Update on Super-Refractory Status Epilepticus

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Outline

- Case Presentation
- Definition
- Super-Refractory Status Epilepticus(SRSE)
- c-EEG monitoring
- Pharmacological Management
- Other Treatment Modalities
- Algorithm
- Key Points

Case Presentation

5 year old previously well little girl who presented to base with new onset generalized seizures

Normal acquisition of development milestones

History of preceding febrile illness at 4 years of age

Normal electrolytes, LP, metabolic screen

Admitted to ICU for management of Status Epilepticus

Progress

Diagnosis: Super-refractory Status epilepticus

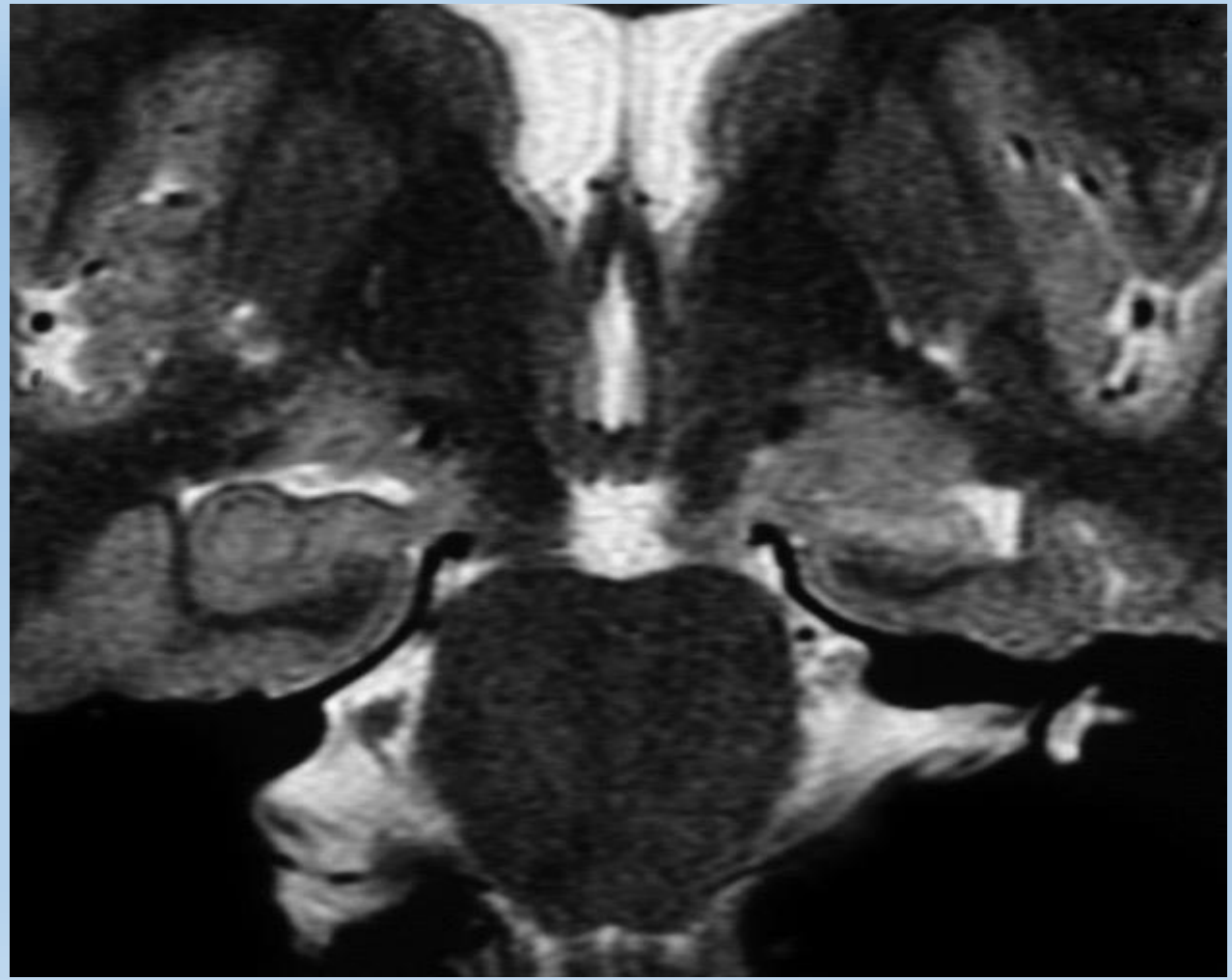
Medications

- Midazolam
- Thiopentone

Maintenance AEDS:

- Sodium Valproate/Topiramate
- Phenytoin/Levetiracetam/Oxcarbazepine/Vigabatrin
- Other modalities: Steroids, IVIG
- Ketogenic diet

MRI brain



Progress of Case

Assessment:

- Febrile infection related epilepsy syndrome (FIRES)

Sequelae:

- Tracheostomy
- Pseudobulbar palsy: NGT Feeds
- Minor seizures
- Global regression with visual impairment

Definition

Status Epilepticus

- "Epileptic seizure sufficiently **prolonged or repeated** at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition."
- t1 5mins and t2 30mins

Refractory status epilepticus

- Seizure activity that persists despite the use of an initial benzodiazepine and a second appropriate antiepileptic medication

Super Refractory SE

- SE that has continued or recurred despite 24 h of general anesthesia (*Shorvon & Ferlisi, 2011).*

Clinical Stages of Status Epilepticus

Stage	Duration
Premonitory	Confusion, Myoclonus
Incipient	0-5mins
Early	5-30mins
Established	30-60mins
Refractory	>60mins
Supra refractory	>24hour

Status Epilepticus and Refractory Status Epilepticus Management Sem Paed Neur 2015

Epidemiology

- Incidence of SE
  - 17–23 episodes per 100,000 children,
  - 10% and 40% develop RSE
  - 10 -25% of children will have 1 episode of SE
  - *Chin RF et al Lancet 2006*
- Kenyan study
  - 28-46 per 100000 per year
  - *Sadarangani et al Lancet Neurology 2008*

Seizure 51 (2017) 55–60

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Convulsive status epilepticus in a quaternary hospital paediatric intensive care unit (PICU) in South Africa: An 8 year review

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Table 2
Aetiology (n = 76).

Aetiology (n = 76)	n[%]
Acute Symptomatic	**65 (86)**
Infections	*40 (61)*
Gastroenteritis with metabolic derangements	*19 (29)*
Trauma related	*3 (5)*
Tumours	*2 (3)*
Intracerebral haematoma	*1 (2)*
Remote Symptomatic	**6 (8)**
Idiopathic Epilepsy Related	**1 (1)**
Prolonged Febrile	**3 (4)**
Unclassified	**1 (1)**

Table 3
Infectious Aetiology Subgroup (n = 40).

Infectious Aetiology Subgroup (n = 40)	n [%]
Presumed viral encephalitis	18 (45)
Bacterial/Viral meningitis	10 (25)
Tuberculosis meningitis	5 (13)
Malaria	2 (5)
Sepsis	4 (10)
HIV Vasculitis	1 (2)

SRSE Aetiology

- Categories
  - New onset RSE (NORSE)
  - With pre-existing epilepsy or neurological d/o

Etiologies and characteristics of refractory status epilepticus cases in different areas of the world: Results from a global audit
Monica Ferlisi1 | Sara Hocker2 | Eugen Trinka3 | Simon Shorvon4 | on behalf of the
International Steering Committee of the StEp Audit*, Epilepssia 2018

Unknown/cryptogenic	Other toxins
Vascular	Metabolic
Anoxic	Tumor
Trauma	ASM withdrawal
Infection (all)	Genetic
Encephalitis	Miscellaneous
Meningitis	Mitochondrial
Immunological	

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	Asia n %	**Europe n %**	**Americas n %**
Unknown/cryptogenic	50 (25.5)	98 (21.6)	34 (22.8)
Vascular	11 (5.6)	75 (16.6)	17 (11.4)
Anoxic	13 (11)	51 (16.6)	17 (17.4)
Trauma	1 (0.5)	28 (6.2)	7 (4.7)
Infection (all)	59 (30.6)	56 (12.3)	23 (15.4)
Encephalitis	41 (20.9)	26 (5.7)	7 (4.7)
Meningitis	6 (3.1)	9 (2)	3 (2)

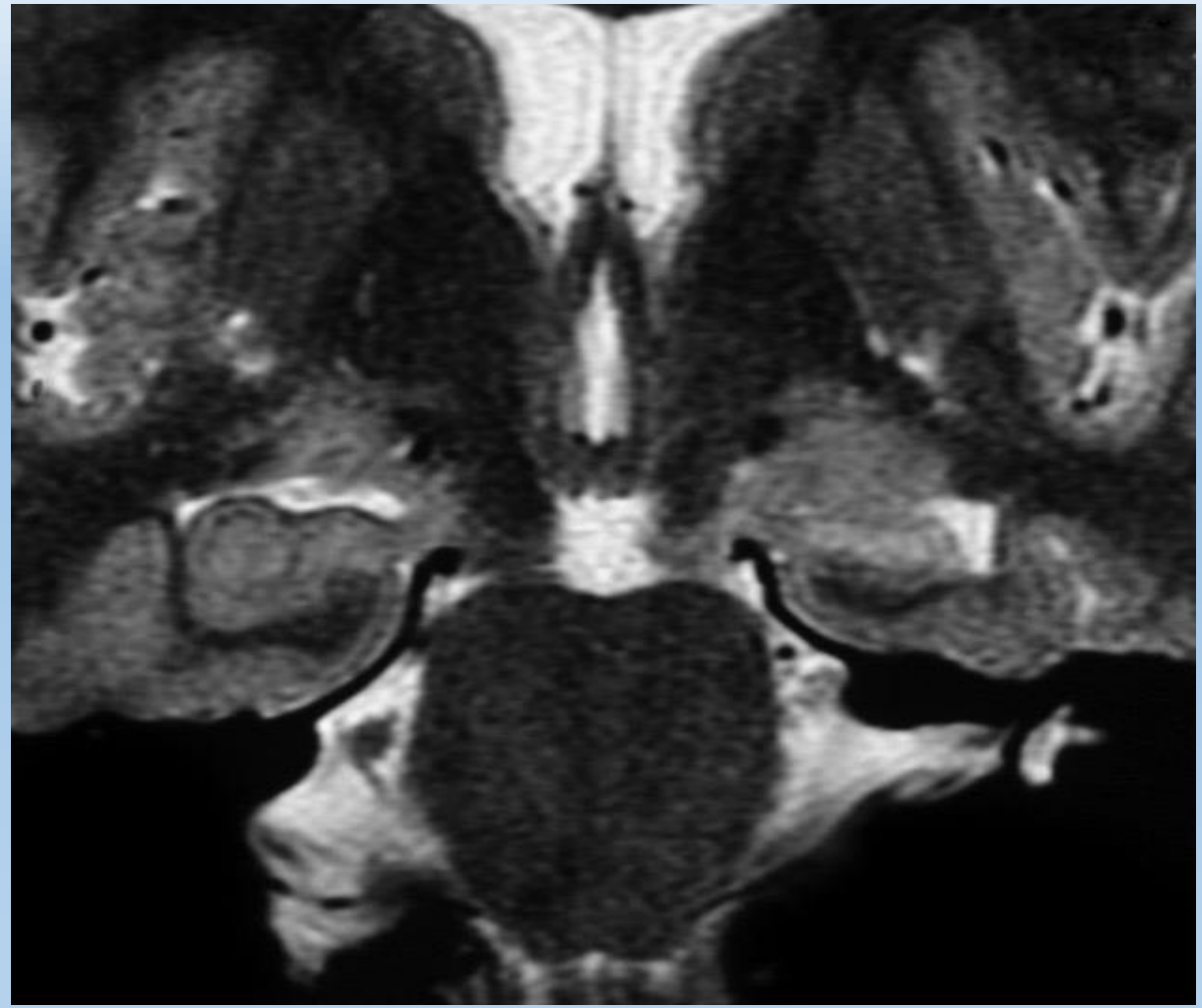
Specific Entities

NORSE

- Clinical presentation without epilepsy or a relevant pre-existing neurological disorder
- who present with RSE without an identifiable acute cause or active structural, toxic or metabolic cause
- It is a **clinical presentation** and not a specific diagnosis
- Elevated levels of pro-convulsant cytokines (e.g interleukin-6) have been documented in the CSF

Febrile Infection-Related Epilepsy Syndrome (FIRES)

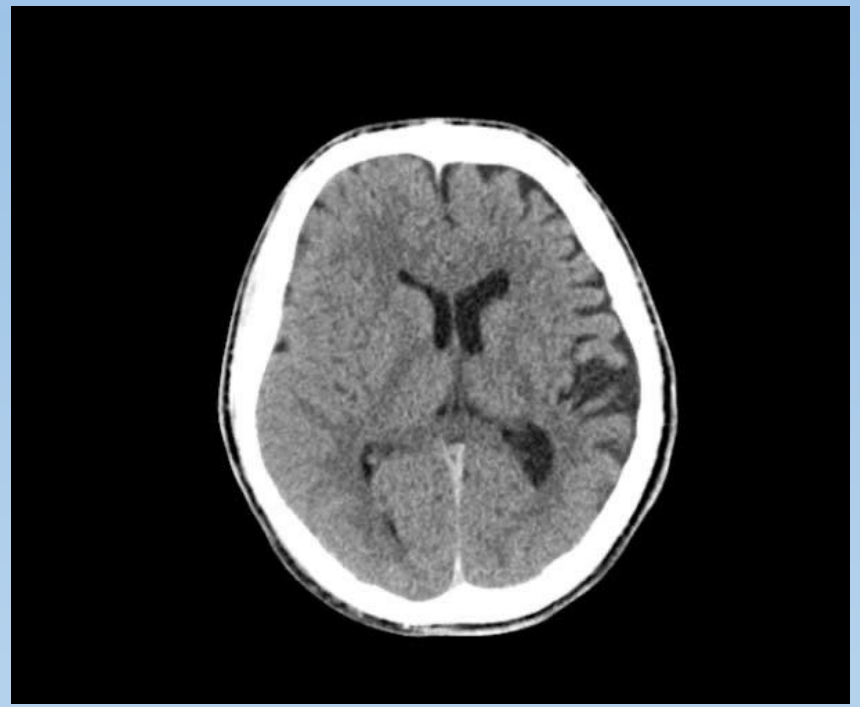
- A syndrome of sudden onset of febrile-illness related refractory status epilepticus in a previously healthy child (2wks to 24hrs prior)
- Aetiology remains unclear>>neuro-inflammatory/infectious
- EEG may show temporal and frontal discharges, diffuse slowing, and bilateral involvement
- Normal MRI Brain in half of the patients (atrophy of mesial temporal lobe)



New onset refractory status epilepticus (NORSE) Claudine Sculier etal. Seizure 2019

Rasmussen's Encephalopathy

Clinical	EEG/MRI	Serology
• Neuroinflammatory disease affecting one hemisphere of the brain • Intractable seizures, hemiparesis, and cognitive deterioration at 6-8yrs	• Hemispheric slowing with or without epileptiform activity • Hemispheric cortical atrophy	• Neuronal membrane receptor anti-GluR3 and the alpha-7 nicotinic acetylcholine receptor



Autoimmune Epilepsies.Anusha K.Yeshokumar and Carlos A.Pardo. Sem Paed Neurology. 2017

Epilepsia Partialis Continua

Condition of continuously repeated fragments of epileptic seizures (motor or sensory), with preserved consciousness, lasting at least 1 hour, and representing locally restricted epileptic activity.

Minimum duration of 60 min

Heterogenous Aetiology

Epilepsia partialis continua: A review Ruta Mameniškien etal. Seizure 2016

Investigations

Table 1
Recommended diagnostic workup for pediatric RSE/SRSE.

Always recommended
- Finger stick blood glucose
- Monitor vital signs
- CT/MRI (almost always appropriate except in epileptic patients with a prior normal neuroimaging or with a generalized seizure syndrome and generalized seizures)
- Serum electrolytes including calcium and magnesium
- cEEG monitoring

Specific circumstances

Known epilepsy patient
- ASD levels
- Consider CT/MRI
- Consider Electrolytes
- *Decision making largely dependent on the patient's seizure history and associated comorbidities.

Febrile patient

SE with fever (presumed Febrile SE) in a patient ≤5 years, improved clinical state and SE resolving (no concerns for CNS infection)
- Identification of primary source of fever

SE with fever in a patient>5 years, improved clinical state and SE resolving
- Identification of primary source of fever
- CT/MRI consider giving IV contrast if possible

SE with fever of unknown etiology and no improvement of clinical state
- CBC
- Lumbar puncture with CSF investigation of infectious etiologies
- CT/MRI consider giving IV contrast if possible

Suspected non-infectious encephalitis (immune/inflammatory)
- CRP
- ESR
- Auto-antibodies including ANA, anti-dsDNA, ANCA, APS & ENA panel
- Serum anti-neuronal antibodies including anti-NMDAR, –AMPA & –VGKC, –GABA
- Lumbar puncture with oligoclonal bands, and CSF anti-neuronal antibodies (as above)
- Paraneoplastic evaluation if appropriate

Suspected genetic syndrome
- Genetic consultation
- Tiered genetic testing per age, clinical exam and seizure phenotype

Additional considerations
- Toxicology screen
- Consider medication side effect (chemotherapeutics, immune-modulators, etc.)
- In rheumatologic disease consider: CRP, ESR, CMP, ANA, ANCA, APS panel, ENA panel

cEEG and Patterns

Approximately 1/3 of the children with convulsive SE may develop non-convulsive SE

- almost 1/2 evolve to electrographic SE

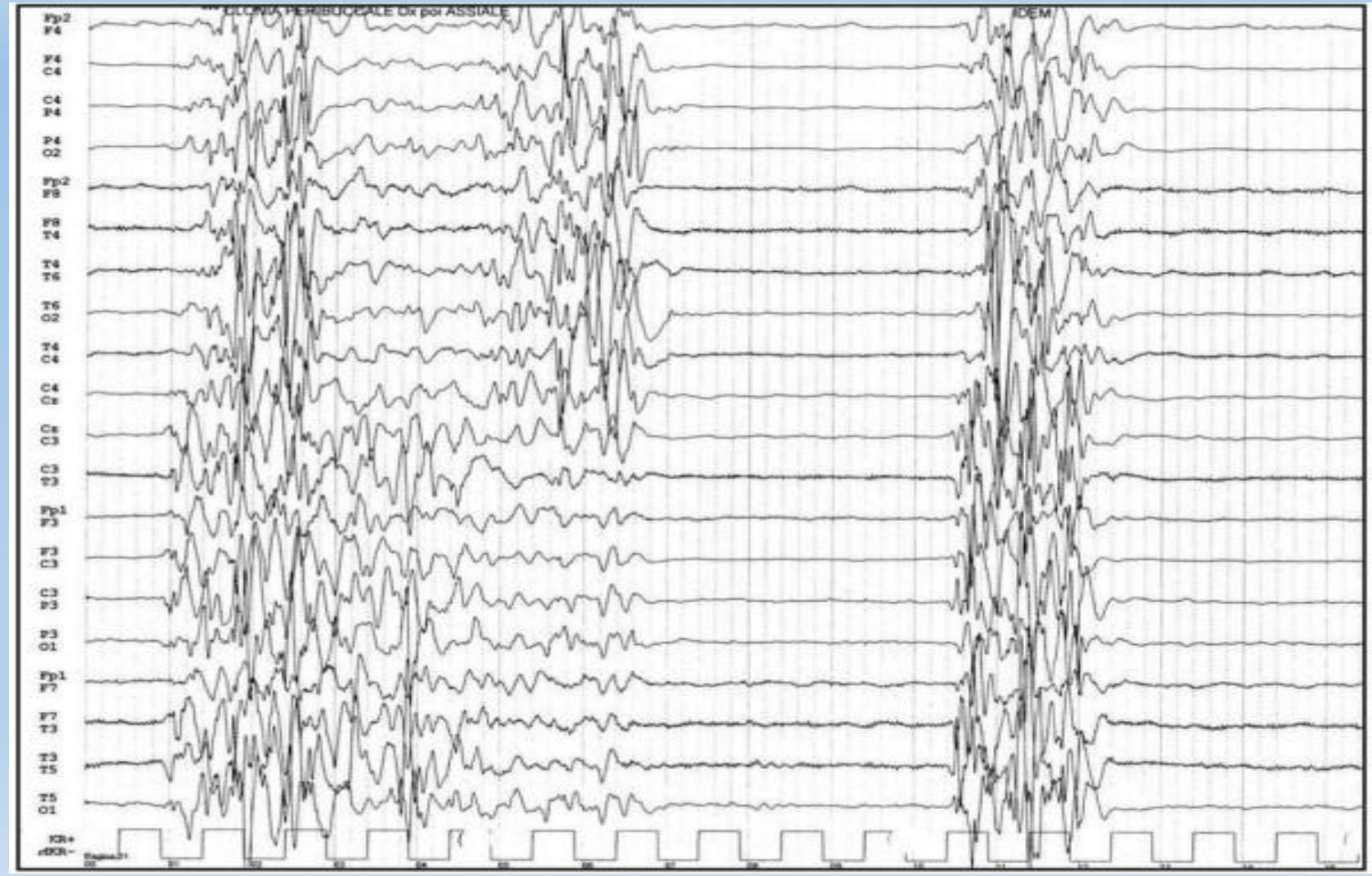
CEEG should be initiated within 1 hour of SE, and continued for at least 24-48 hours,

- often longer in the presence of altered consciousness

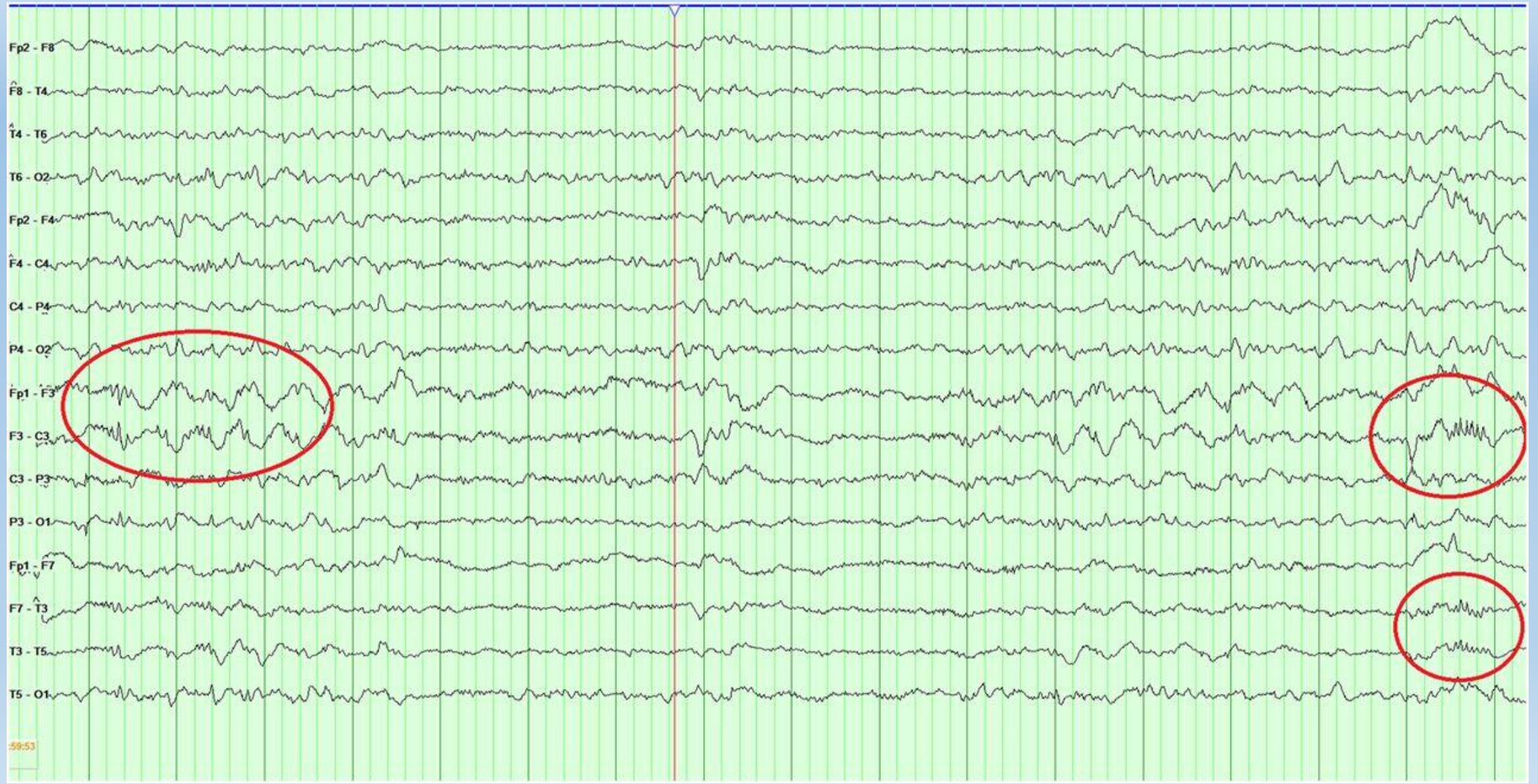
Aim for complete suppression of seizures, and achieve 50%-70% suppression ratio

Debopam Samanta.Refractory and Super-refractory Status Epilepticus. Indian Paediatrics. 2020

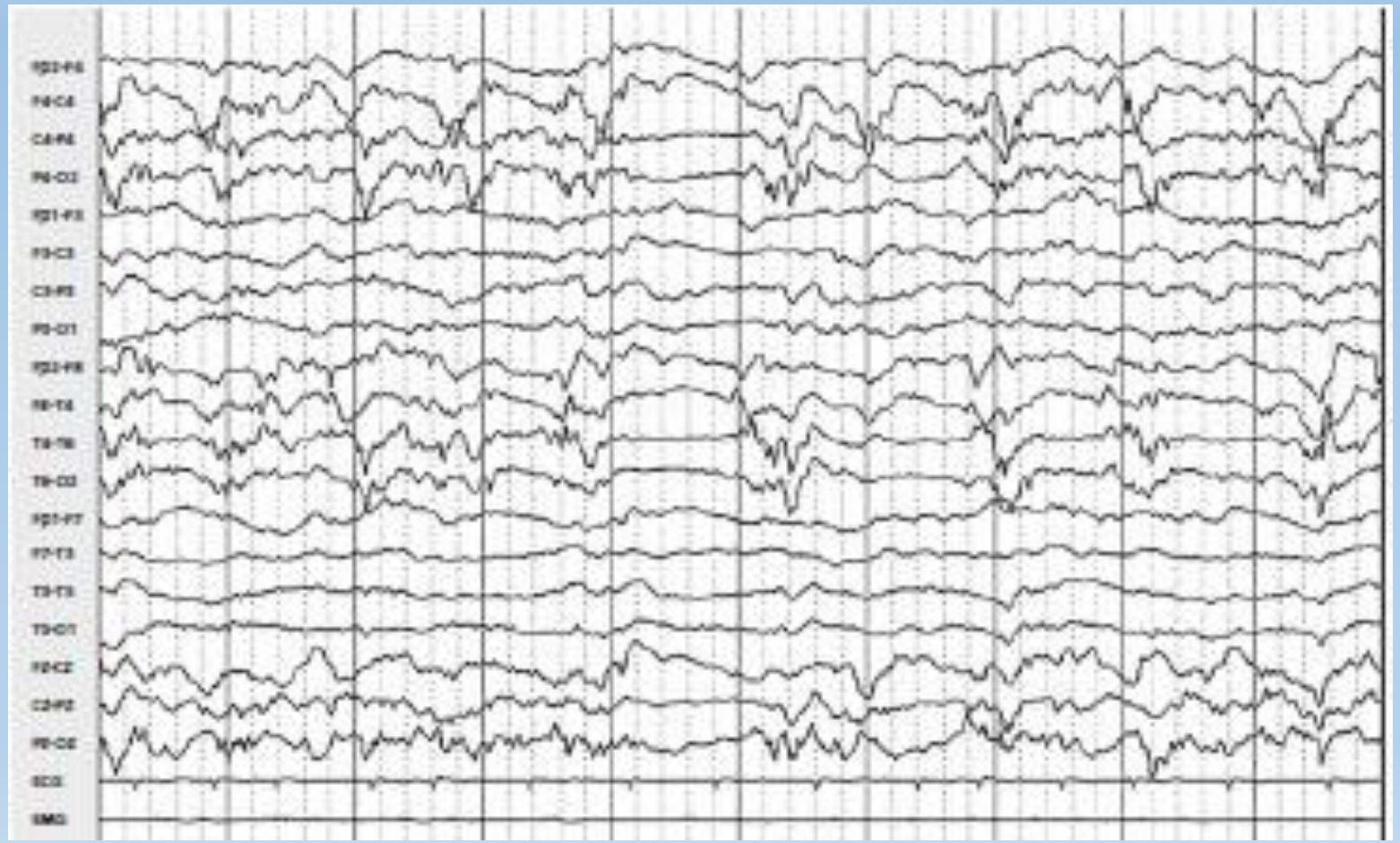
Burst Suppression EEG



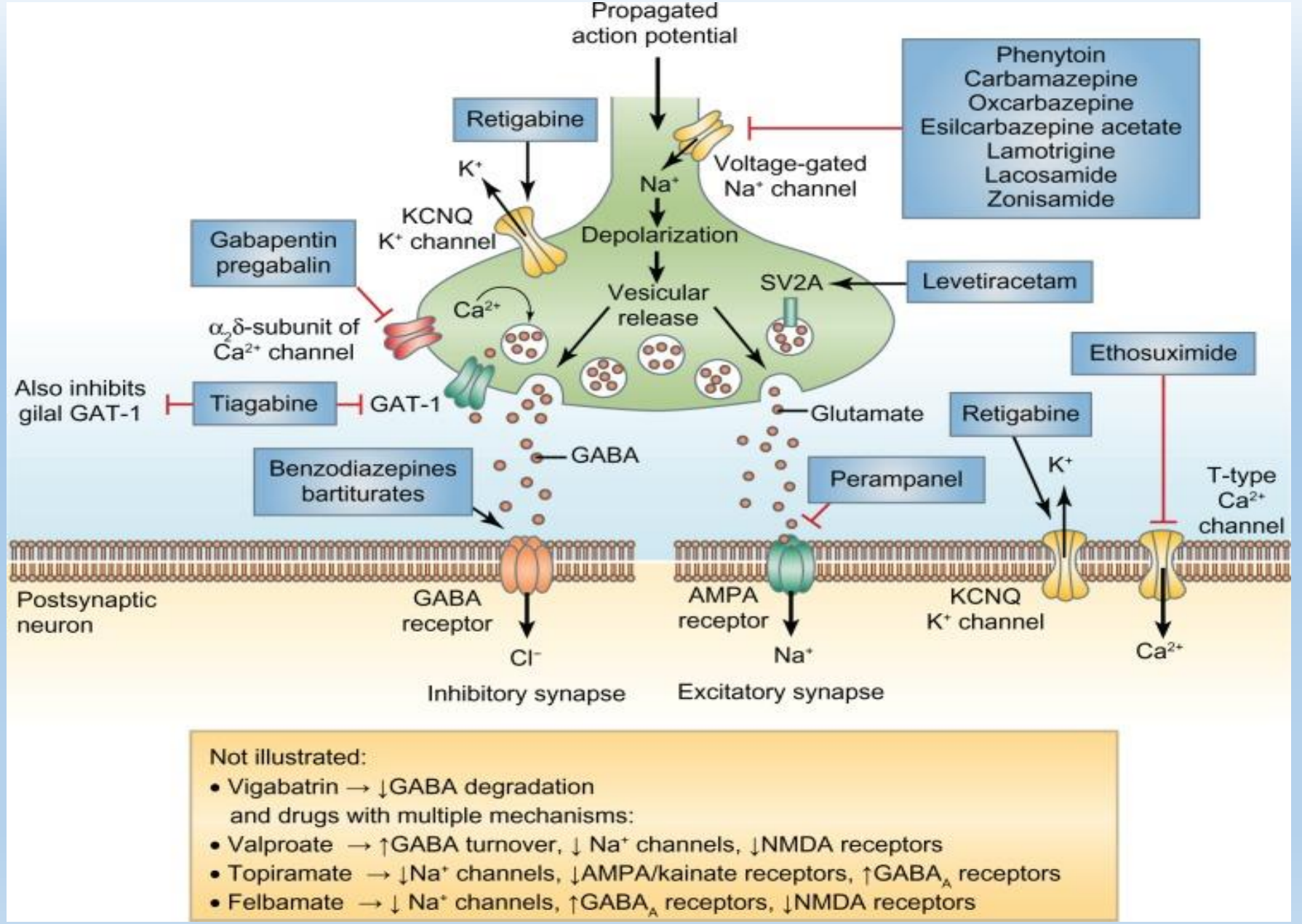
EEG in AI encephalitis



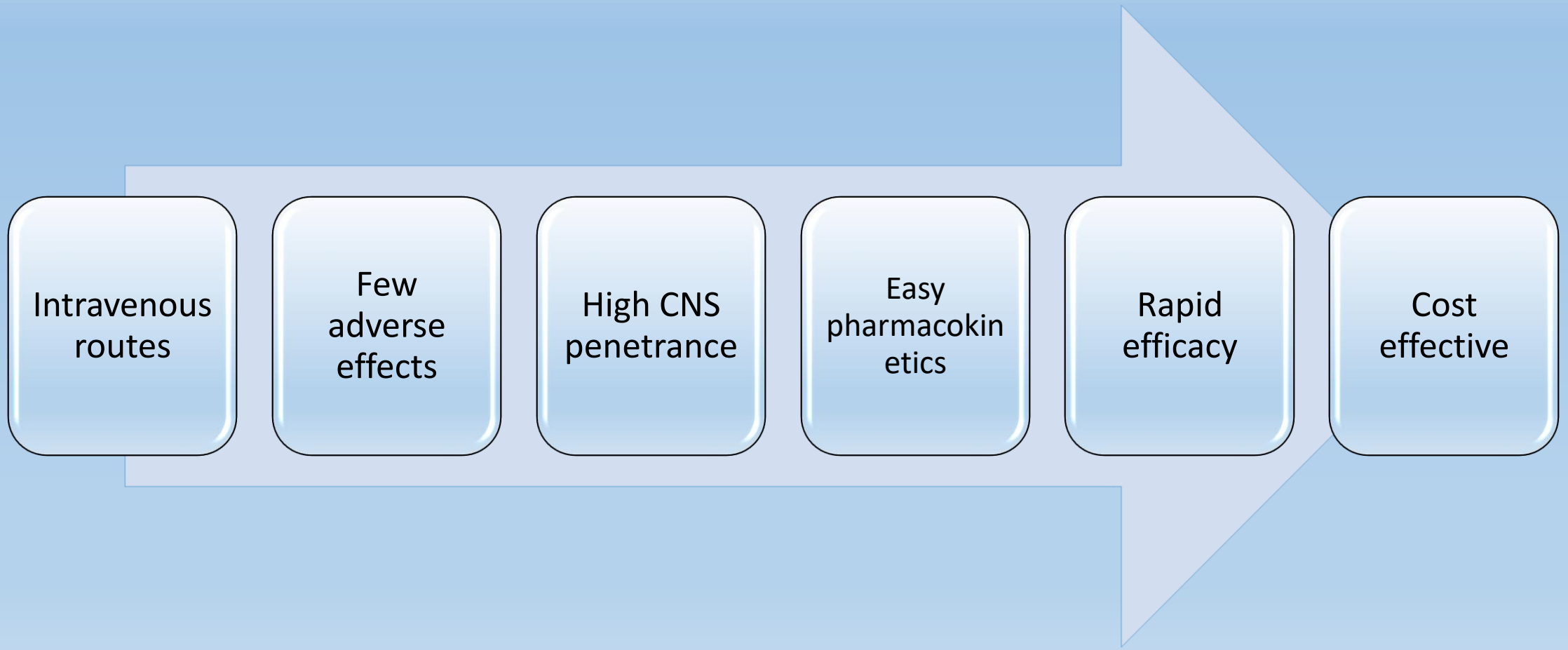
Epilepsy partialis with Right PLEDS



Management of RSE


Propagated action potential
Phenytoin
Carbamazepine
Oxcarbazepine
Esilcarbazepine acetate
Lamotrigine
Lacosamide
Zonisamide
Retigabine
K+
KCNQ K+ channel
Na+
Voltage-gated Na+ channel
Depolarization
Gabapentin pregabalin
α2δ-subunit of Ca2+ channel
Ca2+
Vesicular release
SV2A
Levetiracetam
Ethosuximide
Also inhibits gilal GAT-1
Tiagabine
GAT-1
Glutamate
Retigabine
GABA
Benzodiazepines bartiturates
Perampanel
K+
T-type Ca2+ channel
Postsynaptic neuron
GABA receptor
Cl−
AMPA receptor
Na+
KCNQ K+ channel
Ca2+
Inhibitory synapse
Excitatory synapse
Not illustrated:
• Vigabatrin → ↓GABA degradation and drugs with multiple mechanisms:
• Valproate → ↑GABA turnover, ↓ Na+ channels, ↓NMDA receptors
• Topiramate → ↓Na+ channels, ↓AMPA/kainate receptors, ↑GABA$_A$ receptors
• Felbamate → ↓ Na+ channels, ↑GABA$_A$ receptors, ↓NMDA receptors

Ideal Antiepileptic Drug



Seizure 68 (2019) 62–71

Contents lists available at ScienceDirect

Seizure

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Review

Pediatric refractory and super-refractory status epilepticus

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Table 2
Pharmacological and non-pharmacological therapies for the treatment of RSE/SRSE.

	Mechanism of action	Dose	Adverse Events	Clinical Considerations
Pharmacological therapies				
Benzodiazepines				
Midazolam	Positive allosteric modulation of GABA-A receptors, Increases frequency of CI channel opening	Loading dose: 0.2 mg/kg; administer at an infusion rate of 2 mg/min Infusion rate: 0.05–2 mg/kg/h Breakthrough SE: 0.1–0.2 mg/kg bolus, increase rate by 0.05–0.1 mg/kg/h. every 3–4 h	Hypotension, respiratory depression	Prolonged use may cause tachyphylaxis and drug accumulation
IV anesthetic agents				
Barbiturates	Activation of GABA receptors-increase mean CI channel opening duration, inhibition of NMDA receptors, alteration in conductance of Cl^-, K^+, Ca^{2+} ion channels.	Loading dose: 5–15 mg/kg; infusion rate $\leq$ 50 mg/min Infusion rate: 0.5–5 mg/kg/h Breakthrough SE: 5 mg/kg bolus, increase rate by 0.5–1 mg/kg/h. every 12 h	Hypotension, cardiac and respiratory depression, paralytic ileus, infection	Long half-life (15–50 h) Requires mechanical ventilation. Can exacerbate porphyria Hepatic enzyme inducer Drug accumulation with prolonged use
Pentobarbital	Same as Pentobarbital			

Pharmacological Treatment

Thiopental	Same as the mechanism described above	2–7 mg/kg, infusion rate ≤ 50 mg/min Infusion/ maintenance rate: 0.5–5 mg/kg/h Breakthrough SE:1–2 mg/kg bolus, titrate by 0.5–1 mg/kg/h. every 12 h.	Hypotension, cardiac and respiratory depression	Requires mechanical ventilation, titrate infusion rates to EEG burst-suppression
Propofol	Chloride channel conductance, enhances GABA-A receptor	Initial loading dose: 1–2 mg/kg Initial infusion rate 20 mcg/kg/min titrated by 5–10 mcg/kg/min Use with caution with doses > 65 mcg/kg/min Breakthrough SE: Increase infusion rate by 5–10 mcg/kg/min every 5 min	PRIS, hypotension, cardiac and respiratory depression	Requires mechanical ventilation Prolonged infusion of propofol is a relative contraindication in children (due to risk of PRIS) and in patients with metabolic acidosis, mitochondrial disorders or hypertriglyceridemia Reduces ICP Caution with concomitant use of steroid or catecholamine therapy
Ketamine	Noncompetitive NMDA glutamate receptor antagonist-reduces neuronal excitability	0.5–3 mg/kg Infusion rate: 1–10 mg/kg/h	Tachycardia, hypertension, ICP elevation	Relative contraindication in patients with ICP. Ketamine is an enzyme inducer and inhibitor (CYP2C9)

Inhalational anesthesia				
Isoflurane	Enhancement of GABA-A receptors, noncompetitive antagonist of NMDA receptor	Concentration 1–5% Titrate to achieve burst-suppression on EEG	Hypotension requiring use of vasopressors, atelectasis, paralytic ileus, infection, deep vein thrombosis	High seizure recurrence rate
Immunomodulatory therapy				
IVIG	Alteration of IgG-specific receptors (FcγR) expression and function (decreases cytokine production), attenuation of complement mediated cell damage	1–2 g/kg divided over 3–5 days	Hypersensitivity reactions, transfusion related acute lung injury, thromboembolic events, renal dysfunction with concentrated solutions, aseptic meningitis	Immunomodulatory therapies may be considered in patients with cryptogenic, autoimmune etiologies of RSE/SRSE.
Corticosteroids: Methyl prednisolone	Inhibition of inflammation-associated proteins (e.g. cytokines, chemokines) and immunosuppressive action	1 g/day for 3–5 days	Glucose intolerance, psychiatric disturbances, altered immune function, adrenal suppression	
Prednisone	Same as the mechanism described above	60 mg daily		
Plasmapheresis	Removal of circulating autoantibodies, immune factors or high weight proteins that may participate in inflammatory process	5 exchanges over 5 days		

Immune therapy

Indications

- cryptogenic RSE
- confirmed autoimmune or inflammatory aetiology, such as Rasmussen encephalitis, NMDA receptor encephalitis
- central nervous system vasculitis

IV Immunoglobulin, steroids, plasmapheresis, Anakinra

21 RSE/SRSE cases treated with adjunctive immunomodulatory therapy showed adequate seizure control in only 5% of cases.

Ferlisi M, Shorvon S. The outcome of therapies in refractory and super- refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135:2314–28.

Algorithm for SE

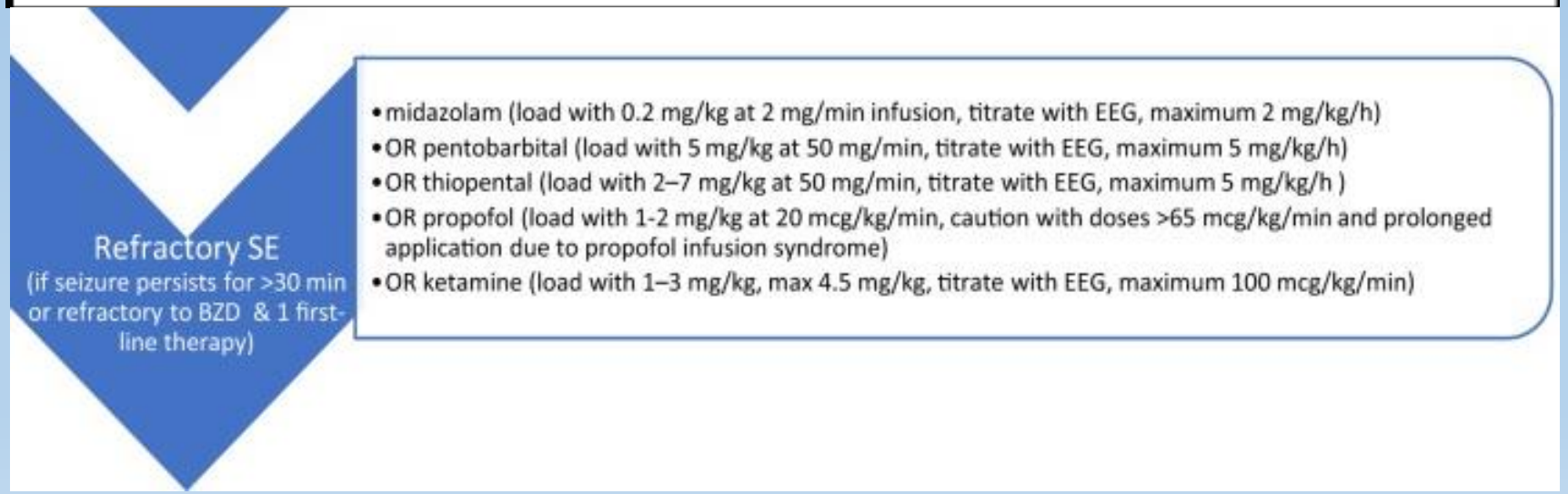
Table 2
Strategy for high-dose intravenous midazolam in refractory SE

Timing from Start of this Strategy	Midazolam Dosing	Steps
0 min: initial bolus	Give 0.5 mg/kg	A
0 min: start continuous infusion	Start at 2 μg/kg/min (0.12 mg/kg/h)	B
5 min: if seizure persists 5 min after bolus (step A)	Give 0.5 mg/kg Increase infusion to 4 μg/kg/min (0.24 mg/kg/h)	C
10 min: if seizure persists or recurs 5 min after step C	Give 0.1 mg/kg Increase infusion by 4 μg/kg/min (0.24 mg/kg/h)	D
15 min: if seizure persists or recurs 5 min after step D	Repeat step D	E
20–45 min: if seizure persists or recurs 5 min after step E, then continue to repeat step D every 5 min until a maximum infusion rate is achieved	Maximum infusion rate of 36 μg/kg/min (1.92 mg/kg/h)	F (5 cycles of D-to-E may be needed)
45 min: by the completion of step F an EEG should be available to confirm seizure control or otherwise. If seizure is not controlled then consider this episode as treatment failure and move to step H	Maintain dose of continuous infusion that achieves clinical and EEG seizure control and 24–48 h later move to step I	G
45–60 min: treatment failure	Discontinue midazolam infusion and start general anesthesia with pentobarbital or isoflurane	H

Pediatric Intensive Care Treatment of Uncontrolled Status Epilepticus. Ryan Wilkes, Robert C. Tasker

Algorithm for SRSE

24–48 h: if patient is free of clinical and EEG seizures then start to wean the infusion	Reduce infusion by 4 μg/kg/min every 6–8 h	I
48–84 h: continued EEG monitoring to observe for breakthrough seizures	Plan to discontinue infusion after optimizing other AEDs. If seizures recur then consider step K for weaning failure; alternatively this episode may be in the category of super-refractory SE	J
Weaning failure	Consider rebolus of 0.1 mg/kg and increase infusion by 4 μg/kg/min and/or Consider alternative AEDs	K



Non Pharmacological Agents

Ketogenic diet

- High-fat, low-carbohydrate, and adequate-protein diet (4:1)
  - anti-inflammatory and anti- seizure properties
  - MAD
- Seizure cessation was achieved in 7 of 8 (87.5%) patients with FIRES that reached ketosis, within 2–4 days of ketonuria
- Collective efficacy rate of 54% in a small case series
- In the absence of a contraindication, KD could be considered in earlier stages of RSE and SRSE management
  - carnitine deficiency, beta-oxidation defects, pyruvate carboxylase def

Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia 2010;51:2033–7.

Other nonpharmacological modalities

- **Therapeutic Hypothermia**
- Adjunctive therapy due to its neuroprotective and antiepileptic properties
- 270 patients with convulsive SE Multicentre RCT
  - Hypothermia was not associated with a lower rate of progression to RSE or SRSE, or improved clinical outcomes
- A/E
  - DVT, infections, cardiac arrhythmias, electrolyte disturbances, acute intestinal ischemia and coagulation disorders
- *Legriel S, Lemiale V, Schenck M, Chelly J, Laurent V, Daviaud F, et al. Hypothermia for neuroprotection in convulsive status epilepticus. N Engl J Med 2016;375:2457–67*

- **Trans-magnetic Stimulation**
- Effective for focal SE- 80% response
  - *Epilepsy Res Treat 2015:670874*
- **Vagal nerve stimulation**
  - Cessation of generalsed RSE in 19/24 (76%)
  - *Zeiler FA, et al. VNS for refractory status epilepticus. Epilepsy Research. 2015;112:100-113*
- **Surgery**

Electroconvulsive Therapy

- Increases GABA levels leading to reduction of neuronal metabolic activity
- Outcomes are variable ranging from transient response to ECT and mild improvement of seizure frequency to no clinical improvement
- Logistically challenging
- Limited availability

Morales OG, Henry ME, Nobler MS, Wassermann EM, Lisanby SH. Elective transcranial magnetic stimulation in children and adolescents: a review and report of two cases of epilepsia partialis continua. Child Adolesc Psychiatr Clin N Am 2005;14:193–210 viii-ix.

Clinical Outcome

- Mortality estimates in pediatric RSE are 13.7–43.5%
- Underlying aetiology is usually recognized as a primary predictor of outcomes
- Acute symptomatic aetiologies less likely to return to baseline neurological function and are at higher risk of developing drug resistant epilepsy
- Not only are patients with RSE/SRSE at risk for higher mortality, they are also at risk for neurological and systemic complications
- 6% in hospital mortality
- Evidence shows that patients with treatment delays , longer RSE duration , and those who present with non-convulsive SE have worse clinical outcomes

Abend NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. Lancet Neurol 2013;12:1170–9.

Take home points

- Super refractory status epilepticus is a medical emergency necessitating aggressive treatment for early seizure control
- High rates of mortality and morbidity
- Literature on SRSE in children is limited despite the morbidity
- Current clinical practice is challenged by the heterogeneous etiologies and multiple factors involved in the progression from SE to RSE and SRSE
- Integrated and comprehensive intensive care approach in this challenging condition
- No large RCT supporting specific algorithms- imperative to have protocol driven approach which impacts on morbidity and mortality

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Thank you