Status epilepticus

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Terms

- Seizure – paroxysmal event due to abnormal excessive neuronal activity in brain
- Epilepsy – recurrent seizures due to chronic, underlying process; epilepsy syndromes
- Classification of seizures – diagnosis, therapy, prognosis
- International League against Epilepsy (ILAE) – clinical features and EEG

Classification of seizures

- Focal – motor, sensory, autonomic, cognitive
- Generalized – absence, tonic-clonic, clonic, tonic, atonic, myoclonic
- Unclear

Classification

Focal seizures

- Arise from neuronal network in one hemisphere
- Spread of activity (movement)
- paresis
- Continue for hours or days
- Auras
- Dyscognitive features
- secondary generalization
- Interictal EEG may be normal or show epileptiform spikes or sharp waves

Generalized seizures

- Engage neuronal network in both cerebral hemispheres
- Generalized tonic-clonic – most common type from metabolic derangement, EEG polyspikes, spike – wave, slow
- Typical absence (spike – wave)
- Atypical absence
- Atonic
- Myoclonic

Causes of seizures and epilepsy

- Shift in balance of excitation and inhibition in CNS

- Normal brain have seizure under appropriate circumstances (endogenous factor, genetic)
- Condition and process of epileptogenesis (trauma, stroke, infection): hyperexcitable neuron network
- Precipitating factors (physiological, physical, exogenous such as toxic substance)

- Age (febrile illness, epilepsy syndromes, acquired CNS lesions, cerebrovascular diseases, metabolic)

Seizure development

- Seizure initiation
  - high frequency bursts of action potentials and hyper-synchronization
  - influx of extracellular Ca^{2+} → opening of voltage gated Na^{+} channels → influx of Na^{+} → generation of repetitive action potentials → hyperpolarizing after potential by GABA receptors or K^{+} channels
  - Synchronized bursts result in spike on EEG
- Seizure propagation
  - prevented by hyperpolarization and inhibitory neurons
  - Increased extracellular K^{+}, accumulation of Ca^{2+} in presynaptic terminals, NMDA receptor activation → Ca^{2+} influx, change in tissue osmolarity and cell swelling
  - Propagate via local connections or long commissural pathways

Evaluation for seizure

- Most patients who have seizures do not have epilepsy
- New onset seizures, breakthrough seizures in epilepsy, conditions mimic seizures
- Vital signs, oxygenation, stop seizure
- History, examination, diagnostic tests, imaging
- Therapy – antiepileptic for structural lesion or abnormal EEG

EEG limitation and value

- The absence of electrographic seizure activity does not exclude seizure disorder (focal)
- EEG is always abnormal during generalized tonic-clonic seizures
- Interictal EEG may be normal in epilepsy, interictal epileptiform activity consists of abnormal discharges (spikes, sharp waves)
- Classification of seizure and selection of antiepileptic therapy
- Assess prognosis of seizure disorder
- Video EEG, continuous EEG

Differential diagnoses of seizures

- Syncope
- Psychogenic seizures
- Hyperventilation
- Delirium tremens
- Psychoactive drugs
- Migraine
- Movement disorders

Treatment of seizures and epilepsy

- Treatment of underlying conditions
  - Metabolic disorder, drugs, CNS lesion
- Avoidance of precipitating factors
  - Sleep deprivation, alcohol
- Suppression of recurrent seizures
  - Antiepileptic drug, preferable single medication
  - Recurrent seizures of unknown etiology or known cause that cannot be reversed
  - (1) Abnormal neurology, (2) status epilepticus, (3) post ictal Todd's paralysis, (4) family history, (5) abnormal EEG
- Address psycho-social issues

Action of antiepileptic drugs

- Blocking initiation and spread of seizures
- Inhibition of Na^+ dependent action potentials (phenytoin, carbamazepine, lamotrigine, topiramate)
- Inhibition of voltage gated Ca^{2+} channels (phenytoin, gabapentin, pregabalin)
- Attentuation of glutamate activity (lamotrigine, topiramate)
- Potentiation of GABA receptors (benzodiazepines, barbiturates)
- Increase availability of GABA (valproate, gabapentin)
- Modulate release of synaptic vesicles (levetiracetam)

First line antiepileptic drugs

- Generalized tonic clonic seizures: Valproic acid (bone marrow suppression, hepatoxicity), lamotrigine (SJS), topiramate (psychomotor slowing, risk in glaucoma and renal stones)
- Focal seizures: Carbamazepine (leucopenia, hepatoxicity, skin reaction in Asian carrying HLA 1502), lamotrigine, phenytoin (saturation kinetics, hirsutism, gingival hypertrophy), levetiracetam
- Typical absence (Valproic acid, ethosuximide)
- Atypical absence, myoclonic, atonic (Valproic acid, lamotrigine, topiramate)
- Dose related side effects: sedation, ataxia, diplopia
- To minimize side effects start lowest dose, increase after 5 or more half lives (c.f. the priority on stopping seizure in attack)
- Serum drug levels measure total drug (free and protein bound), increased ratio of free to bound drug in low serum proteins (sub therapeutic drug level) and free drug adequate for seizure control

Adding and stopping therapy

- The goal of monotherapy
- Refractory epilepsy: multiple drugs, surgery, vagal nerve stimulation
- Favor seizure free after discontinue therapy: (1) complete seizure control for one to five years, (2) single seizure type, (3) normal neurology, (4) normal EEG
- Reduce dose over three months

Other issues

- Psychosocial and interictal (memory, attention)
- Employment, driving and other activities
- Mortality (2 to 3 times greater, SUDEP)
- Women and epilepsy
  - Catamenial epilepsy (estrogen and progesterone)
  - Pregnancy (seizure unchanged in 50%, PK, drug)
  - Fetal abnormalities (5 to 6 %, Valproic acid)
  - Contraception (decrease efficacy by CZ, PH, PB)
  - Breast feeding should be encouraged

Status epilepticus (SE)

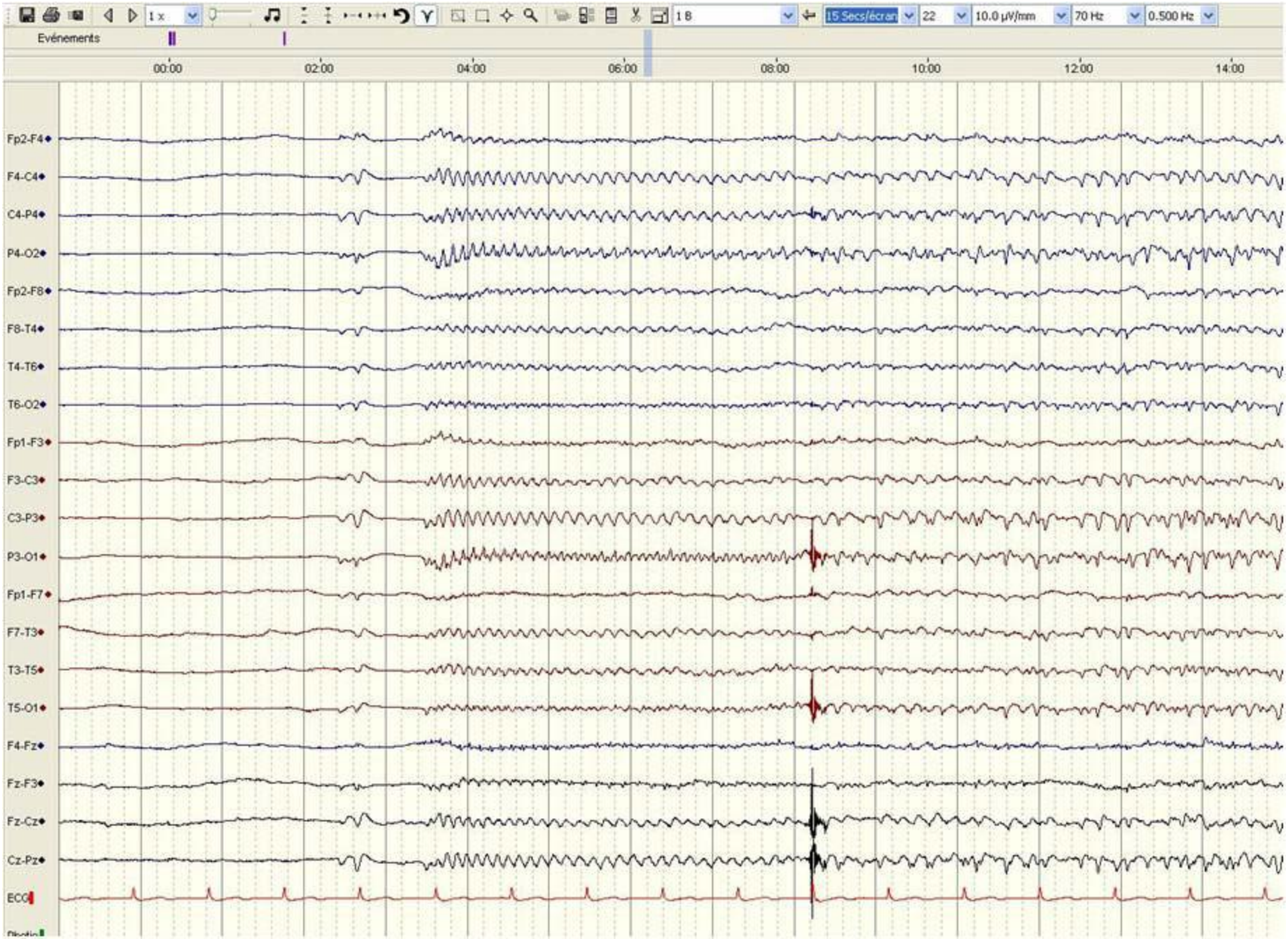
- Self sustaining within 15 to 30 min (animals)
- Distinct damages after 30 min of seizure
- Time dependent pharmacoresistance
- Delay in starting treatment → Prognosis

Definitions

- Established SE – continuous seizure lasting 30 min or intermittent seizures lasting 30 min during which consciousness is not regained
- Impending SE – continuous or intermittent seizures lasting more than 5 min, without full recovery of consciousness between seizures
- Subtle SE – motor and EEG expression become less florid in prolonged seizures, more subtle in encephalopathy
- Partially treated SE – continuation of electrographic seizure activity despite cessation of clinical seizure
- Refractory SE – seizures lasting more than 2 hours or failure to respond to first and second line antiepileptic drugs
- Malignant SE – RSE recur within 5 days after tapering of anesthetic

Generalized convulsive SE (GCSE)

- Generalized seizures last more than 5 min, and when two or more seizures occur during which the patient does not return to baseline consciousness
- Subtle physical manifestations, rhythmic nystagmoid eye movement, low amplitude twitches of one or more fingers, coma
- Resolution of suspicious EEG pattern after benzodiazepine may be diagnostic (caution)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1 8
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22
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Evénements
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02:00
04:00
06:00
08:00
10:00
12:00
14:00
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
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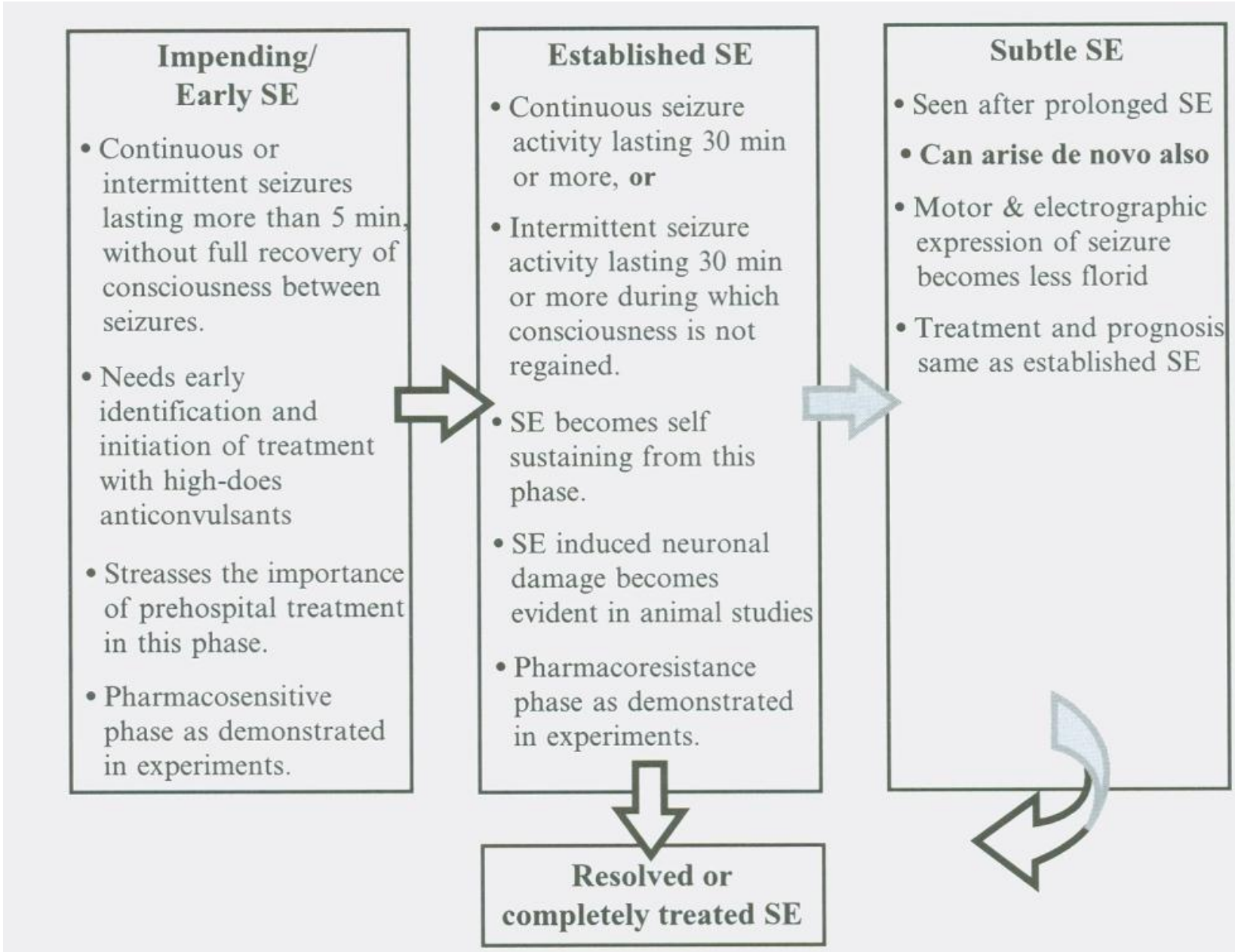
Fz-Cz
Cz-Pz
ECG


Impending/
Early SE
• Continuous or intermittent seizures lasting more than 5 min, without full recovery of consciousness between seizures.
• Needs early identification and initiation of treatment with high-does anticonvulsants
• Streasses the importance of prehospital treatment in this phase.
• Pharmacosensitive phase as demonstrated in experiments.
Established SE
• Continuous seizure activity lasting 30 min or more, or
• Intermittent seizure activity lasting 30 min or more during which consciousness is not regained.
• SE becomes self sustaining from this phase.
• SE induced neuronal damage becomes evident in animal studies
• Pharmacoresistance phase as demonstrated in experiments.
Subtle SE
• Seen after prolonged SE
• Can arise de novo also
• Motor & electrographic expression of seizure becomes less florid
• Treatment and prognosis same as established SE
Resolved or completely treated SE

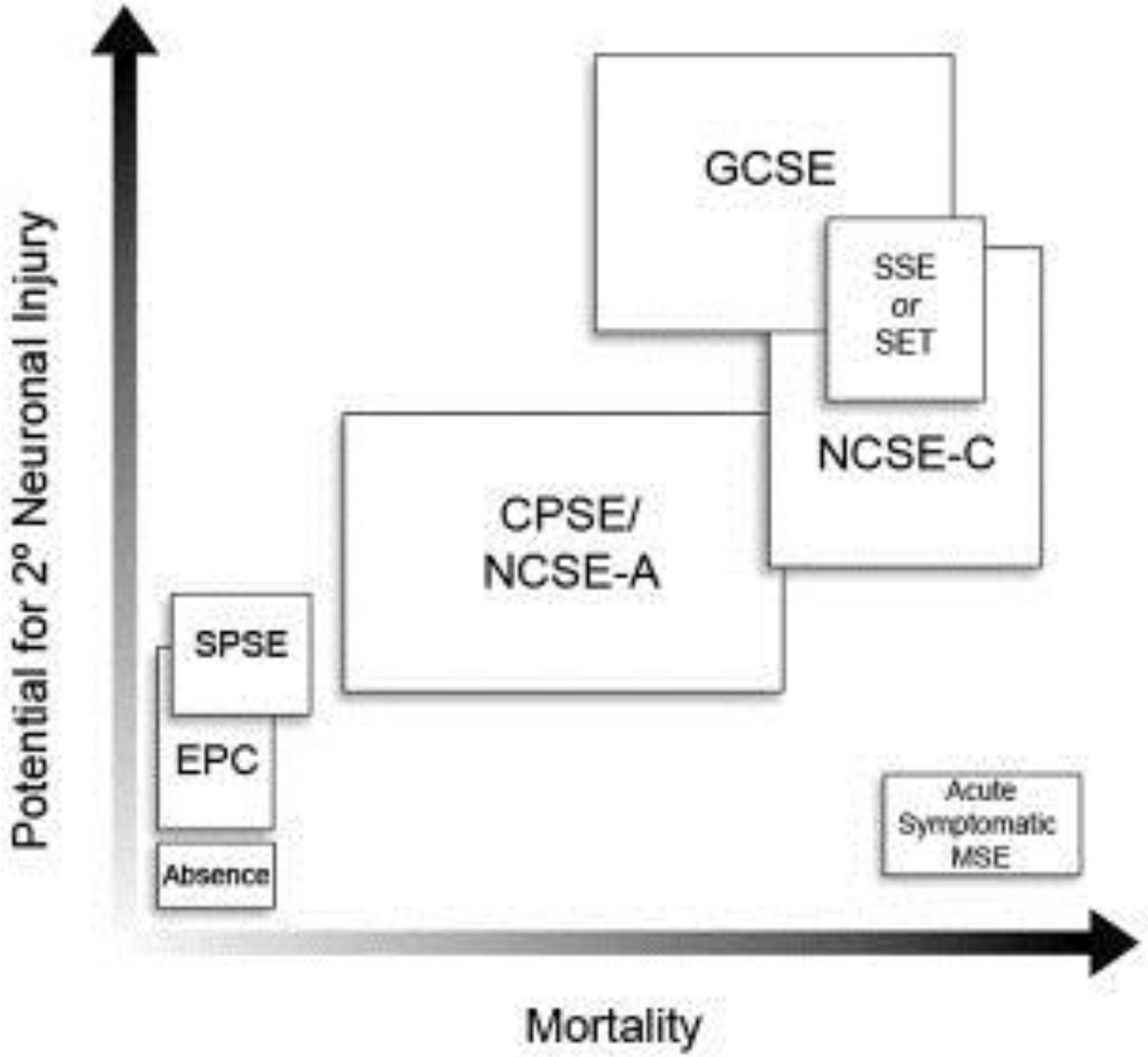
ILAE Classification of SE

Generalized

- Convulsive
  - Tonic-clonic
  - Tonic
  - Clonic
  - Myoclonic
- Nonconvulsive
  - Absence
- Unilateral
- Non-classifiable

Focal

- Simple
  - Elementary
  - Motor
  - Sensory
  - Somatosensory
  - Dysphasic
  - Epilepsia partialis continua
- Complex


Potential for 2º Neuronal Injury
GCSE
SSE
or
SET
NCSE-C
CPSE/
NCSE-A
SPSE
EPC
Absence
Acute
Symptomatic
MSE
Mortality

Status Epilepticus Severity Score (STESS)

	Features	STESS
Consciousness	Alert or confused	0
	Stuporous or comatose	1
Worst seizure type	Simple partial, complex partial, idiopathic	0
	Generalized convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History	Yes	0
	No or unknown	1
Total		0 – 6

STESS on treatment strategy

	Alive	Dead	P
Score 0 – 2	72 (97%)	2 (3%)	
Coma induction –	61	2	
Coma induction +	11	0	1.000
Score 3 - 6	49 (61%)	31 (39%)	
Coma induction –	34	18	
Coma induction +	15	13	0.301
Total	121	33	154

Epidemiology of SE

- Incidence and recurrence age specific, highest in the young (less than 1 year old) and elderly
- Initial seizure focal in 2/3 of cases and major final form as generalized tonic clonic SE
- (Subtle) Continuation of electrographic seizure in up to 1/3 of cases
- Refractory in 1/3 of cases, increased hospital LOS and disability
- RSE recur within 5 days of tapering anesthetic in 1/3 of cases

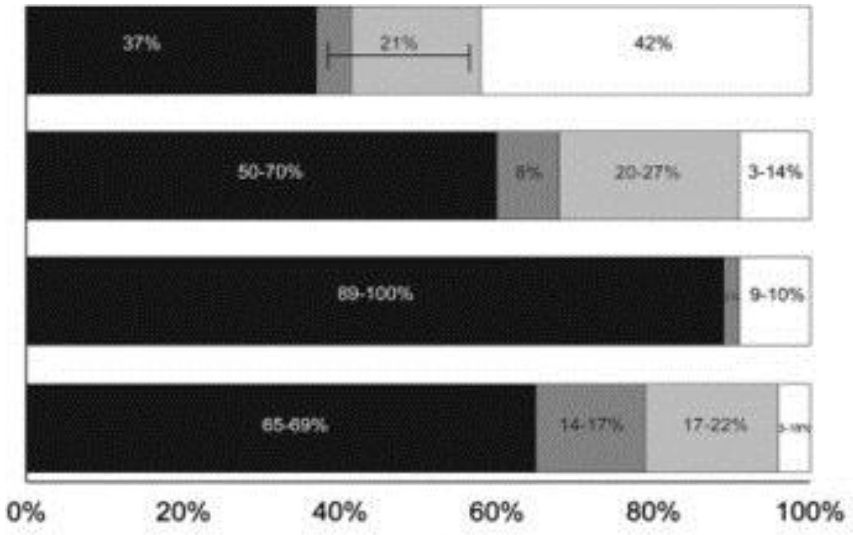
Causes of SE

Children

- Infection and fever
- Remote symptomatic cause
- Low antiepileptic drug level
- Cerebrovascular accident
- Metabolic
- Idiopathic
- Hypoxia
- CNS infection
- Drug overdose
- Trauma
- Tumor

Adults

- Low antiepileptic drug level
- Remote cause (e.g. stroke)
- Cerebrovascular accident
- Metabolic (↓Na, renal, liver)
- Hypoxia
- Alcohol withdrawal
- Tumor
- Systemic infection and fever
- Trauma
- Drug overdose (e.g. cocaine)
- CNS infection



Acute Symptomatic

- TBI
- Ischemic Stroke
- Hemorrhage (SDH, ICH, or SAH)
- Venous Sinus Thrombosis
- CNS Infection (>50% are unidentified)
- CNS Tumor (Initial Presentation)
- Post-Neurosurgical
- Toxic (i.e. environmental, illicit substances, and medications)*
- Alcohol Withdrawal or Intoxication
- Eclampsia
- Metabolic (i.e. sepsis, liver failure, renal failure, hyperglycemia, low Na, PO4, glucose, Mg, Ca, or osmolality)
- Low AED Levels
- Miscellaneous (i.e hypertensive encephalopathy or PRES, pyridoxine deficiency 2/2 pregnancy or INH, or TTP)

Progressive Symptomatic

- CNS Tumor (Incompletely or Unsuccessfully Treated)
- Chronic Infection (i.e. CJD, SSPE, HIV, or Neurosyphilis)
- Autoimmune Paraneoplastic (i.e. anti-NMDA, anti-VGKC, anti-GAD, and other anti-neuronal antibody syndromes)
- Autoimmune Inflammatory (i.e. Hashimoto's, Lupus Cerebritis, Neurosarcoidosis, MS, ADEM, or Rasmussen's encephalitis)
- Metabolic (i.e. mitochondrial disorders, porphyria)
- Degenerative (i.e. Alzheimer Disease)

Remote Symptomatic

- TBI
- Ischemic Stroke
- CNS Infection
- Pre- and Perinatal Risk Factors
- Alcohol, not acutely withdrawing or intoxicated
- Benign/Static CNS Tumor
- ICH

Idiopathic or Epilepsy

- Cortical dysplasia
- Genetic epilepsy syndromes

Medications that lower seizure threshold

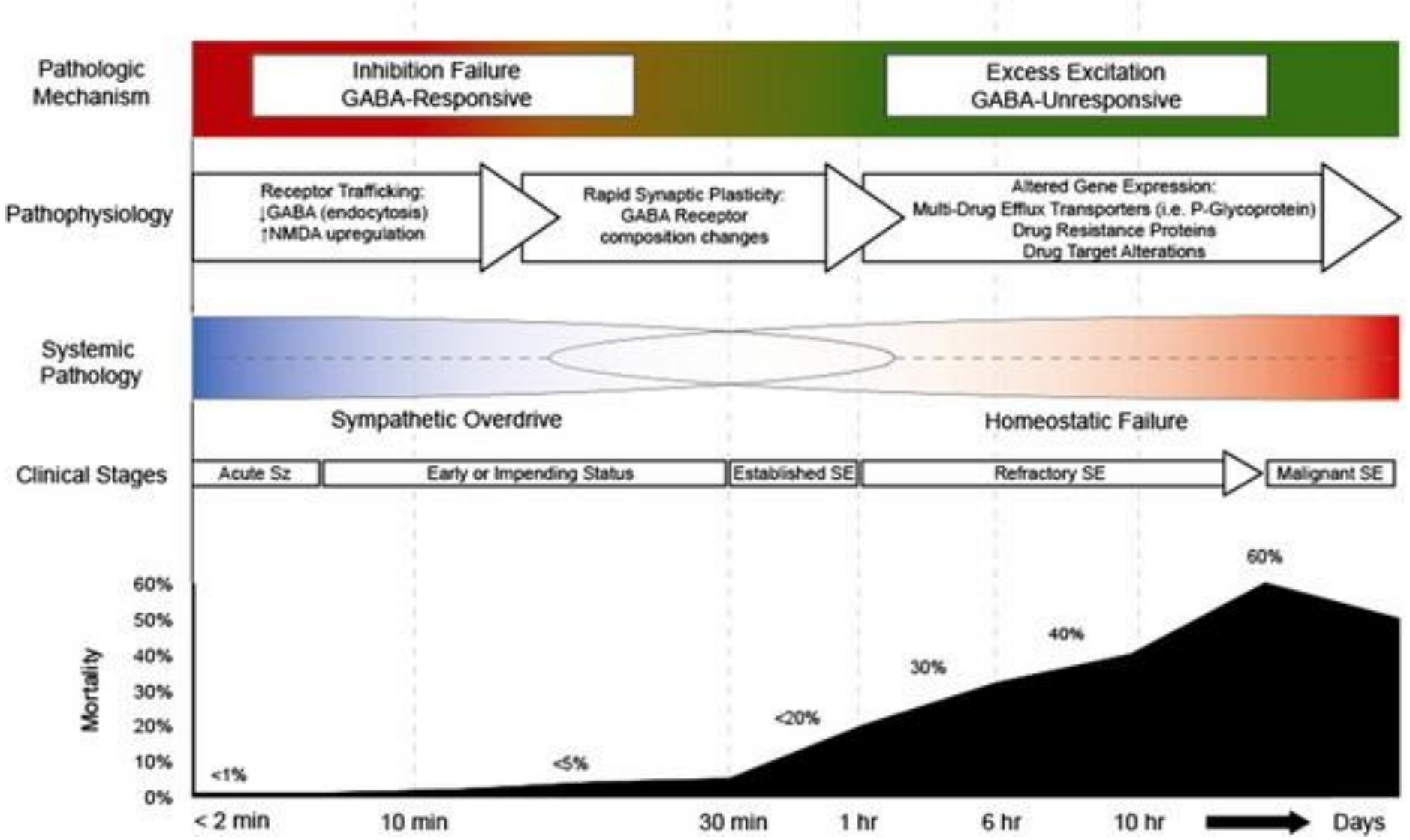
- Analgesics: meperidine, fentanyl, tramadol
- Antiarrhythmics: mexiletine, lidocaine, digoxin
- Antibiotics: β-lactams (benzylpenicillin, cefazolin, imipenem)
- Antidepressants: bupropion
- Antiepileptic drugs: phenytoin at supratherapeutic levels
- Baclofen
- Calcineurin inhibitors: cyclosporine, tacrolimus
- Alkylating agents: chlorambucin, busulfan
- Neuroleptics: clozapine, phenothiazines
- Lithium
- B-interferon, α-interferon
- Radiographic contrast agents (intrathecal and IV)
- Theophylline
- Withdrawal: opiates, alcohol, antiepileptic drugs

Investigations

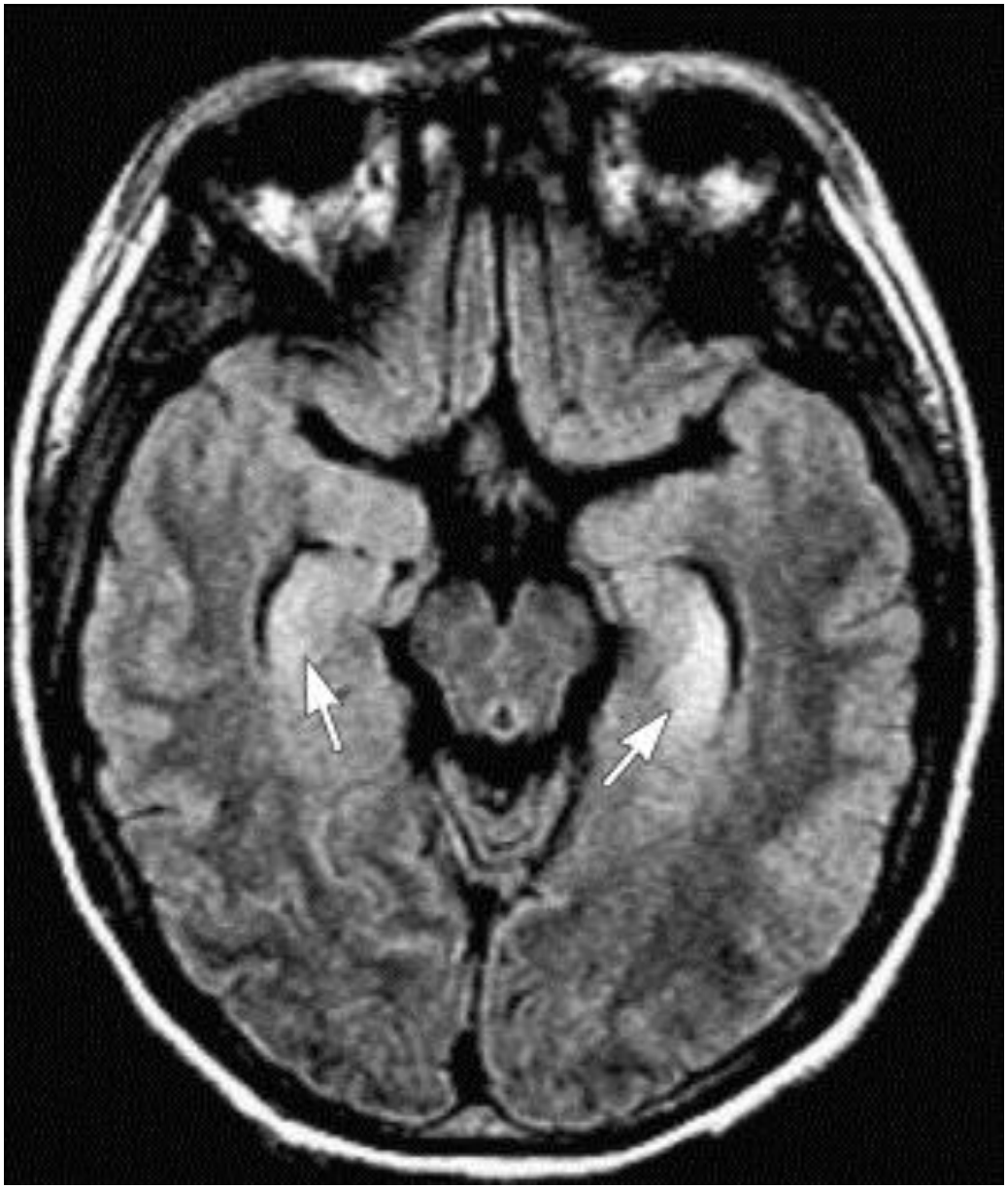
- Diagnosis of SE is often clinical
- Investigations done to find etiology, define type of SE, differentiate from other conditions
- Brain imaging, lumbar puncture
- Assessment should not delay treatment
- Less than half of patients receive treatment before 30 min

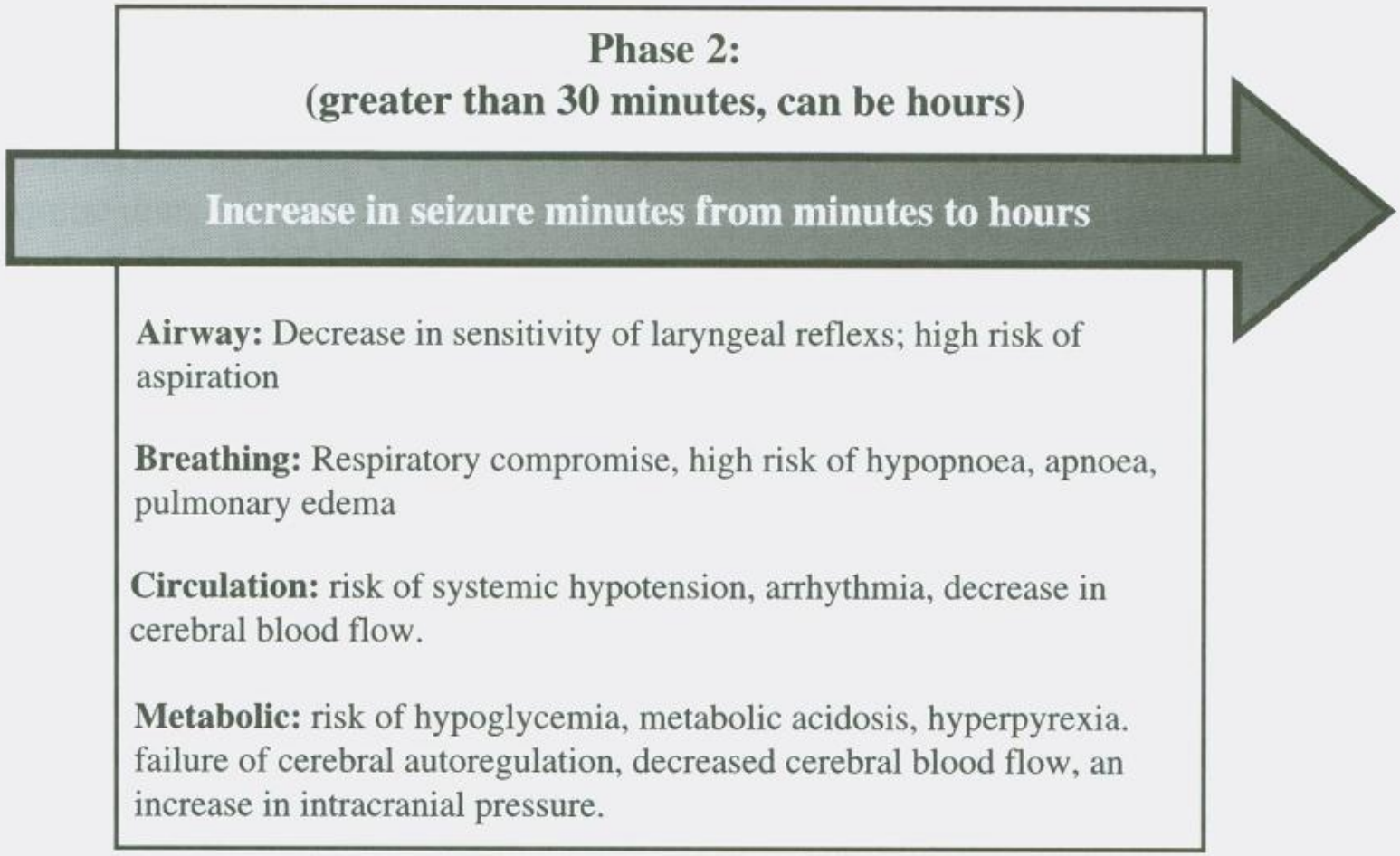
Pathophysiology

- From isolated seizure to SE
  - Lower seizure threshold, failure in inhibitory mechanisms, excessive excitation (glutamate)
- Time dependent pharmacoresistance
  - Decreased potency of benzodiazepine by 20 min
- Seizure induced neuronal injury and death
  - Mitochondrial dysfunction, apoptosis, increased neuron specific enolase (neurone death marker)


Pathologic Mechanism
Inhibition Failure
GABA-Responsive
Excess Excitation
GABA-Unresponsive
Pathophysiology
Receptor Trafficking:
↓GABA (endocytosis)
↑NMDA upregulation
Rapid Synaptic Plasticity:
GABA Receptor
composition changes
Altered Gene Expression:
Multi-Drug Efflux Transporters (i.e. P-Glycoprotein)
Drug Resistance Proteins
Drug Target Alterations
Systemic Pathology
Sympathetic Overdrive
Homeostatic Failure
Clinical Stages
Acute Sz
Early or Impending Status
Established SE
Refractory SE
Malignant SE
Mortality
60%
50%
40%
30%
20%
10%
0%
<1%
<5%
<20%
30%
40%
60%
< 2 min
10 min
30 min
1 hr
6 hr
10 hr
Days

Mesial temporal hyperintense signal on MRI FLAIR in GCSE




Phase 2:
(greater than 30 minutes, can be hours)
Increase in seizure minutes from minutes to hours
Airway: Decrease in sensitivity of laryngeal reflexs; high risk of aspiration
Breathing: Respiratory compromise, high risk of hypopnoea, apnoea, pulmonary edema
Circulation: risk of systemic hypotension, arrhythmia, decrease in cerebral blood flow.
Metabolic: risk of hypoglycemia, metabolic acidosis, hyperpyrexia. failure of cerebral autoregulation, decreased cerebral blood flow, an increase in intracranial pressure.

Complications of SE

- Cardiovascular
  - Arrhythmia, CHF, ↑/↓BP
- Respiratory
  - Apnea, laryngeal spasm, aspiration, APO, ARDS, PE
- CNS
  - Brain edema, hypoxia, hemorrhage
- Metabolic
  - Metabolic acidosis, ↑K, ↓Na, ↑/↓glucose
- Renal
  - Rhabdomyolysis, ARF
- Endocrine
  - ↑prolactin, cortisol, vasopressin, ↓weight
- Miscellaneous
  - Hyperthermia
  - DIC, dysautonomia, loss of intestinal motility, MODS, fractures

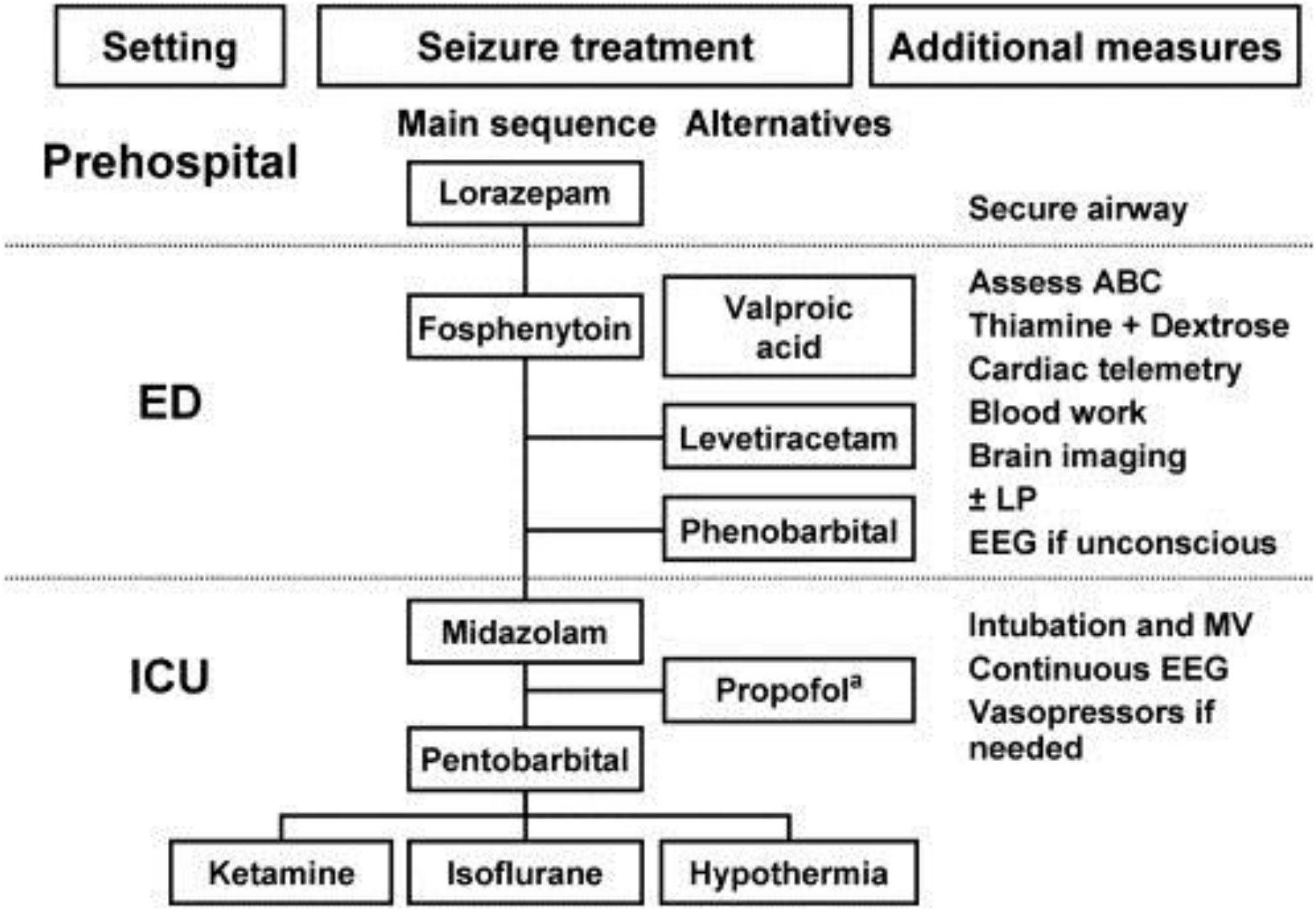
Management of SE

- Pre-hospital
  - Early treatment improve seizure control and outcome
  - Lorazepam has longer duration of action
- Acute setting
  - Airway, ABG, ECG, SBP >120mmHg, CPP>60mmHg
  - Hypoxia and respiratory acidosis → Intubation
  - Mannitol, glucose, thiamine
  - Correct underlying cause, prevent recurrence
- ICU

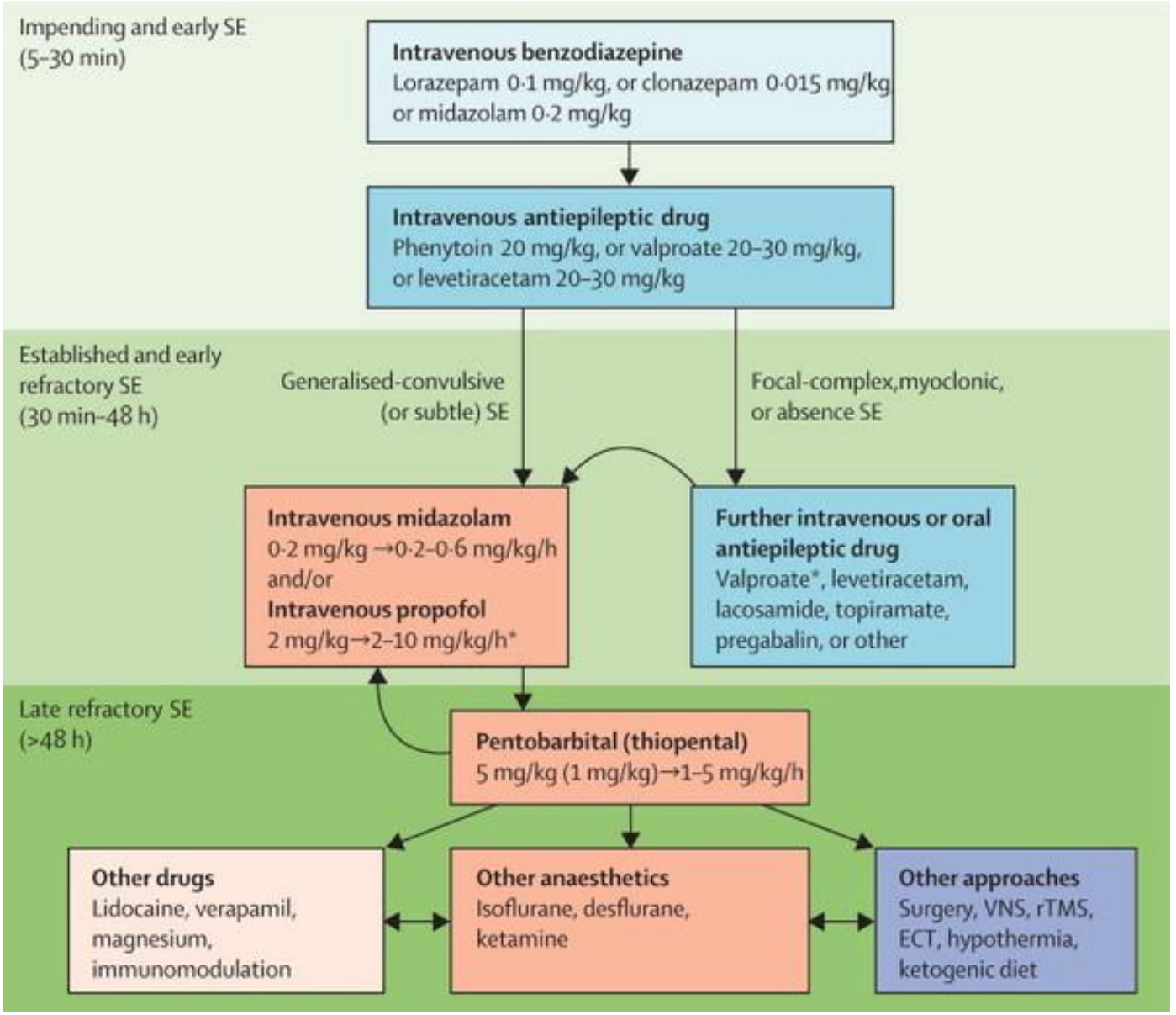
Pharmacotherapy of SE

- Rapid use of effective drugs in adequate doses
- The most effective antiepileptic is the first one given
- IV benzodiazepines enhance GABA inhibition of repetitive neuronal firing, response 79%
- 2nd line: Phenytoin and valproic acid
- 3rd line: Barbiturates, propofol
- Magnesium for seizures due to eclampsia (5g MgSO4 iv over 30 min follow by continuous iv 1g/hr, target serum Mg 1.7 to 3.0 mmol/L)
- Isoflurane, levetiracetam, topiramate
- Clonazepam for myoclonus following hypoxia

Treatment algorithm



Treatment algorithm



Drug	Mechanism	Loading dose	Infusion rate	Side effects
Lorazepam	GABA agonist	0.1mg/kg	2mg/min	Sedation, respiratory depression
Diazepam	GABA agonist	0.2mg/kg	5mg/min	Sedation, respiratory depression
Phenytoin	Prolong recovery of Na channels	20mg/kg	50mg/min	Hypotension,, arrhythmia, soft tissue necrosis
Valproic acid	Act on Na and Ca channels, GABA receptor	25-45mg/kg	Up to 6mg/kg/min	Hypermmonemia , dose related thrombocytopenia, cytochrome P450 inhibitor
Levetiracetam	Synaptic vesicle ligand SV2A inhibits Ca channel current	20mg/kg	Over 15 min	Renal clearance, sedation, thrombocytopenia, LFT
Phenobarbital	Modulate GABA receptor	15-20mg/kg	100mg/min	Hypotension, respiratory depression
Midazolam	Modulate GABA receptor	0.2mg/kg	0.2 to 5mg/kg/hr	Sedation, hypotension, respiratory depression, tachyphylaxis
Propofol	Modulate GABA receptor, act on Na and Ca channels and NMDA receptor	2mg/kg	2-10mg/kg/hr	Sedation, hypotension, respiratory depression, infusion syndrome
Pentobarbital / Thiopental	Modulate GABA (different receptor isoform), NMDA receptor antagonist	5-10mg/kg 1-2mg/kg	1-5mg/kg/hr 1-5mg/kg/hr	Sedation, hypotension, respiratory & myocardial depression, ileus, liver dysfunction, infection

Refractory SE (RSE)

- Associated with acute potentially fatal causes (e.g. encephalitis, stroke)
- Electrographic seizure activity present in up to half of patients after cessation of clinical GCSE
- Treatment failure in continuous iv: Midazolam 21%, Propofol 20%, Pentobarbital 3%
- Treatment is not evidence based. Intense metabolic and electrical suppression may reduce seizure recurrence. Anesthetic therapy plus cEEG monitoring in ICU is probably the strategy
- Maintain seizure suppression for 12 to 24 hours plus adequate serum level anticonvulsants before tapering of anesthetic agent over 6 to 24 hours on cEEG monitor

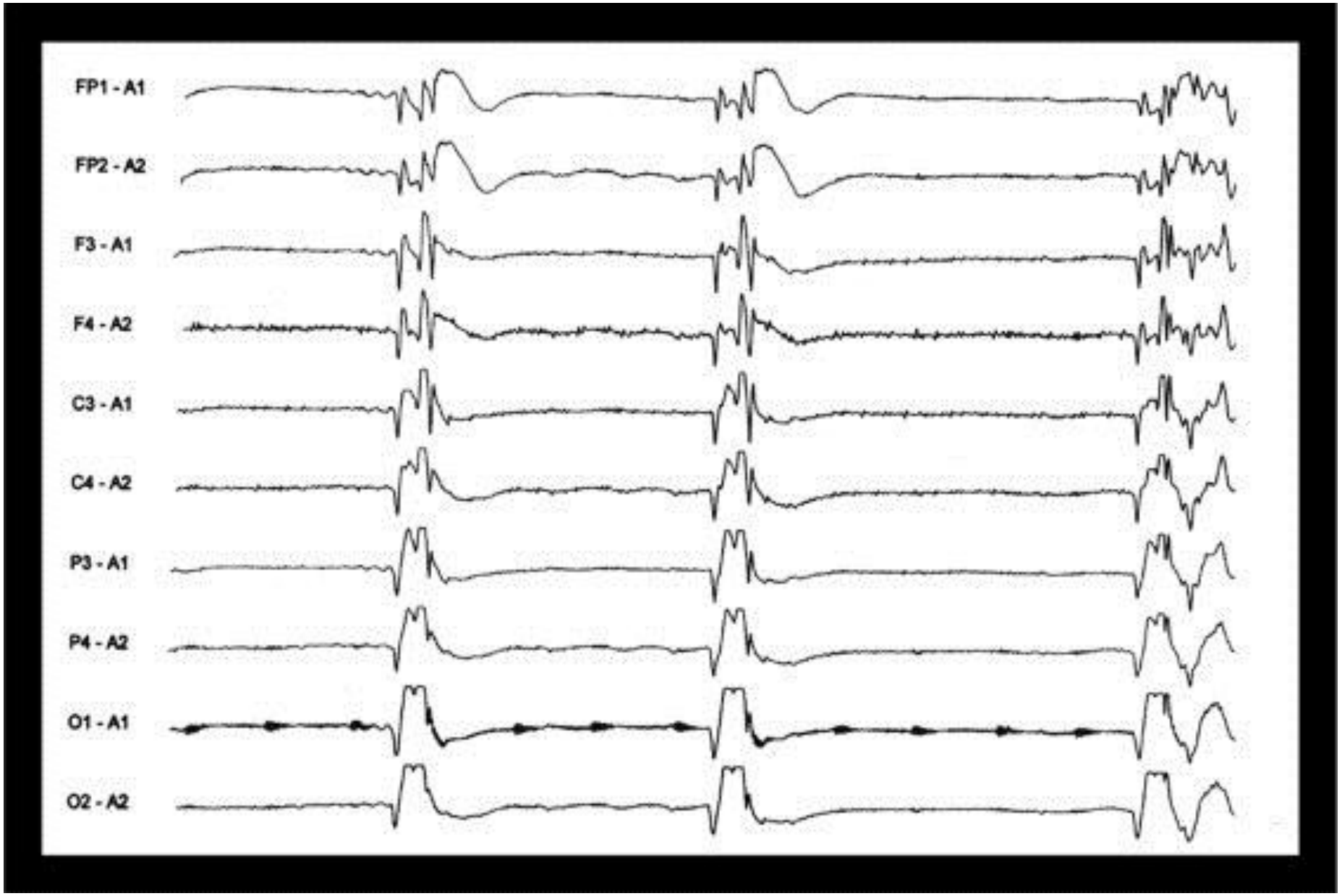
Choice of anesthetic for RSE

Drug	Mechanism	Half life	Advantage	Disadvantage
Midazolam	Modulation of GABA receptor	Short, 6-50 hr after prolonged administration	Combination with Propofol, safest profile. (↓hypotension c.f. thiopental)	Tachyphylaxis
Propofol	Modulation of GABA receptor, Na, Ca channel, NMDA receptor	Short. Avoid >5mg/kg/hr for over 48 hours	Rapid titration and withdrawal (Reduce IPPV c.f. thiopental)	Impairment of mitochondrial activity, use free fatty acid
Thiopental (metabolite of pentobarbital)	Modulation of GABA receptor, NMDA receptor antagonist	Long, up to 36 hr, accumulate in fat tissue	Complete cerebral suppression (Achieve more burst suppression c.f. Propofol)	Long elimination time

EEG target

- Uncertainty on targets for seizure suppression, burst suppression or flat recording
- Uncertainty on optimal length and tapering of anesthetic treatment
- For midazolam, target EEG burst suppression with inter-burst interval about 10 seconds for 24 hours
- In critically ill comatose patients, recommend cEEG for 48 hours to look for nonconvulsive seizure or SE
- Regard lateralized periodic discharge as ictal interictal continuum associated with nonconvulsive seizure or SE, cEEG for 48 hours and give non-sedating antiepileptic drug for period of acute illness
- Difficult to differentiate between drug induced burst suppression and seizure suppression by automated amplitude integrated measure of 2-channel EEG (bispectral index)

EEG burst suppression



Other pharmacological approach

Drug	Advantage	Disadvantage
Isoflurane	In part on GABA receptor, fast acting, 1.2-5%	Gas delivery system, possible neurotoxicity
Ketamine	NMDA receptor antagonist, up to 7.5mg/kg	Possible neurotoxicity, use with benzodiazepines
Lidocaine	Act on Na channel, bolus up to 5mg/kg, iv 6mg/kg/h	Cardiac monitoring, possible seizure induction
Magnesium	↑NMDA receptor blockade, stabilize endothelium	Possible induction of neuromuscular blockade
Levetiracetam Lacosamide	SV2A inhibit Ca channel ↑ inactivation Na channel	Thrombocytopenia, LFT PR interval prolongation
Ketogenic diet	Action through metabolic acidosis (e.g. Ketocal 4:1)	Refer dietitan, ketonuria and hypoglycemia
Immunological therapy (corticosteroid, PE, IVIG)	RSE immunological process	Exclude infection before treatment

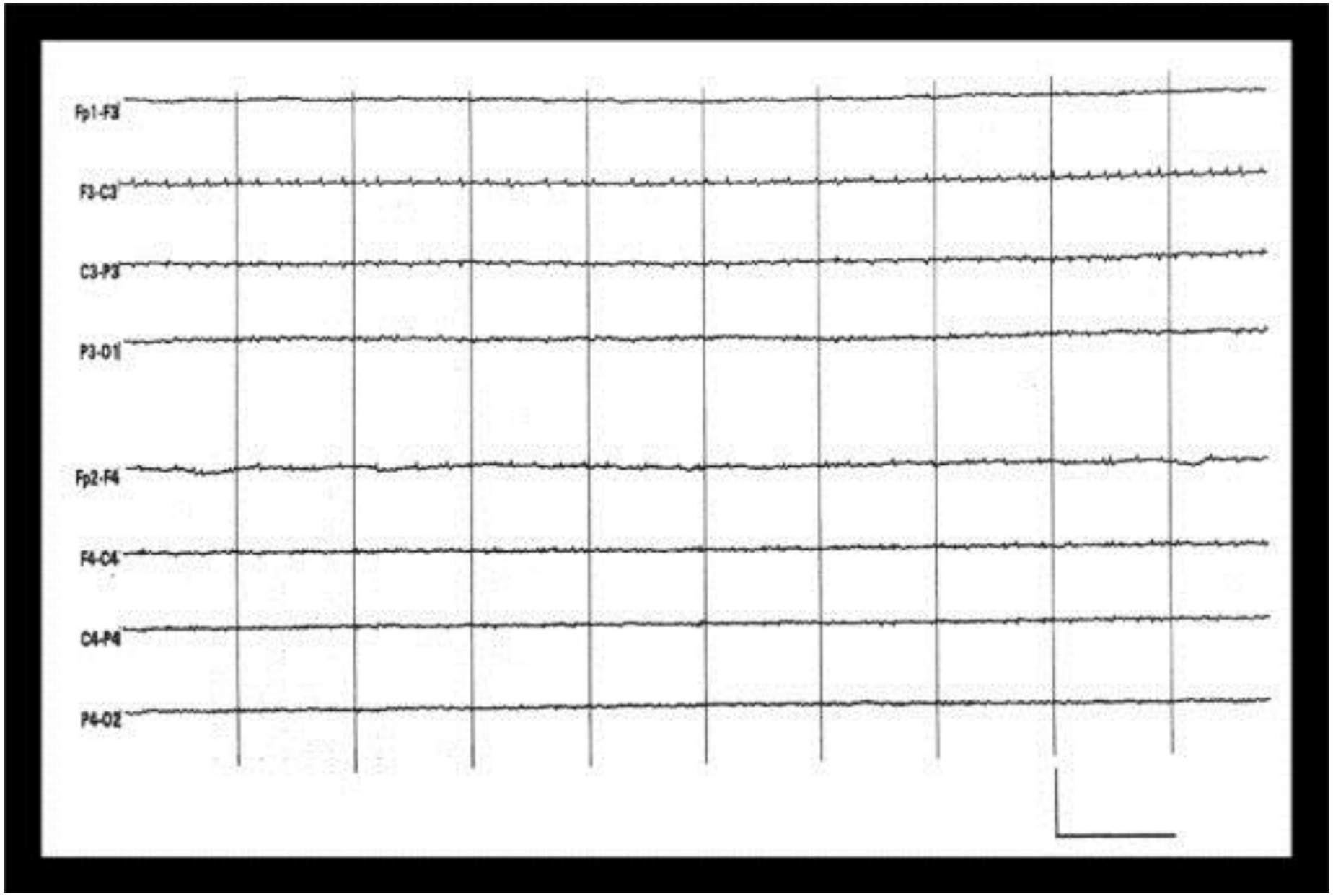
Non-pharmacological approach

Therapy	Advantage	Disadvantage
Resective surgery	Definite seizure focal in non-eloquent brain area	Not for multifocal SE, surgical risk
Vagal nerve stimulation	Progressive titration up to 1.25mA	Transient bradycardia or asystole
Repetitive transcranial magnetic stimulation	Non-invasive, 0.5-1Hz, may apply after high frequency	Possible seizure induction, need repetitive treatment
Electroconvulsive therapy	Induce signal pathway, ↑refractory period, 1-4 daily	Possible seizure induction
Therapeutic hypothermia	Reduce epileptic discharge, 31-36^{o}C, plus midazolam	Ileus, avoid barbiturates, seizure recur in rewarming
Classical music	Unknown mechanism	Reported in few patients

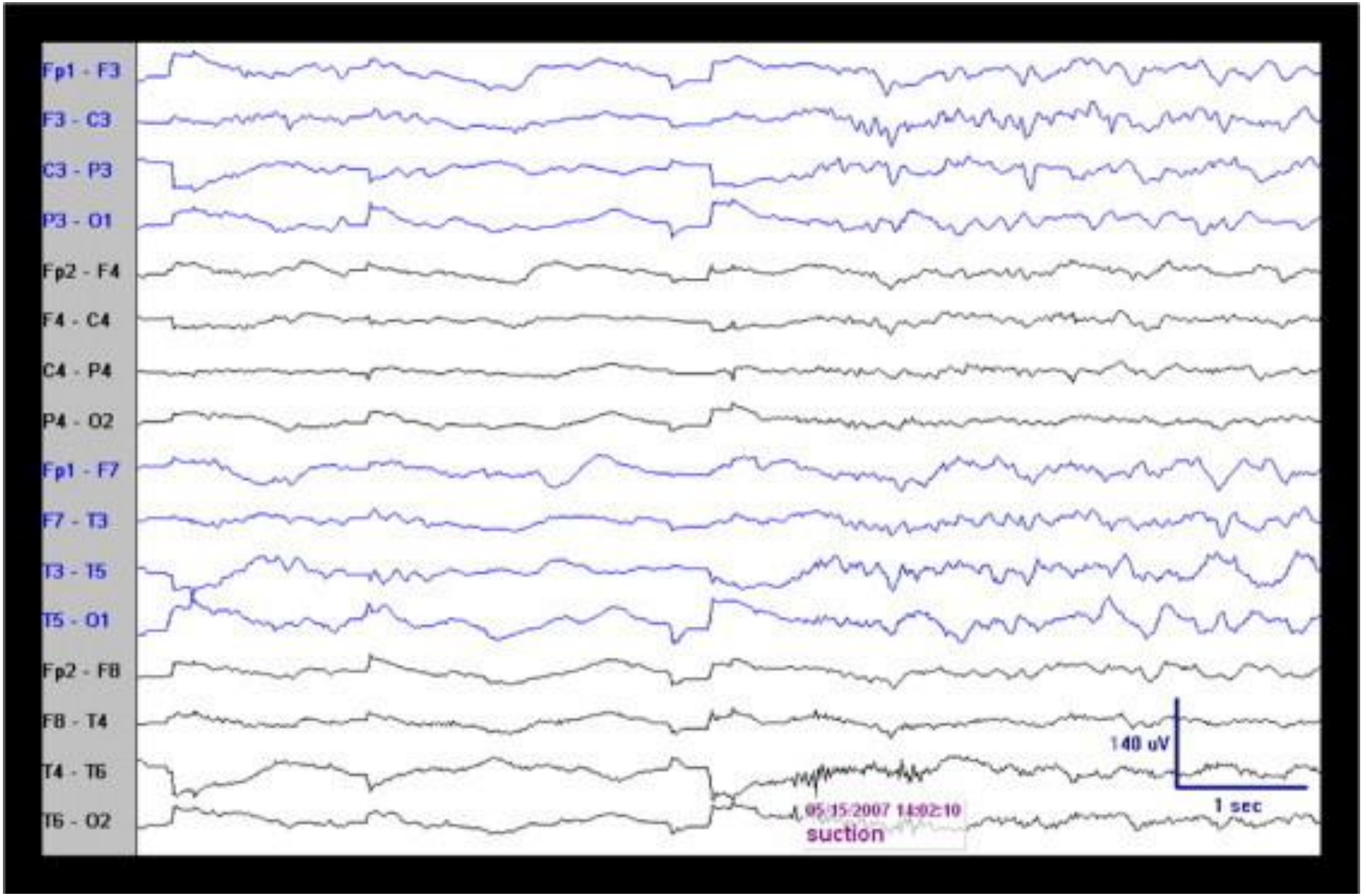
Prognosis

- Mortality of SE 11% to 34%, higher in adults and often related to anoxia, stroke, metabolic abnormality, brain tumor or head injury, mortality of refractory SE 50% or 3 times SE
- Outcome prediction variables include (1) etiology, (2) time from SE onset to treatment, (3) seizure duration, (4) age, (5) response to early treatment
- Cerebral anoxia SE (burst suppression EEG) or non-reactivity during therapeutic hypothermia suggest severe brain damage and poor outcome
- Morbidity: SE recurrence, epilepsy (41%), seizure risk ↑3 times, cognitive impairment, return to baseline function after refractory GCSE (21%), long term care (10%)

EEG non-reactivity



EEG reactivity on stimulation (e.g. pharyngeal suction)



Reminders

- Status epilepticus is the 2nd most frequent neurologic emergency (1st: acute stroke)
- Seizures lasting for more than a few minutes should be treated immediately, especially GCSE
- More conservative approach for nonconvulsive SE with preserved consciousness
- Negative predictive value of STESS on treatment strategy based on age, seizure type, consciousness impairment, previous seizure
- Avoid complications of over treatment in mimics, e.g. movement disorders, clonus in spasticity, shivering, psychogenic (serum lactate, prolactin, CK)
- Patients with RSE may recover with good functional outcome, continue supportive treatment if neuroimaging is relatively normal in young patients, even if prolonged intensive care is required

Question

- A 22 years old woman was admitted into medical ward for dizziness and headache. She has enjoyed good past health and work as a clerk. There was no recent travel or contact history. After admission she was noted to be confused and displayed limb twitching. Two doses of diazepam 5mg IV and one dose of phenytoin 1000mg IV have been given. Limb twitching has decreased but the patient remained unconscious. ICU was consulted.
- (1) What was the patient suffering from? (2) What are the possible common causes in this patient? (3) How will you manage this patient? (4) What is drug treatment strategy? (5) What are the possible complications that will occur in this patient? (6) All initial work up were negative, what diagnosis should be excluded in this patient and how?

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