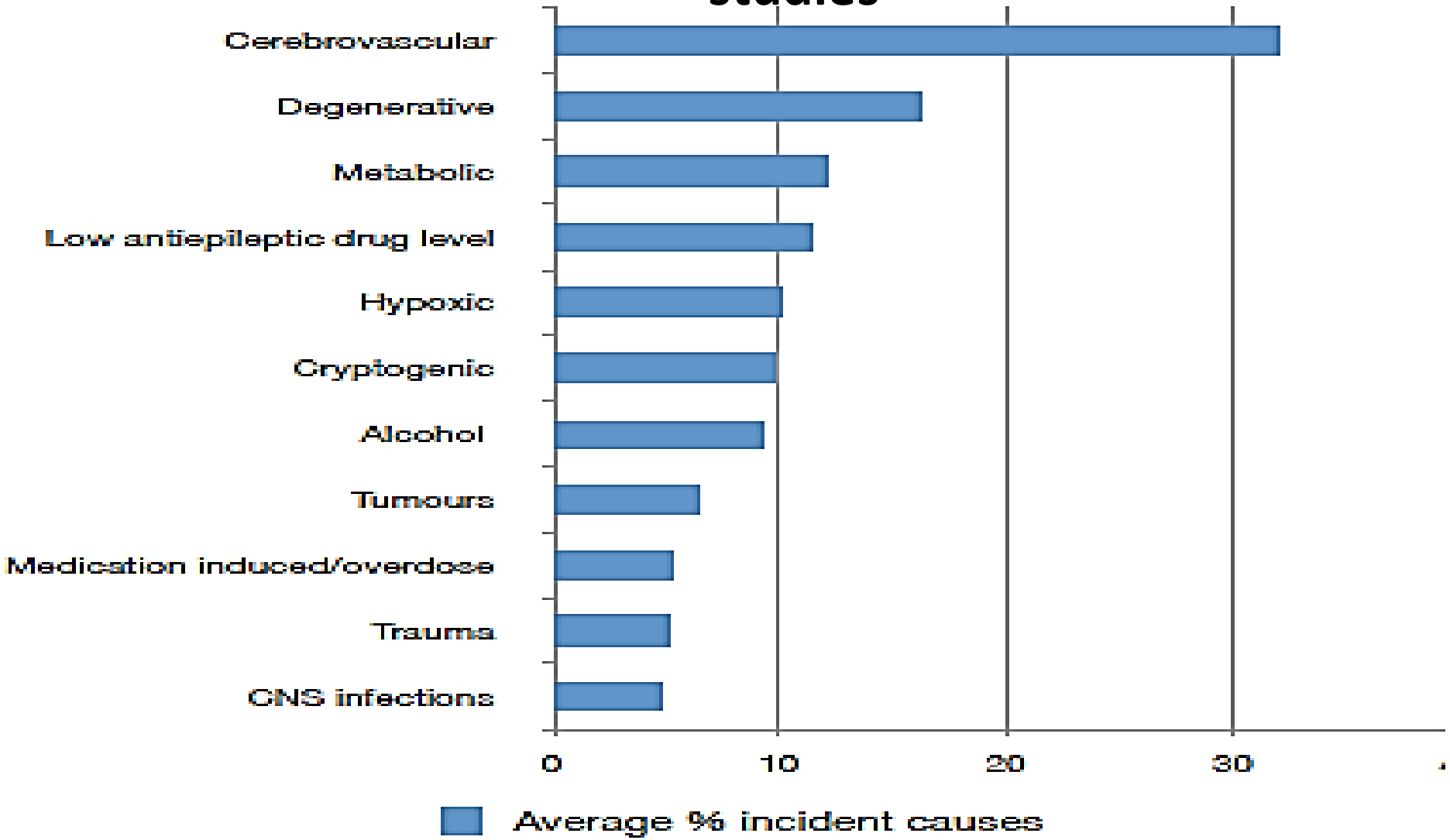
Aaetiology cont.

- 50% of seizures/SE are acute symptomatic
  - Stroke
  - Trauma
  - Cerebral hypoxia
  - Infection
  - Tumor

Aetiology of Status Epilepticus

- Symptomatic status epilepticus
  - Anoxic encephalopathy
  - Encephalitis, meningitis
  - Congenital malformations of the brain
  - Electrolyte disturbances, drug/lead intoxication, extreme hyperpyrexia, brain tumor

Identified aetiology of status epilepticus across major studies



Causes of Status Epilepticus (Cont.)

- In adults symptomatic SE makes up 48-63%

  - stroke – 14-22% (36% in pts >56yrs SE caused by remote stroke)

- Neuroinfection
- (Illicit) Drug Intoxication including Alcohol
- Cerebral Mass lesions

Clinical features and outcomes dependent on cause of SE!!!

- Anoxia is associated with a substantial mortality (72%).
- The lowest mortality is in patients with epilepsy who have provoked seizures, for example with low serum antiepileptic drug levels (mortality rate 4 - 8.6%)
- Age, duration of SE, whether there have been any prior episodes, depth of coma at presentation, and response to treatment have also been shown to be important.
- The main modifiable factor is the duration of SE, highlighting the importance of urgent treatment.
- Duration of seizure activity has been shown to be an important predictor for mortality

<30 min - 2.6%, >30min - 19%

Status Epilepticus

- Categorized electroclinically (focal or generalized)

–Morbidity

–Identify etiology

- Classified as Convulsive and Nonconvulsive

Clinical - Generalized SE

- At onset - usually obvious muscle activity – tonic/clonic
- Muscle activity reduces as seizure progresses, may be only subtle twitches (eyes, face, limbs): NB History!!
- May be NO observable motor convulsions ***still risk for CNS injury - assume still in status if SE consciousness is not restored; NCSE!!
    - need EEG to definitely dx - not uncommon in comatose hospital inpatients
    - SE DD for all patients brought in with altered mental status/unconscious.

Status Epilepticus

Convulsive

•Convulsions associated with rhythmic jerking of the limbs

•Types

– Generalized (most common)

- Myoclonic
- Clonic
- Tonic
- Tonic –Clonic

– Focal

- preserved awareness
- Altered awareness

Non-convulsive

•Sz activity seen on EEG without clinical findings

•Types

–Focal (preserved and altered awareness)

–Absence

–Others (rare)

•Diagnosed based on

-- aetiology

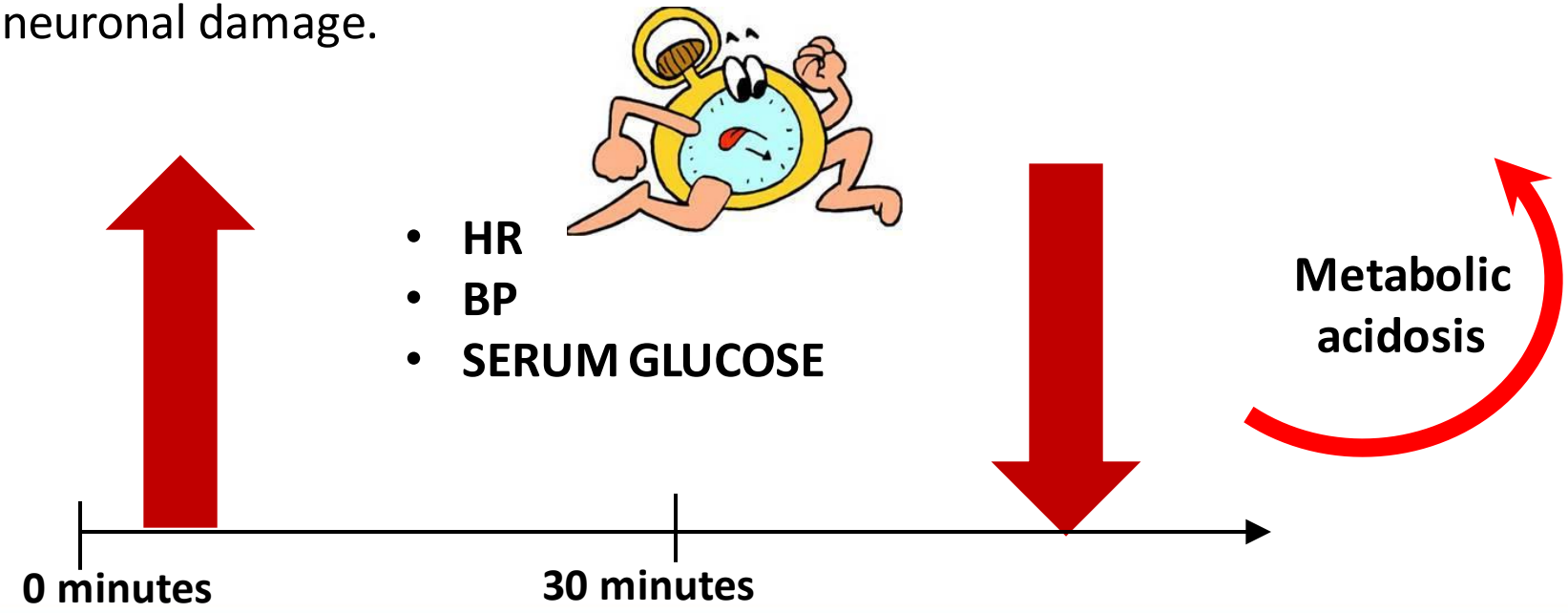
–EEG findings

- Captures 56% of seizures in first hour
- 88% of seizures in first 24h

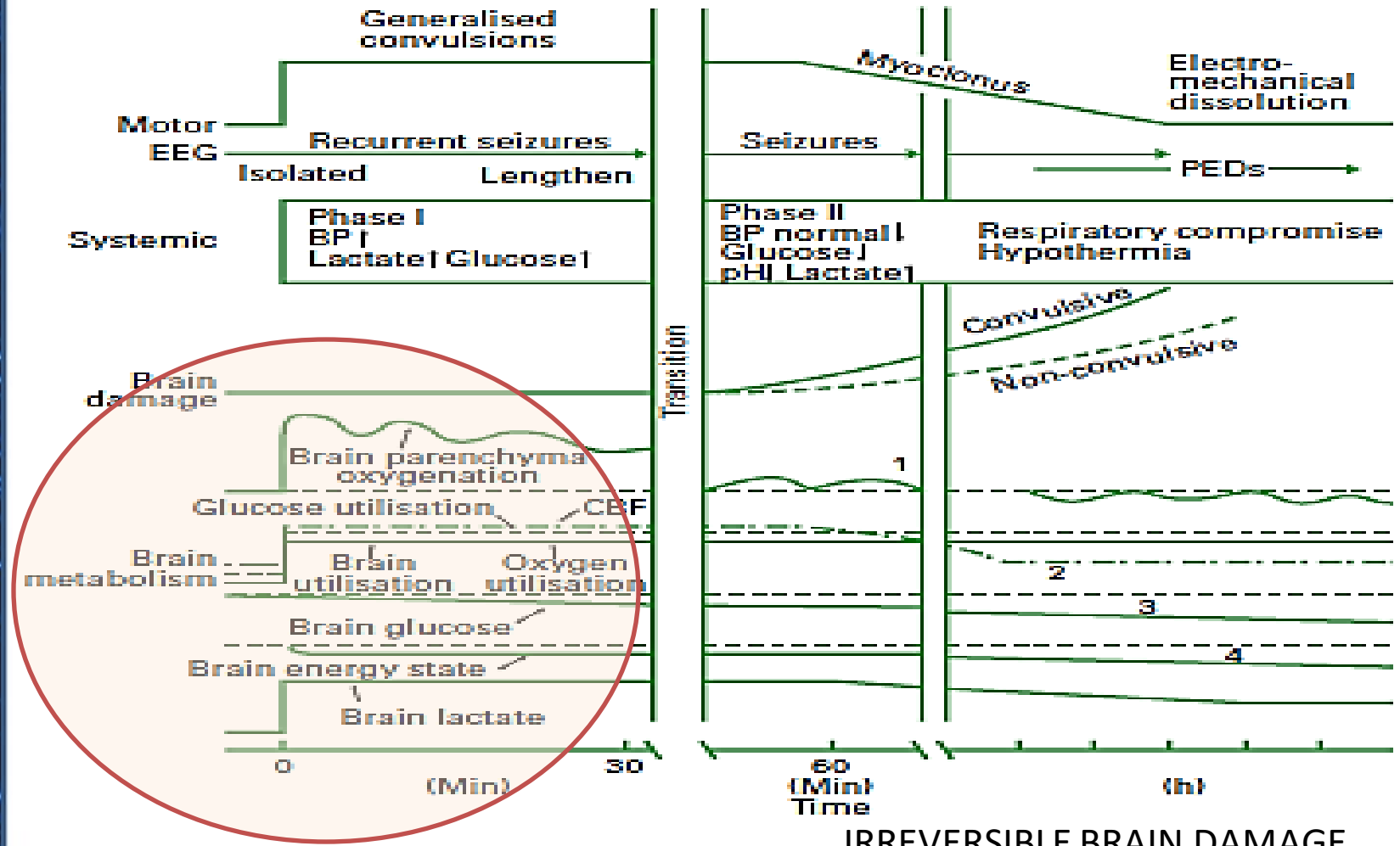
–Clinical status of patient

Pathophysiology of SE

For the first 30 minutes physiological compensation occurs to meet the increased metabolic demands. Heart rate, blood pressure and serum glucose level are all elevated to minimize the risk of cerebral damage. After 30 minutes, decompensation occurs with hypotension, hypoxia, metabolic acidosis, cardiac arrhythmias and cerebral auto-regulatory failure ensuing, all of which can lead to neuronal damage.



Pathophysiology of SE



IRREVERSIBLE BRAIN DAMAGE

1. loss of reactivity of brain oxygen tension;
2. mismatch between the sustained increase in oxygen and glucose utilisation and a fall in cerebral blood flow;
3. a depletion of cerebral glucose and glycogen concentrations;
4. a decline in cerebral energy state.

Shorvon SD.
A handbook of epilepsy treatment

Approach: Diagnostic workup

All patients
• Obtain IV access
• Monitor vital signs (ABC).
• Head CT (appropriate for most cases)
• Labs: blood glucose, FBC, renal function tests, Calcium, Magnesium, electrolytes, AED levels. Retroviral screening as indicated
• cEEG monitoring (preferably)
Consider based on clinical presentation
• Brain MRI
• Lumbar puncture
• Toxicology panel (i.e. isoniazid, TCAs, theophylline, cocaine, sympathomimetics, organophosphates, cyclosporine)
• Other relevant investigations as per the need

Brophy, et al NCC 2012

SE management protocol

1st line (seizures ongoing for 5-10 mins)

- **Lorazepam** 4mg IV (push over 2mins), If controlled within 5mins, repeat 4mg IV x 1
- **Diazepam** 10mg IV stat (0.3 to 0.5 mg/kg max: 10 mg/dose)

If no IV access:

- **Diazepam** 20mg rectally (using IV sol)
- or, **Midazolam** 10mg intranasal/buccal/IM (using IV sol).

1) **Airway, Breathing, Circulation**
2) **Vital signs** (cont. monitoring): HR, BP, O2, ECG
3) **Blood Glucose;** If glucose low/unknown: ***give thiamine 100mg IV, then D50 (50mL IV)***
4) **Obtain IV access**
5) **Temperature**, - if Tº C ↑ **-** antipyretics, cooling, a/biotics
6) **Labs**: FBC, electrolytes, ABG, LFTs, BUE+Cr, toxicology (blood & urine), blood c&S (esp if febrile), AED levels (in pts w/ prior hx of epilepsy), HCG (females)

SE management protocol

2nd line (10-30 mins)

Choose from the following (may be used in combination):

1) **Phenytoin** 20 mg/kg IV (max rate 25-50mg/min)

Or: **Fosphenytoin** 20mg PE/kg IV (max rate 150mg PE/min) If no effect, can give additional dose: Fosphenytoin 10mg PE/kg IV or Phenytoin 10 mg/kg IV

2) **Phenobarbital** 20mg/kg IV (max rate 50-75mg/min)

3) **Valproic acid** 40mg/kg IV (max rate 6mg/kg/min)

4) **Levetiracetam** 20mg/kg IV (max rate 100mg/min)

5) **Lacosamide** 400mg IV over 5 min (need ECG pre/post)

Check anti-convulsant levels post-load and re-bolus if needed

(see box below for therapeutic levels):

PHT, VPA, PHB - send level 1hr after load

FOS-PHT - send level 2hrs after load

SE management protocol

3rd line (30 - 60 mins) REFRACTORY STATUS EPILEPTICUS

If seizures persist → **INTUBATE** → **ICU**
Start continuous EEG monitoring

Choose from the following (may be used in combination):

1) **Midazolam** (esp. if BP unstable) Load 0.2mg/kg IV. Repeat q5mins until szs stop (max load 2mg/kg) Maint. infusion 0.1-- 2 mg/kg/hr

2) **Propofol** - Load 2mg/kg IV. Repeat q5mins until szs stop (max load 10mg/kg) Maint. infusion 1--10mg/kg/hr (< 5 if treatment > 48hrs)

Continue maintenance anticonvulsants and adjust doses for therapeutic level:

MAINTENANCE DOSES & THERAPEUTIC LEVELS

1) **Phenytoin** 5-7 mg/kg/day (TID), or, 'Fosphenytoin 5-7 PE/kg/day (TID) 15-25 ug/mL* (total) (1.5-2.5 ug/mL (free)
2) **Phenobarbital** 1-4mg/kg/day (BID) 20-50 mg/mL
3) **Valproic acid** 30-60 mg/kg/day (BID) 70-120 ug/mL
4) **Levetiracetam** 2-4 g/day (BID) 25-60 mg/L
5) **Lacosamide** 400-600mg/day (BID) Unknown

Continue workup to determine underlying cause of SE
1) Neuroimaging - brain MRI (preferred) or head CT
2) Lumbar puncture - evaluate for infection, inflammatory, autoimmune causes

SE management protocol

4th line (> 72 hrs) SUPER-REFRACTORY STATUS EPILEPTICUS

Choose from the following (may be used in combination):

1) Repeat burst suppression for 24-48hrs

2) Add other AEDs (consider CBZ, TOP, not listed above)

3) IV magnesium (bolus 4g, then infuse 2-6g/hr)

4) Ketamine Load w/ 1.5mg/kg IV; Repeat q5mins until szs stop (max load 4.5mg/kg) Maint. infusion at 1.2-7.5mg/kg/hr

5) Pentobarbital (titrate to burst suppression); Load 5mg/kg IV (max rate 50mg/min). Repeat q5mins until szs stop (max load 15mg/kg) Maint. infusion 1-10 mg/kg/hr

6) IV pyridoxine (200mg/day)

7) Immune modulation

Steroids (methylprednisolone 1g IV qd x 3-5 days)

and/or IVIG (0.4g/kg/day x 5 days)

and/or plasma exchange (every other day x 5-7 days)

7) Ketogenic diet

8) Therapeutic hypothermia

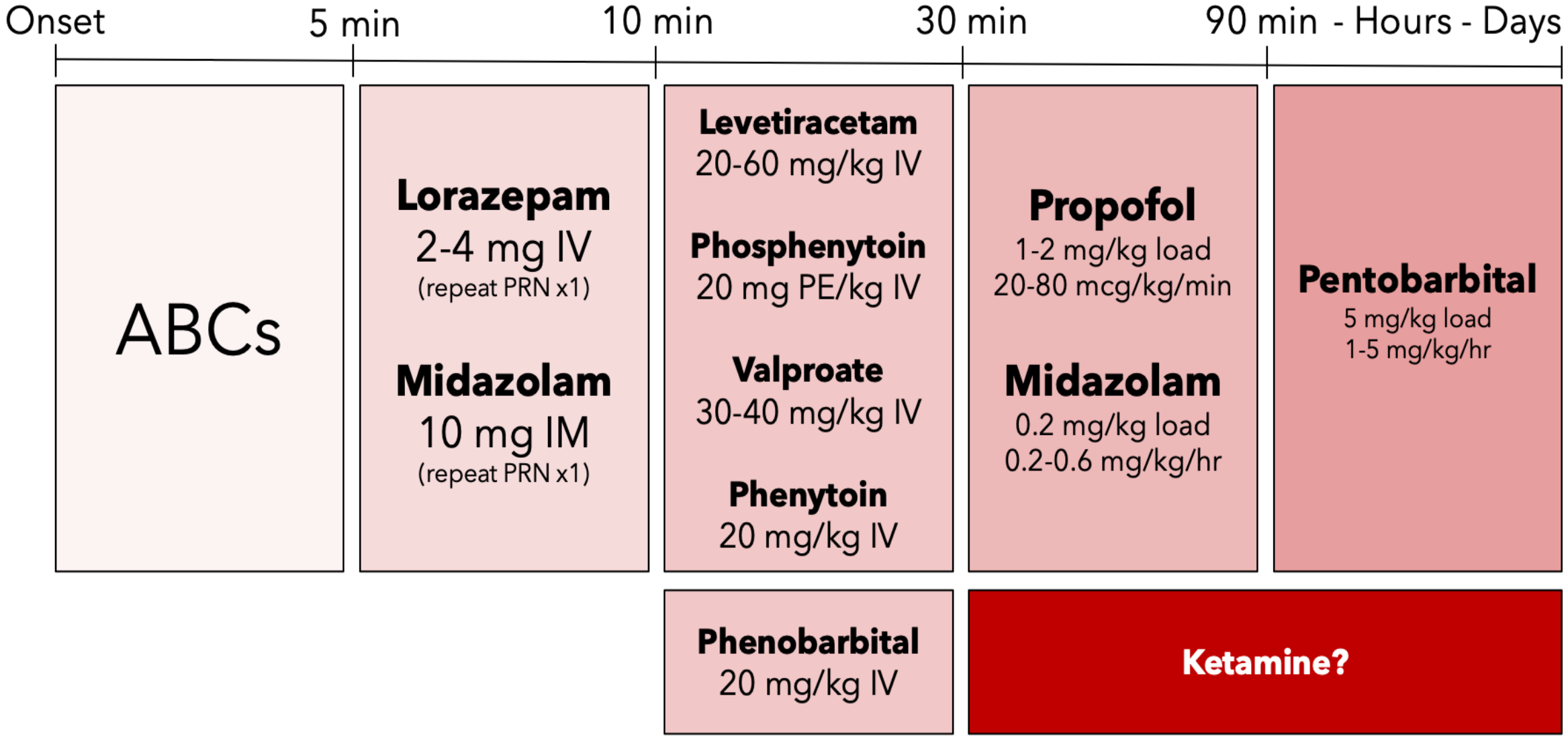
9) Electroconvulsive therapy (ECT)

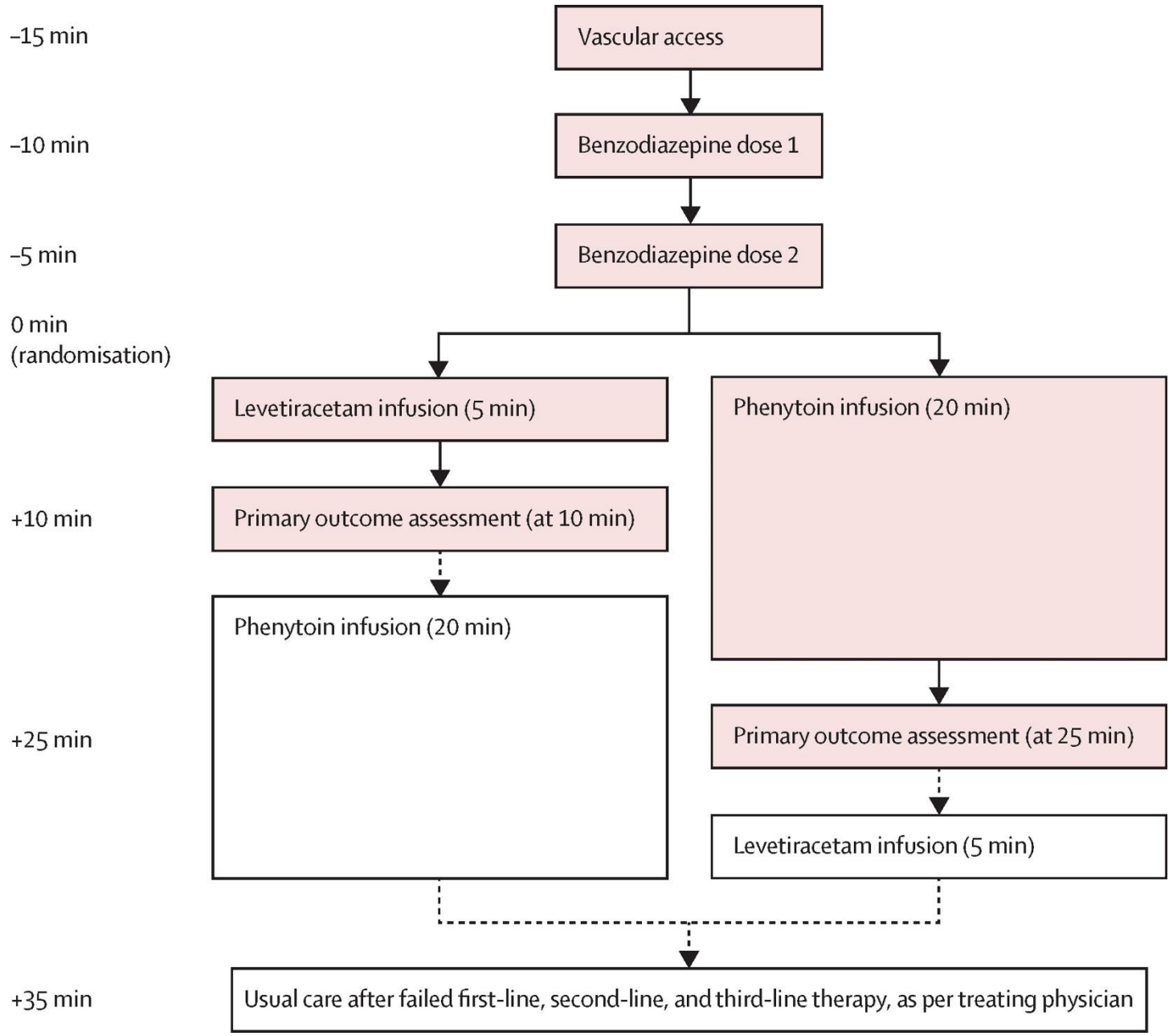
10) Neurosurgical treatment (eg, resection of focal lesion)

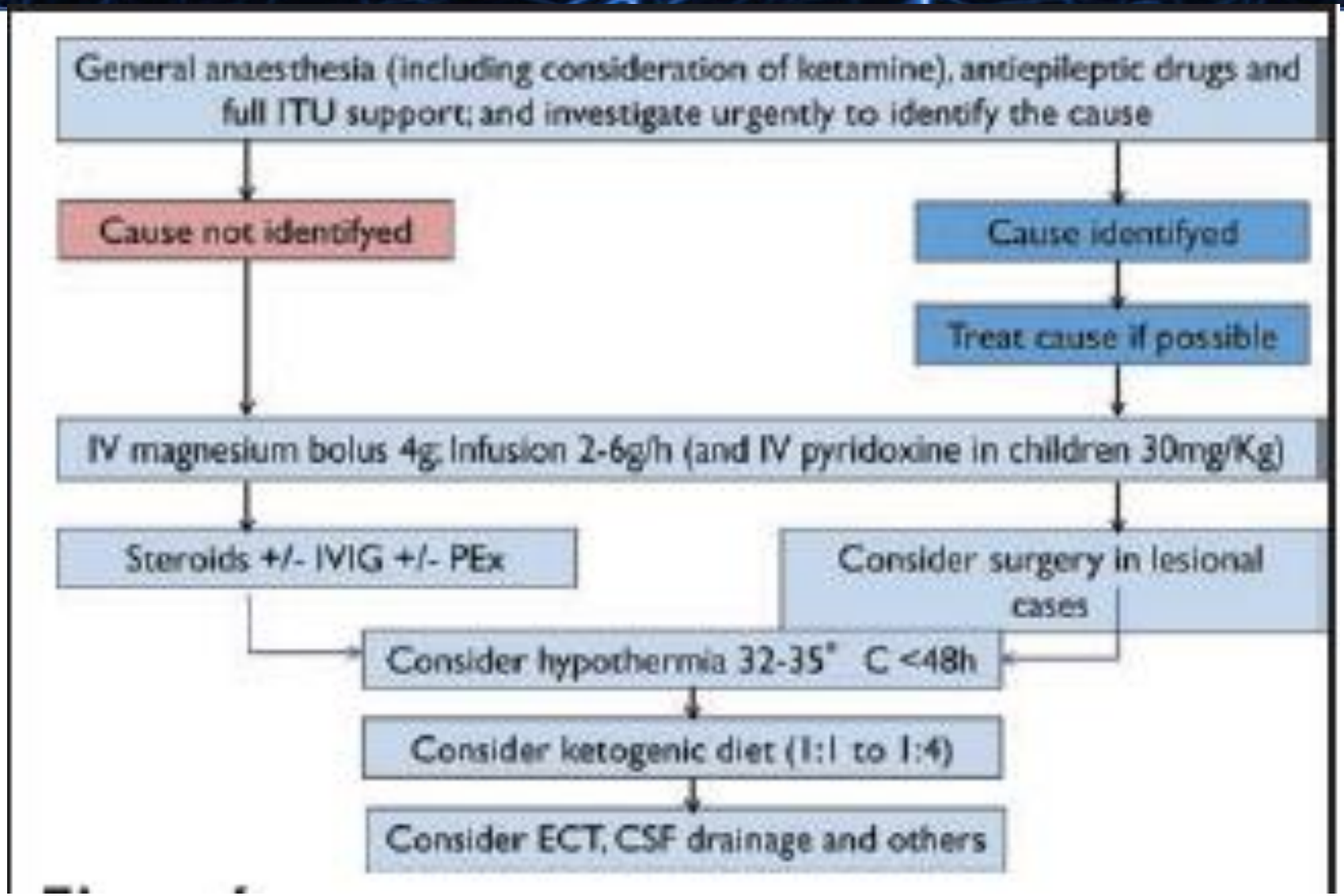
11) TMS

No strong evidence to guide best treatment here.

Treat underlying cause of status epilepticus.


Onset
5 min
10 min
30 min
90 min - Hours - Days
ABCs
Lorazepam
2-4 mg IV
(repeat PRN x1)
Midazolam
10 mg IM
(repeat PRN x1)
Levetiracetam
20-60 mg/kg IV
Phosphenytoin
20 mg PE/kg IV
Valproate
30-40 mg/kg IV
Phenytoin
20 mg/kg IV
Propofol
1-2 mg/kg load
20-80 mcg/kg/min
Midazolam
0.2 mg/kg load
0.2-0.6 mg/kg/hr
Pentobarbital
5 mg/kg load
1-5 mg/kg/hr
Phenobarbital
20 mg/kg IV
Ketamine?


–15 min
Vascular access
–10 min
Benzodiazepine dose 1
–5 min
Benzodiazepine dose 2
0 min
(randomisation)
Levetiracetam infusion (5 min)
Phenytoin infusion (20 min)
+10 min
Primary outcome assessment (at 10 min)
Phenytoin infusion (20 min)
+25 min
Primary outcome assessment (at 25 min)
Levetiracetam infusion (5 min)
+35 min
Usual care after failed first-line, second-line, and third-line therapy, as per treating physician



Treatment algorithm for superrefractory status epilepticus. Modified after Shorvon & Ferlisi, 2011.
Epilepsia © ILAE

Other Management cont.

- If Sepsis, Meningitis, Meningoencephalitis suspected as indicated by history and preliminary physical findings, Start ASAP broad spectrum antibiotics eg:
  - IV Ceftriaxone 2-4g daily
  - IV Vancomycin 1g q12H

Other Management Cont.

- A Lumbar puncture should be performed as soon as is feasibly possible if indicated by the likelihood of Infection as a cause of SE
- **<u>Contraindications:</u>**

  - Focal Neurologic deficit in the absence of neuroimaging or lesion with mass effect on imaging

  - papilloedema

Steroids and Immunotherapy

- Rationale that refractory SE may be due to antibodies directed against neural elements.
- Increasing recognition the role of inflammation in epileptogenesis.
- SE may be the initial presenting feature of some immune mediated encephalopathies.

Shorovan M et al,The treatment of refractory status epilepticus
Brain 2011

Steroids and Immunotherapy

- IV Methylprednisolone (adult dose) 1g daily for 3-5 Days OR IV Dexamethasone 8mg qid
- IV Immunoglobulin 400mg/kg BW daily 2-5 days
- Plasmapheresis

KETOGENIC DIET

- Similar in content to the Atkins Diet (High fat, adequate protein, low to no carbohydrate)
- Induces ketosis in body and thought to suppress seizures by release of Leptin.
- Complications: Renal Impairment/ Renal Calculi, constipation
- Difficult to maintain (Local diet very high in carbohydrates)
- In ICU setting better control delivered via Nasogastric Tube.

NONPHARMACOLOGICAL TREATMENTS

- Resective surgery
- Vagal nerve stimulation
- Hypothermia- decrease brain metabolism which is neuroprotective
  - Temperature goal – 32-34°C for up to 48hrs
- Electroconvulsive therapy - **ECT**-dose-1 session daily for 3-8 days.

  Mechanism-not known

Complications

- Cardiac arrhythmias
- Hypotension
- Hypoventilation/Hypoxia
- Aspiration pneumonitis
- Neurogenic pulmonary edema
- Metabolic lactic acidosis
- Hyperthermia
- Cardiac injury 2/2 catecholamine release

Distinguishing SE from non-epileptic/psychogenic seizures

- **NO ABSOLUTES!!!!**

CLINICAL FEATURE	SE	PSEUDO-SEIZURE
ONSET	Sudden onset. May have focal seizure activity at onset.	Gradual onset potentially lasting minutes, can have a lead in of panic symptoms (which may not be recalled by the patient). At times can start with sudden onset.
Motor state	Tonic, then evolving into clonic synchronous movements. PERSISTENTLY RHYTHMIC	Whole body stiffening, with some voluntary movements at times, can be flaccid. Largely during the ictus (ictal atonia), back arching, side to side head movements, undulating pelvic thrusting.

Distinguishing SE from non-epileptic/psychogenic seizures

CLINICAL FEATURE	SE	PSEUDOSEIZURE
Evolution	A definite tonic phase, then clonic phase. As Progresses the clonic movements become less pronounced, with perhaps nystagmus or subtle twitching as the only manifestation.	Varying, tonic/clonic movements. Not following specific sequence, with pauses during the ictus. Movements usually asynchronous. Subtle eye movements may occur
Vocalisation	At onset, may have loud guttural cry as air is forced out past a tonic larynx.	May occur in the middle of a seizure, crying and shouting are possible.

Distinguishing SE from non-epileptic/psychogenic seizures

CLINICAL FEATURE	SE	PSEUDOSEIZURE
Eyes	Eye closure is not typical. Eyes maybe deviated. Pupils tend to be unresponsive.	Eyes are commonly forcibly closed. (This is not always the case). Typically could be deviated away from the observer. Pupils are normal.
Tongue	**Can have deep lateral tongue biting.**	**Typically superficial frontal tip of the tongue location.**
Cyanosis	**Present**	**Absent**
Responsive?	**None. No withdrawal from painful stimulus.**	**Variable withdrawal from painful stimulus. Limb movements may change with mild restraint**

Distinguishing SE from non-epileptic/psychogenic seizures

CLINICAL FEATURE	SE	PSEUDOSEIZURE
Consistency	Usually stereotyped seizure episodes.	Variable nature to events.
Recovery	Delayed recovery after event, with amnesia.	Prompt recovery. Non-organic amnesia observed.

Pseudo-SE should be considered in all patients presenting with apparent SE. Differentiating between the two on clinical grounds alone can be difficult, even for experienced practitioners. Given the limited access to EEG, when the clinical diagnosis is not established beyond reasonable doubt, it is best to err on the side of caution and treat as SE.

THE END

THANK YOU