Teaching Course at the 24th World Congress of Neurology
Oct. 27th -31th, 2019, Dubai World Trade Centre, Dubai, UAE

Management of Status Epilepticus:
Treating the Seizures vs. the Etiology?

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DISCLOSURES

NONE

Management of Status Epilepticus:
Treating the Seizures vs. the Etiology?

- **Learning Objectives**
  - Understand the importance of timely control of seizure in patients presenting with status epilepticus (SE)
  - Understand systemic complications of convulsive SE
  - Understand the importance of simultaneous evaluation and diagnosis of the un derlying cause of SE
  - Understand the diagnostic approaches of refractory status epilepticus
  - Understand the current management strategies of New-onset refractory status epilepticus (NORSE)

Management of Status Epilepticus: Treating the Seizures vs. the Etiology?

- **Key Messages**
  - Treatment delay is the most common cause of treatment failure in SE
  - Systemic complications of SE are related to both recurrent seizures and therap eutic measures
  - SE without known cause (cryptogenic SE) is frequently is usually difficult to con trol with serial use of antiepileptic drugs.
  - If initial diagnostic evaluation was negative and SE is refractory, a thorough diag nostic workup including CSF exam is mandatory
  - Immune- related causes are the most common etiology of new-onset refractor y status epilepticus (NORSE)

Management of Status Epilepticus:
Treating the Seizures vs. the Etiology?

FACTs

- SE is a simultaneously a neurologic and systemic emergency carrying significant morbidity and mortality

  - Incidence: 18 and 41 patients per year per 100,000 population.
  - Approximately 31% to 43% of status epilepticus episodes will become refractory
  - Mortality of status epilepticus ranges from 19% to 26% and rises with increasing age.
  - Outcomes are usually worse if:
    - The duration of SE is long,
    - The patient is medically ill,
    - The patient has systemic complication.
  - HOWEVER, The strongest factor influencing outcome is **ETIOLOGY**

Management of Status Epilepticus:
Treating the Seizures vs. the Etiology?

1. Why should we treat SEIZURES in patients presenting with SE?

- SE is the result of failure of seizure terminating mechanisms
  → unlikely to be terminated spontaneously without intervention
  → 5 min is the temporal definition of SE (T1 in ILAE operational dimension)

- Series of seizures may cause irreversible neuronal damage
  → 30 min is the temporal window for reversible injury (T2 in ILAE operational dimension)
  → in patients with acute brain insults, seizures may precipitate additional brain damage

- Seizures may precipitate serious systemic complications requiring ICU care

- Compared to isolated seizure, SE may precipitate enduring long-term consequences

I. Why should we treat SEIZURES in SE ?

1. SE results from failure of mechanisms terminating seizures

- Theodore et al. (Neurology 1994;44:1403-1407)
  - Video-EEG of 120 GTCs of 47 pts.: none lasted for ≥ 2 min.
- De Lorenzo et al. (Epilepsia 1999;40:164-9)

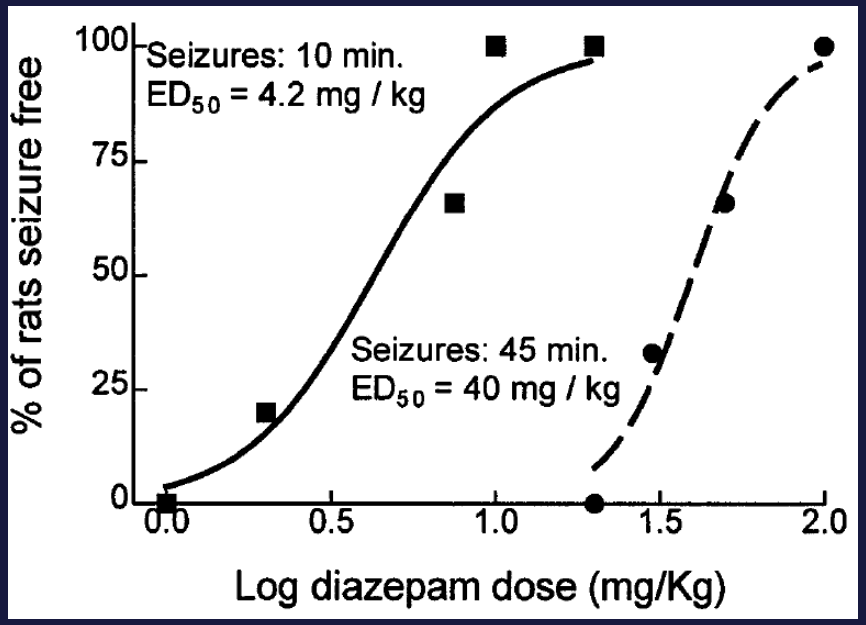
Seizure lasting for	10-29min(n=81)	≥ 30 min(n=226)
Spont. Sz termination	43%	7%
Mortality	2.6%	19%

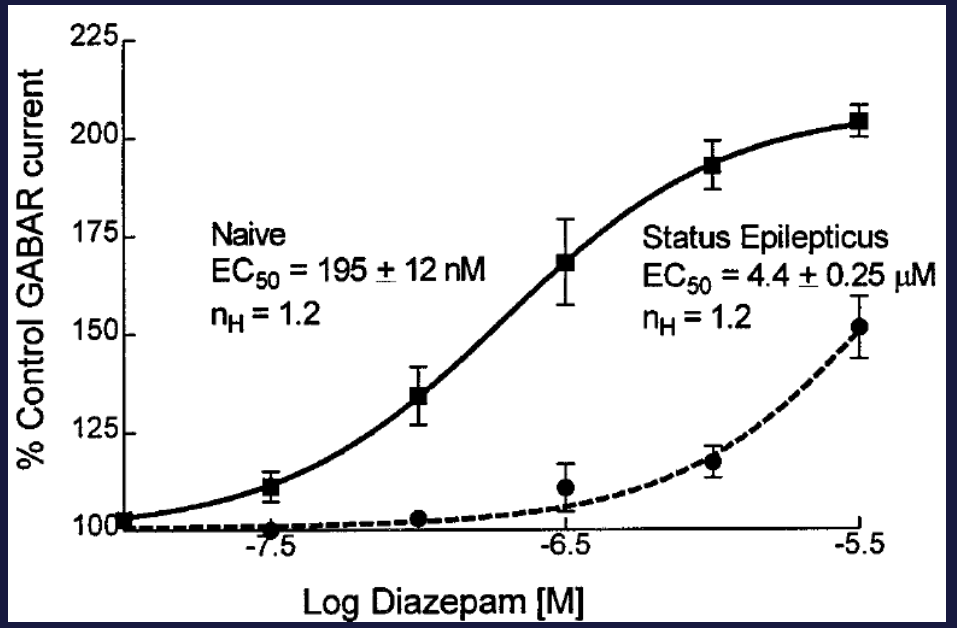
- Erikson et al. (Neurology 2005;65:1316-1318)
  - Correlation between treatment delay and prolonged SE when treatment started 30 min after onset of SZ → *Time dependent decrease in response of AEDs treatment in SE*
- Alldredge et al. (Ped Neurol 1996;12:213-216): N=49 episodes of SE
  - Pre-hospital treatment by paramedics (IV or rectal valium) were associated with shorter durati on of SE and lower chance of recurrent seizures in ER

	Prehospital Rx (n′ = 19)*	No Prehospital Rx (n′ = 26)*	*P* Value
Duration of SE episode (min)†	31.7 ± 19.6	59.7 ± 39.0	.007
Recurrent Seizures in ED (%)	57.9	84.6	.045
Intubation Required (%)	31.6	38.5	.634
ICU Admission (%)	47.4	42.3	.736
Length of ICU Stay (days)†	0.9 ± 0.5	2.5 ± 3.2	.180
Length of Hospital Stay (days)†	2.0 ± 1.6	4.3 ± 5.1	.081

Time Dependent Decrease of AED Responses in SE
- Preclinical Studies -

- Kapur and Macdonald (J Neurosci 1997;17:7532-7540)
  - SE model by lithium + Pilocarpine
    - IV-BDZ: effective at 10 minute after Sz onset
      not-effective at 45 min of SE



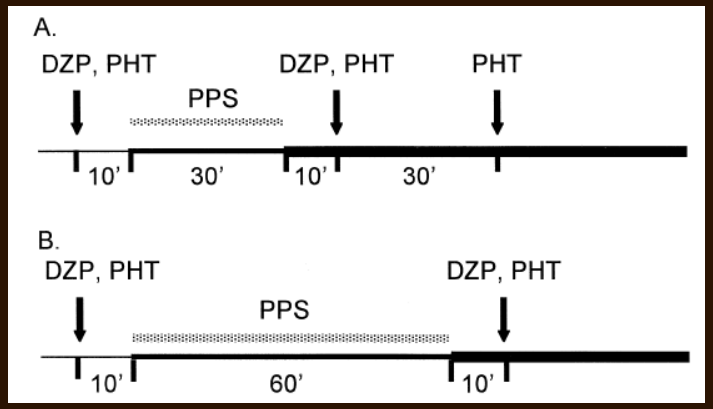


- The reduction of BDZ sensitivity of dentate granule cell GABARs reflect reduc ed effectiveness of BDZ in treatment of SE

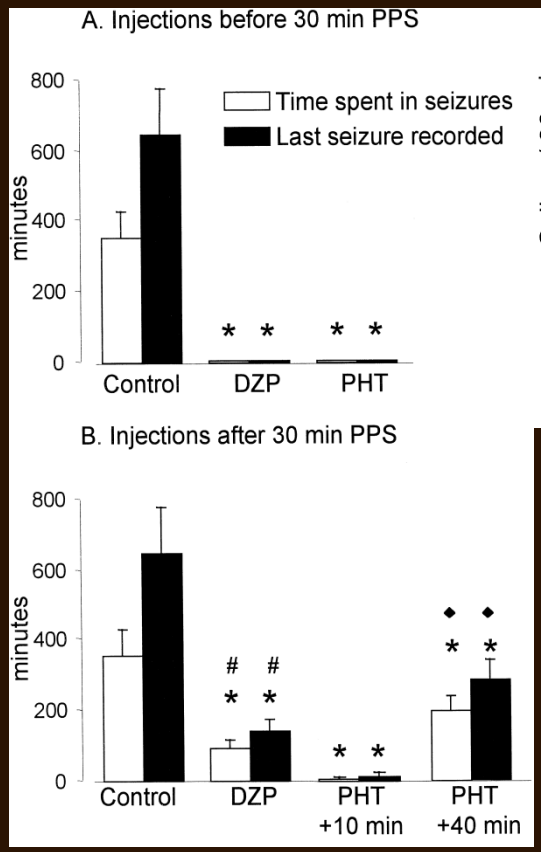
Mechanisms of SE: Self-sustaining SE
-Augmentation of Glutamatergic Excitation-

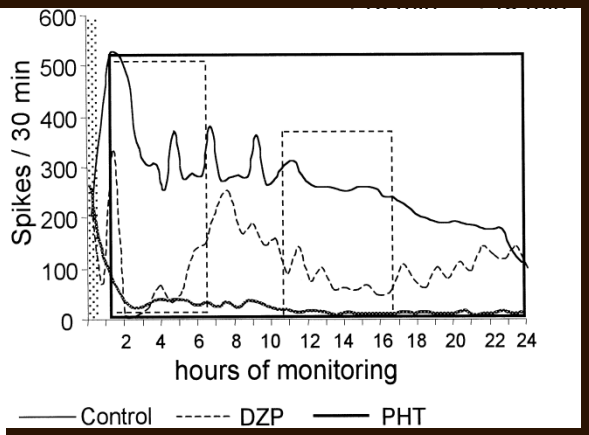
- Time-dependent decrease in the effectiveness of AEDs during SE

  (Mazarati et al., Brain Res. 1998;814:179-185)



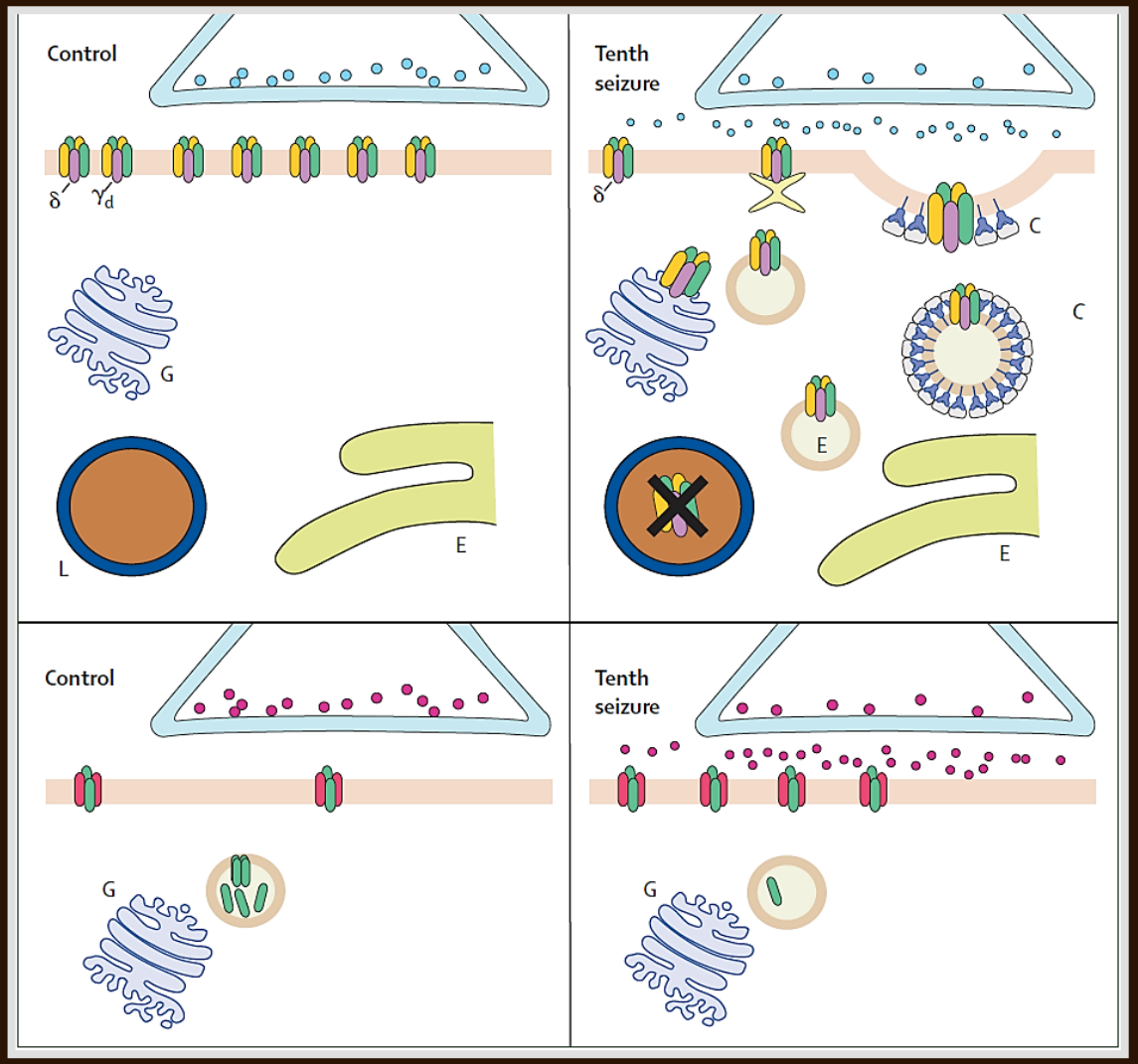
Protocol used for drugs administration. PPS of 30 m in A. and 60 min B. duration is indicated by gray bar. BDZ or PHT were injected as indicated by arrows 10 min before PPS, or 10 min after the end of PPS, or PHT. 40 min after the end of PPS.
Thin horizontal line: absence of seizures
Medium horizontal line: seizure activity during PPS
Bold horizontal line: SSSE





- Poor efficacy of delayed injection of PHT; Why?

I. Mechanism of SE
-Hypothesis-



Model of Receptor Trafficking *in transit ion of single Sz to SE*

Top: after repeated seizures, the synaptic me mbrane of $GABA_A$ receptors forms clathrin-c oated pits, which internalise as clathrin-coate d vesicles (C), inactivating the receptors beca use they are no longer within reach of the ne urotransmitter. These vesicles develop into e ndosomes (E), which can deliver the receptor s to lysosomes (L) where they are destroyed, or to the Golgi apparatus (G) from where th ey are recycled to the membrane.

Bottom: by contrast, in NMDA synapses, su bunits are mobilised to the synaptic membra ne and assemble into additional receptors. As a result of this trafficking, the n umber of functional NMDA receptors per sy napse increases whereas the number of funct ional $GABA_A$ receptors decreases.

Chen and Wasterlain Lancet Neurol 2006;5:246-256

Time Dependent Decrease of AED Responses in SE

- Mechanisms ? -

- Receptor Trafficking of (1) GABAA-receptors from synaptic membrane to the cytoplasm of neurons and (2) NMDA and non-NMDA glutamate receptors fro m cytoplasm to the membrane
- Alterations of ion channels
- Altered neuropeptide expression:↑substance P(Excitatory peptide)
  ↓neuropeptide Y(Inhibitory peptide)
- DNA methylation, micro-RNA regulation and altered gene expression
- Others: BBB breakdown and ↑Inflammation
  ↑P2X7 Receptors in neurons

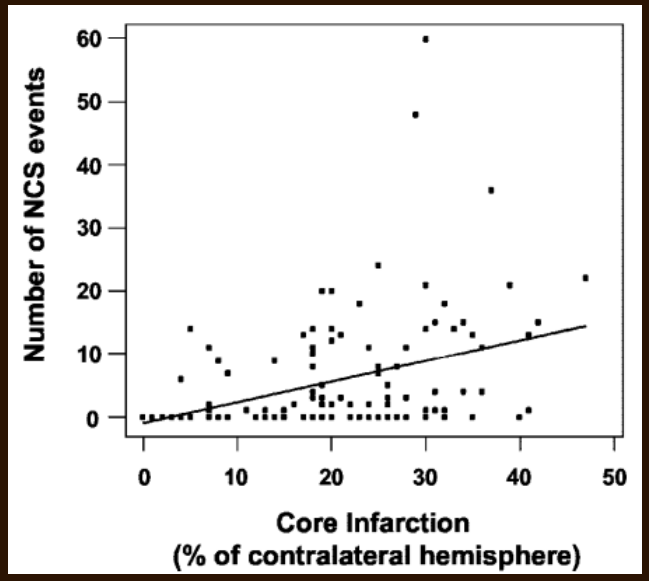
from Trinka et al(Current Opin 2016;29:189-198), Naylor et al.(J Neurosci 2005;25;7724-7733), Rajasekaran et al.(Semin Pediatr Neurol 2010;17:136-143), Betjem ann and Lowenstein(Lancet Neurol 2015;14:615-624), Barros-Barbosa et al.(Epilepsia 2016;57:99-110), Ravizza and Vezzani(Neurosci 2006;137:301-308), Engel et al.(FASEBJ 2012;26:1616-1628)

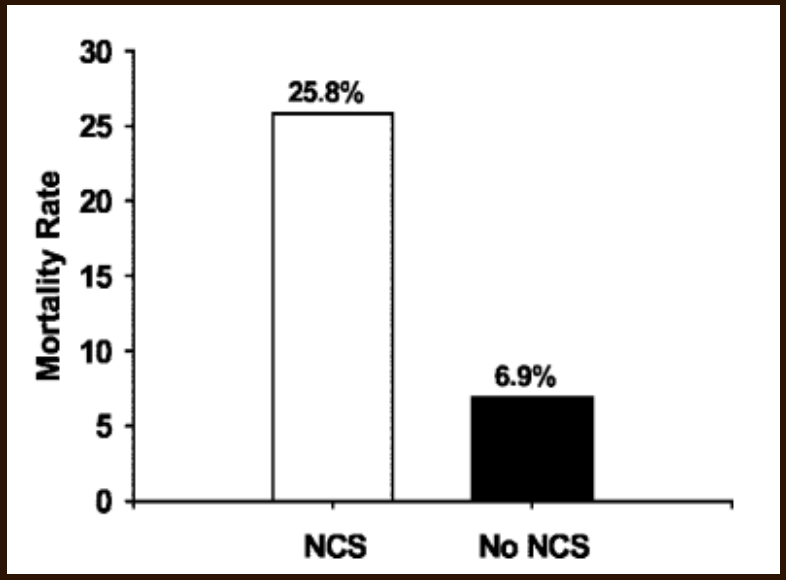
I. Why should we treat SEIZURES in SE ?

2. SE (beyond T2) may precipitate irreversible Brain Damage

- ***Animal Experiments:***
  - Recurrent and prolonged electrical ictal discharges precipitate widespread neuronal damages *(Meldrum et al. Arch Neurol. 1973; 128 : 10-17)*
  - Post-stroke rat model (MCA-occlusion) with epidural screw electrodes

    (Williams et al. JPET 2004; 311: 220-227)
    - Prevention of non-convulsive seizures (NCS) by iv- AEDs was associated with lower mortality and lower volume of infarction

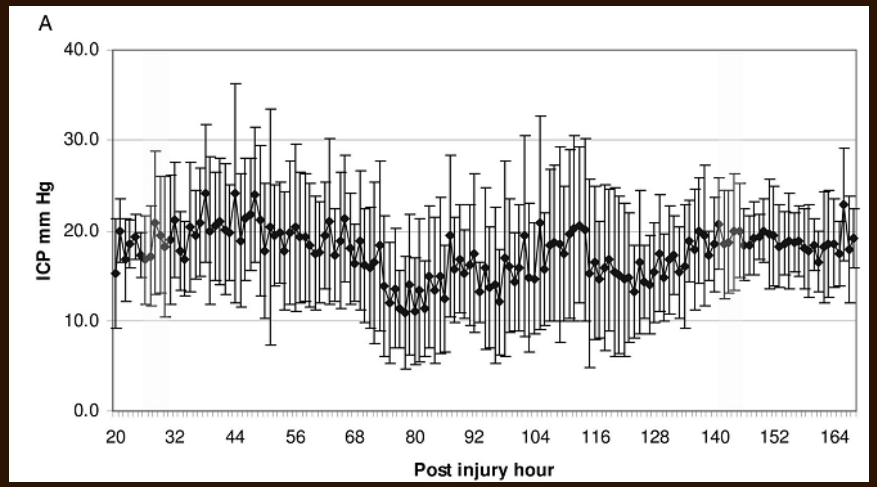


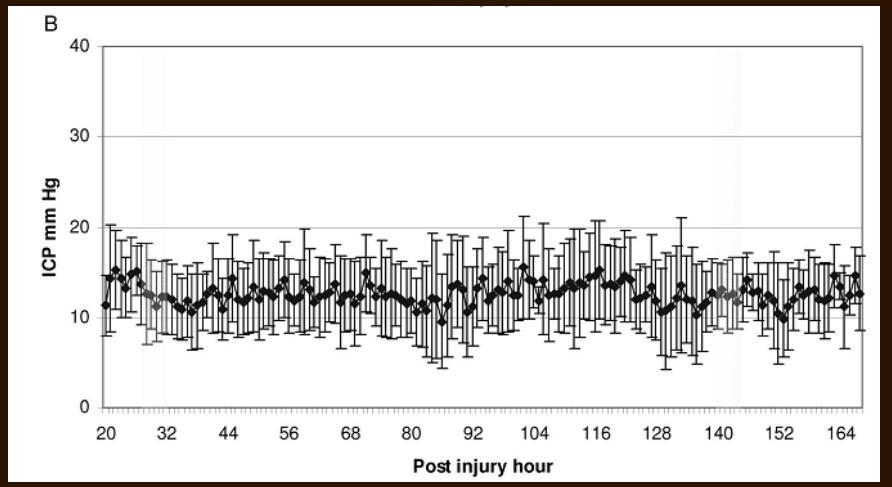


I. Why should we treat SEIZURES in SE ?

2. SE (beyond T2) may precipitate irreversible Brain Damage

- **Clinical Studies**
  - **Synergistic Interactions between *NCSE* and *Acute Brain Insults?***
    - **Vespa et al.** *(Crit Care Med 2007: 35; 2830-2836)*
      - 20 patients with moderate to severe traumatic head injury (GCS: 3-13), underwent cEEG and cerebral microdialysis
      - 10 patients with seizures were compared with matched cohort of TBI without seizures
      - Post-traumatic seizures were associated with
        - Episodic increase in ICP ($p < 0.001$) and lactate/pyruvate ratio ($p < 0.001$)
        - Higher mean ICP ($p < 0.001$) and mean LPR ($p < 0.001$)





1. Why should we treat SEIZURES in SE ?

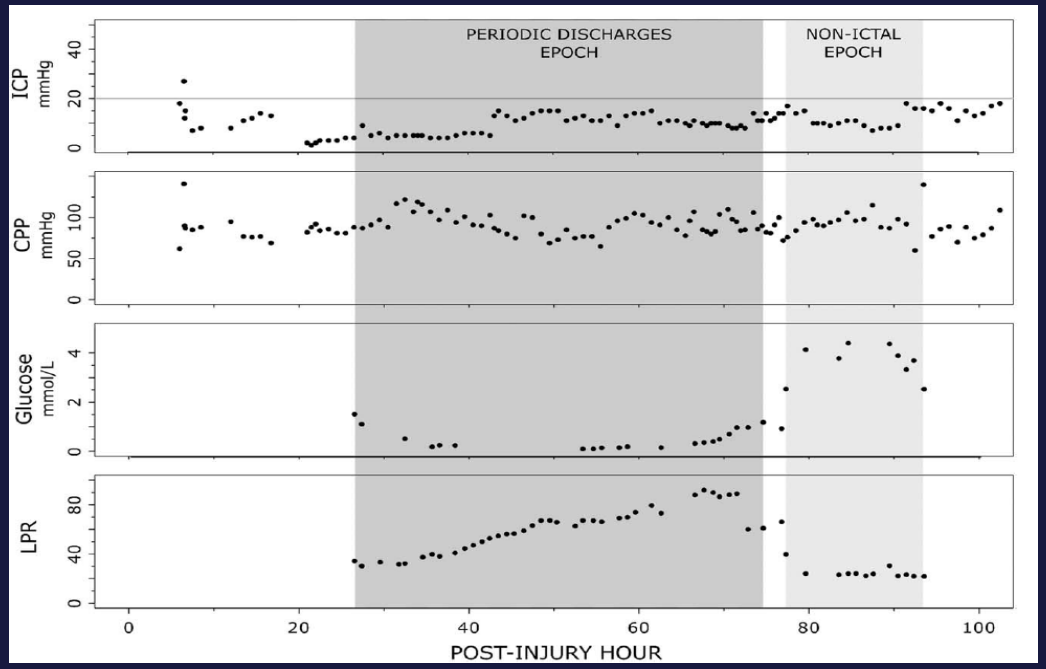
2. SE (beyond T2) may precipitate irreversible Brain Damage

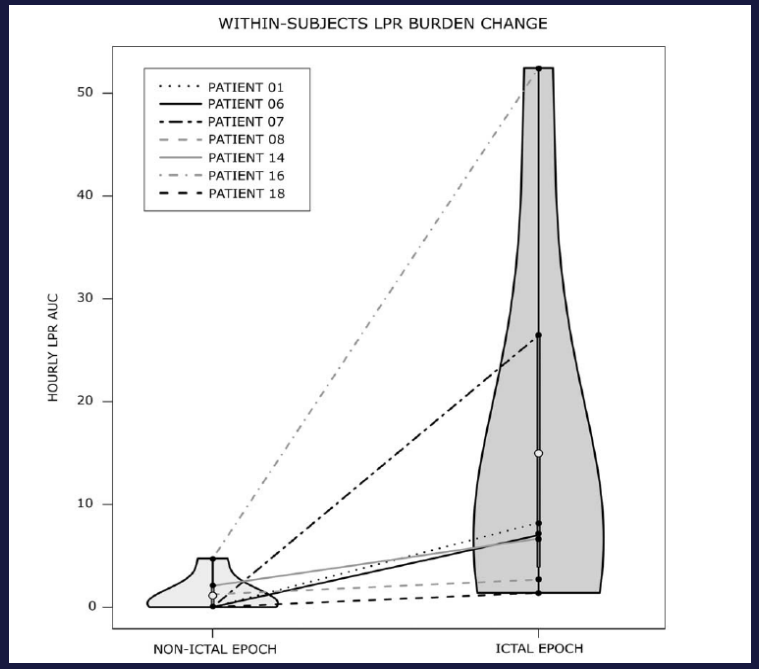
- **Clinical Studies**

➢ **Vespa P et al.** (Ann Neurol 2016;79:579-590)

- A prospective study of surface and intracortical depth EEG in conjunction with cerebral microdialysis in a cohort of severe TBI patients(n=34)
- Seizures or PDs occurred in 61%(21 of 34): surface EEG in 12 of 21(57.1%)
  intracorical depth EEG only in 9 of 21(42.9%)
- Metabolic crisis as measured by ↑cerebral microdialysis Lactate/Pyruvate ratio(LPR) occurred during seizures or PDs but not during electrically nonepileptic epochs

→ **SZ and PDs represent a therapeutic target** for future study





I. Why should we treat SEIZURES in SE ?

3. Seizures generate Systemic Complications worsening the outcome

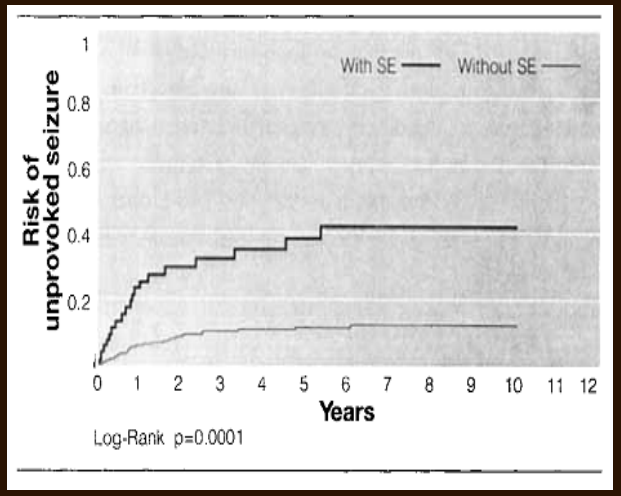
- **Hocker S.** (Epilepsy & Behav 2015;49:83-87)
  - At early stage, a massive catecholamine release and hyperadrenergic state may result in neurocardiogenic, pulmonary, and, sometimes, musculoskeletal or renal injury.
  - Iatrogenic medical complications related to the use of AEDs, anesthetic drugs etc. are frequent
  - Later, sequelae of prolonged immobility and critical illness add to the cumulative morbidity

Early systemic complications	Complications relating to treatment	Complications of prolonged intensive care unit care
Acidosis (respiratory > metabolic) • Increased CO_2 production • Decreased CO_2 removal • Depletion of glycogen stores	Nonanesthetic drugs • Benzodiazepine — respiratory depression, and sedation • Valproic acid — platelet and clotting dysfunction and hyperammonemia • Fosphenytoin/phenytoin — cardiac arrhythmias and hypotension • Levetiracetam — sedation • Lacosamide — PR prolongation, sedation, angioedema, and rash	Venous thromboembolic disease • Pulmonary embolism • Deep venous thrombosis
Hypoxia • Apnea • Upper airway obstruction • Aspiration of gastric contents • Mucous plugging • Neurocardiogenic pulmonary edema	Propofol • Propofol infusion syndrome • Hypotension	Pulmonary complications • Recurrent mucous plugging • Pleural effusions • Atelectasis • Tracheostomy Ventilator-associated pneumonia
Hyperadrenergic state • Hyperpyrexia • Hypertension • Tachycardia • Hyperglycemia • Peripheral leukocytosis	Midazolam • Accumulation in obesity and renal or hepatic dysfunction • Hypotension	Other infectious complications • Catheter-associated urinary tract infections • Sepsis • Bloodstream infections • Pseudomembranous colitis
Cardiac injury • Left ventricular stunning • Cardiac arrhythmias • Cardiac troponin elevation • Electrical conduction abnormalities • Cardiac contraction band necrosis	Barbiturates • Hypotension • Paralytic ileus • Increased risk of infection • Propylene glycol toxicity • Hepatic toxicity • Pancreatic toxicity • Lingual edema • Prolonged half-life	Skin complications • Skin breakdown • Yeast infections
Musculoskeletal injury • Tongue bites • Long bone fractures • Vertebral body compression fractures • Posterior shoulder dislocation	Ketamine • Tachyarrhythmias	Intensive care unit acquired weakness • Critical illness myopathy • Critical illness neuropathy
Renal injury • Rhabdomyolysis and acute renal failure	Inhalational anesthetics • Hypotension • Increased risk of infection • Paralytic ileus Hypothermia • Acid base and electrolyte disturbances • Coagulopathy • Impaired immunity • Cardiac arrhythmias • Paralytic ileus • Thrombosis	

I. Why should we treat SEIZURES in SE ?

4. SE may precipitate enduring long-term consequences

- *Records-linkage system of the Rochester Epidemiologic Project from 1965 to 1984*
  - *N=416, with ASS (SE= 95 vs. isolated Sz= 321)*
  - Risk of unprovoked Sz at 10yr-f/u
  - Patients with **ASSE vs ASS:** 41% vs 13%, (p = 0.0001)
    - Structural Causes (n=206): 45% vs. 17% (p = 0.0007)
    - Metabolic Causes (n=178): 29% vs. 8% (p = 0.02)
    - Anoxic encephalopathy(n=21):57% vs.17%(p=0.15)



- *Increased risk of US after **ASSE**, Why?*
  - *SE is a marker of severity of injury*
  - *Damage by SE*
  - *Biological substrate ass. with SE*

Variable	Crude RR	95% CI	Adjusted RR	95% CI
Whole group[a]				
SE	4.0	2.2–7.1	3.3	1.8–6.1
No SE	1.0	Referent	1.0	Referent
By cause[b]				
Structural, SE	6.7	3.0–15.0	7.1	2.9–16.9
Structural, no SE	2.1	0.96–4.6	2.4	1.1–5.5
Metabolic, SE	3.6	1.1–11.5	3.6	1.1–11.9
Metabolic, no SE	1.0	Referent	1.0	Referent
Encephalopathic, SE	16.7	3.6–78.1	18.8	3.6–98.6
Encephalopathic, no SE	2.2	0.29–17.4	1.9	0.23–15.3

[a]Adjusted RR adjusts for cause of acute symptomatic seizure, age, and sex.
[b]Adjusted RR adjusts for age and sex.

RR = rate ratio; CI = confidence interval; SE = status epilepticus.

Management of Status Epilepticus:
Treating the Seizures vs. the Etiology?

II. Why should we treat the ETIOLOGY in patients presenting with SE?

- SE is a symptom caused by the etiology, thus treatment of SE alone is not solving the problem
- Etiology is the most important factor influencing the outcome
- Treatment of SE alone without treating underlying etiology usually fails to stabilize the condition
- Most common cause of control of SE is unknown etiology (e.g., NORSE)
- Etiology of SE is quite diverse requiring different management stratagies in individual patient
- In patients with refractory SE, exhaustive search for underlying etiology is indicated

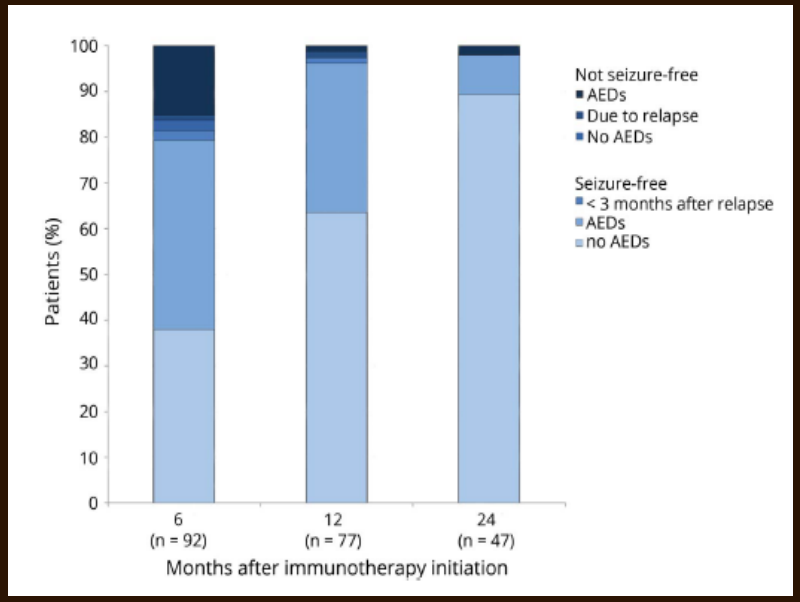
⟶ ***Rapid evaluation and diagnosis of etiology is the most important step of SE management***

Treatment of Seizures in Autoimmune Encephalitis

Marienke A.A.M. et al. Neurology 2019;92:e2185-e2196

- A Nationwide Cohort Study of 153 patients with autoimmune encephalitis (AIE) in Netherla nd (53 LGI1, 75 NMDAR, 25 GABABR)

- 110 (72%) patients had epileptic seizures, and 89% of them reached seizure freedom.
  - Seizure freedom was achieved shortly after immunotherapy in 53% of patients compared to 14% of seizure freedom by AEDs only (p<0.0001)
  - Median time to seizure freedom from AEDs start was 59 days and 28 days from start of immunotherapy (p < 0.0001)
  - At 24 months of FU (n=48), only 1 patient had developed epilepsy after resolved encephalitis(2%) and 46(98%) patients were seizure free and only 4 of them(9%) were on AEDs therapy



- Immunotherapy is crucial for the treatment of seizures in Autoimmune Encephalitis and AED s should be considered as add-on treatment, similar to treatment of other encephalitis symp toms

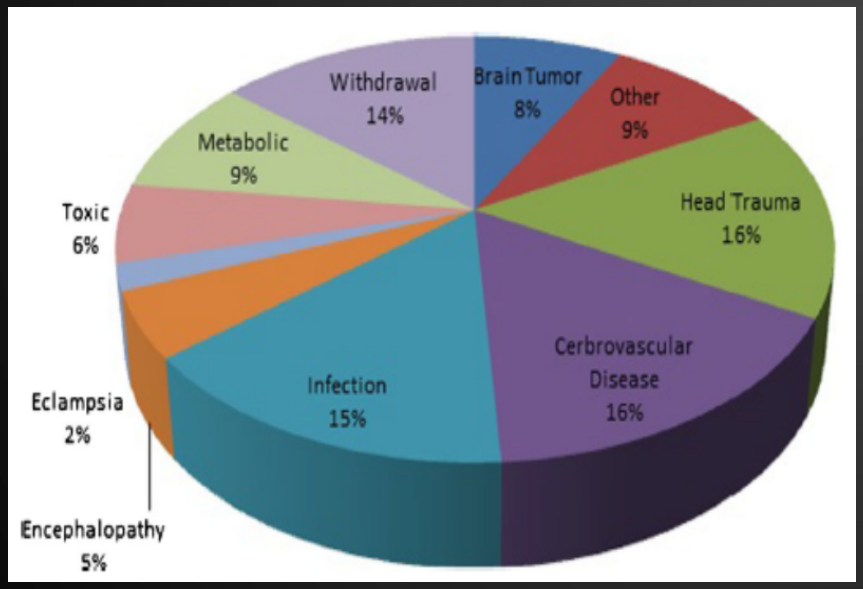
II. Why should we treat the ETIOLOGY in SE?

- Hesdorffer et al. Neurology 1999;50: 735-741(N=199, first episode of SE)
  - Acute symptomatic: SE occurred in association with (within a week) the onset of brain trauma, CNS infection, cerebrovascular disease, acute diffuse encephalopathy (primarily anoxia), and toxic/ metab olic insults including alcohol or drug withdrawal.
  - progressive symptomatic: SE in the presence of nonstatic CNS conditions such as CNS tumors and degenerative neurologic diseases
  - Remote symptomatic: SE in the presence of a history of a CNS insult, such as stroke, head trauma, o r meningitis, thought to lead to a static lesion and associated with an increased risk of epilepsy. The t ime between SE and the neurologic insult had to be more than 1 week
  - Idiopathic/cryptogenic : absence of an acute precipitating factor or a history of a prior neurologic i nsult.

Etiology	No of patients(%)
Acute symptomatic	100 (50.0%)
Idiopathic/cryptogenic	27 (13.6%)
Remote symptomatic	39 (19.6%)
Progressive symptomatic	17 (8.5%)
febrile	16 (8.0%)
History of Epilepsy before SE	18 (9.0%)

Etiology of Acute Symptomatic Seizures and Status Epilepticus

- **Diverse Etiologies**
  - Metabolic abnormality (30-35%)
  - Drugs, Toxins, or ETOH related (10-15%)
  - Neurological Insults (50-70%)
  - Others



J. F. Annegers et al., Epilepsia, 1995; 36:327-333

Etiology of Acute Symptomatic Seizures

Neurological insults

Cerebrovascular disease: ischemic stroke, hemorrhagic stroke, hypertensive encephalopathy/posterior reversible encephalopathy syndrome
Infection: meningitis, encephalitis, brain abscess
Head trauma: contusion, subdural hematoma, subarachnoid hemorrhage
Anoxic brain injury
Neoplasms: primary or secondary brain tumor
Demyelinating disorders
Postneurosurgical supratentorial procedure
PRES

Metabolic abnormalities

Hyponatremia
Hypocalcemia, hypophosphatemia, hypomagnesemia
Uremia, dialysis disequilibrium syndrome
Hypoglycemia, hyperglycemia with hyperosmolar state
Alterations of serum osmolarity
Fever, acidosis

Drugs/toxins

Drug overdose or Side effects
e.g., Antibiotics, anticancer drugs, antipsychotics, etc.
Illicit drugs (cocaine)
Alcohol
Chemicals
Vitamin deficiency: pyridoxine

Systemic disease

Organ failure (renal, hepatic)
Systemic infection/sepsis

II. Why should we treat the ETIOLOGY in SE?

- Diagnostic Evaluation in patients with New-onset refractory SE

(CMC Kang et al., Seizure 2017;46:24-30)

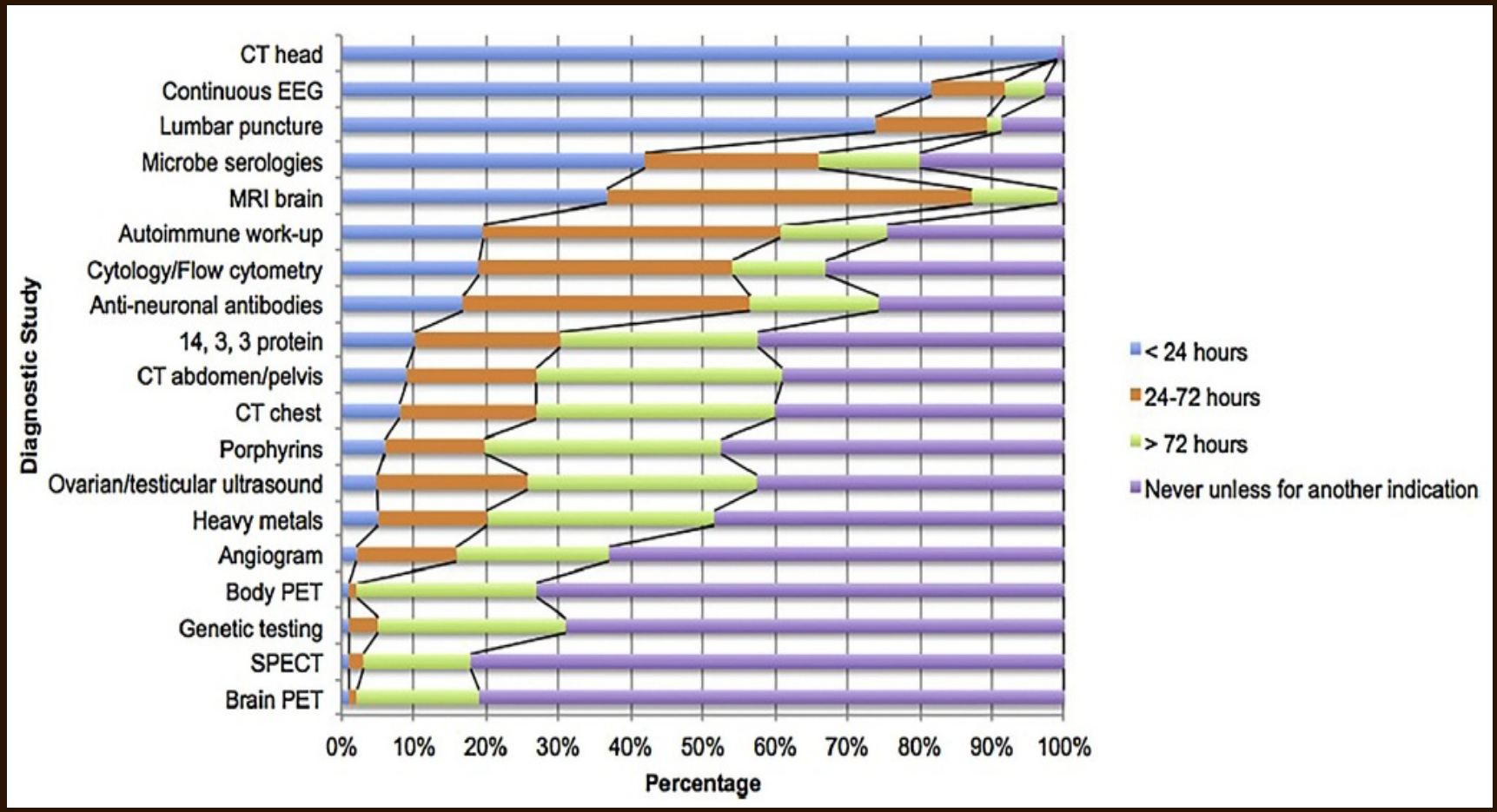


Fig. 1. Diagnostic Approach to NORSE. Survey respondents categorized each diagnostic study into time at which they would obtain the test in the setting of NORSE: <24 h, 24–72 h, >72 h, or never unless indicated for another reason.

Treatment of Refractory SE
NORSE

- ***Proposed Consensus Definition*** *(Epilepsia 2018; DOI:10.1111/epi.14016)*

  - **New-onset Refractory Status Epilepticus(NORSE)** is a clincial pr esentation of a new onset of refractory SE in previously healthy individu als without a clear acute or active structural, toxic or metabolic causes
    - NORSE includes patients with viral infections and autoimmune syndromes of ne w onset, even if these are diagnosed in the initial 72 hours
    - NORSE includes patients with remote brain injuries or resolved epilepsy
    - Determination of NORSE requires imaging, CSF, Toxicology, or other blood tests recommended for evaluation of SE
    - **Cryptogenic NORSE** applies to patients with the clinical presentation of NO RSE, but in whom the cause remains unknown after extensive workup

  - **FIRES(Febrile Infection-Related Epilepsy Syndrome)** is a subcate groy of NORSE, applicable for all ages, that requires a prior febrile infecti on starting between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at onset of SE.

NORSE: *Dignostic Categories*

(Sculier and Gaspard Seizure 2019;68:72-78)

NORSE: Prominent presentation features of the most frequent etiologies.

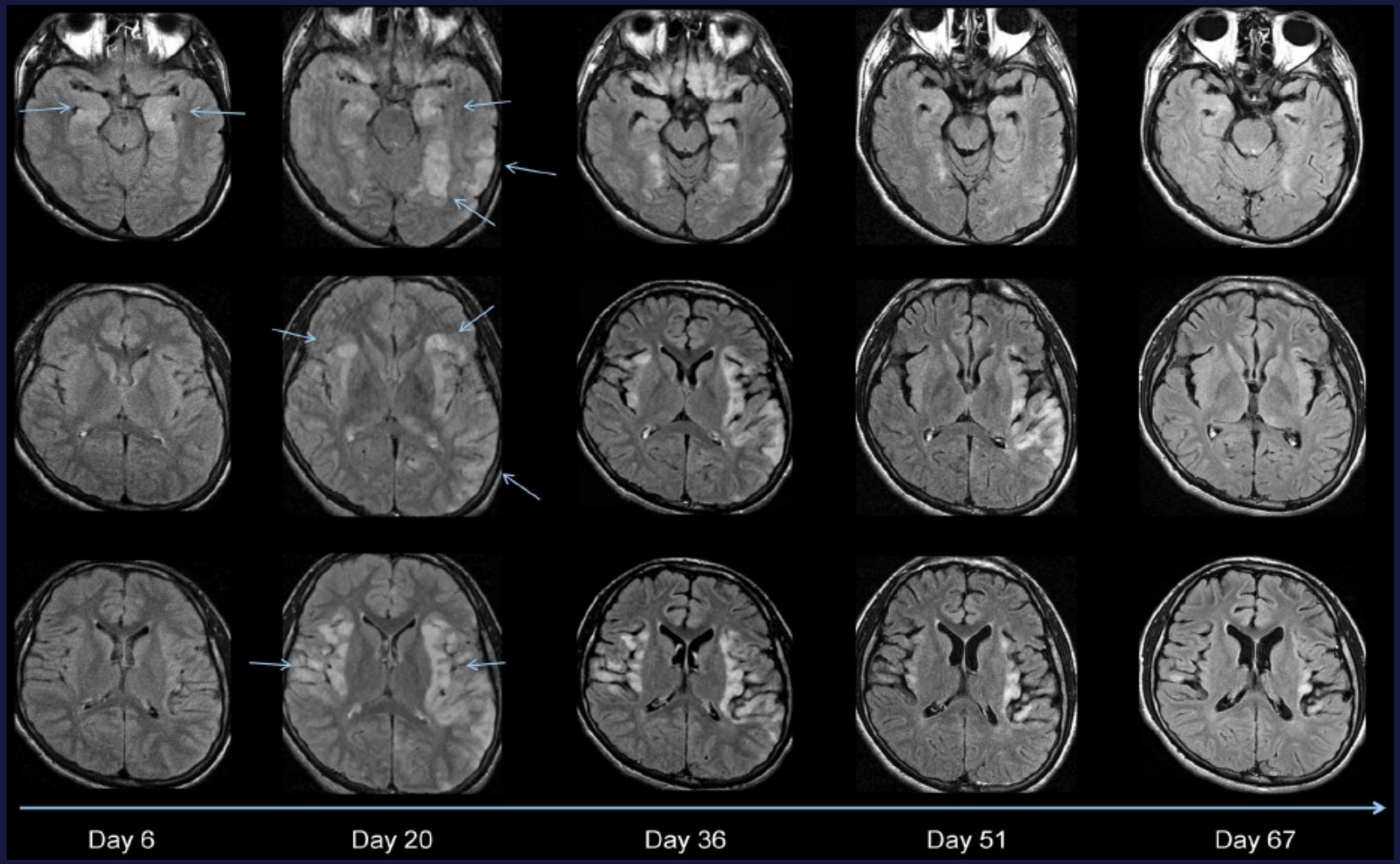
Categories	*	Most frequent findings	Clinical clues
Unknown	50%		No specific findings Prodromal mild febrile illness in 65% of cases Typically severe and prolonged SE
Inflammatory and auto-immune encephalitis	40%	Paraneoplastic limbic encephalitis (Anti-Hu, -Ma2/Ta, -CV2/CRMP-5, -amphiphysin, -VGCC, -mGluR5)	Cognitive, especially memory impairment, behavioral changes, temporal lobe seizures, sleep disturbance Hu: often more diffuse encephalomyelitis Ma2/Ta: hypothalamic dysfunction CV2/CRMP5: diffuse encephalomyelitis, chorea
		Surface-binding autoantibodies	
		Anti-NMDAr	Mostly young females Prodromal fever, short-term memory loss, psychiatric symptoms, hallucinations, oro-lingual dyskinesia, autonomic and respiratory failure *Children*: behavioral changes, movement disorders *EEG*: extreme delta brushes (50%)
		Anti-VGKC complex	Mostly elderly males LGI-1: limbic encephalitis, facio-brachial dystonic seizures, SIADH Caspr2: episodic ataxia
		Anti-GABA(B)r	Limbic encephalitis
		Anti-GABA(A)r	Multifocal neocortical encephalitis
		Anti-AMPAr	Prominent psychiatric symptoms, cerebellar ataxia
		Anti-Glycine-r	No specific features
		Anti-GAD	No specific features
		Steroid responsive encephalopathy with autoimmune thyroiditis	Rapid-onset dementia, myoclonus, stroke-like episodes Anti-TPO, anti-TG
Infectious encephalitis	10%	HSV1	Temporal involvement
		Enterovirus	Rash, acute lower motor neuron syndrome
		CMV	*Immunodeficiency*: Gastro-intestinal symptoms, retinitis, pneumonitis
		EBV	Adenopathies, ataxia
		VZV	*Immunodeficiency*: CNS lymphoma
		Mycoplasma pneumoniae	Rash
		Bartonella henselae	Respiratory symptoms, EEG: extreme spindles
		Arboviruses (West Nile virus, tick-borne virus etc..)	Children. Cat-scratch disease with skin lesion and regional adenopathy Flu-like episode; WNV: parkinsonism, acute lower motor neuron syndrome, EEG: triphasic waves
Genetic disorders	Rare	SCN1A	Dravet syndrome
		PCDH19	Epilepsy and mental retardation limited to female
		CADASIL	Migraine, strokes, visual problems, cognitive deterioration
		Mitochondrial disorders	Elevated CSF lactate and stroke-like episodes.
		MELAS	Occipital seizures, *epilepsia partialis continua*, liver failure, nystagmus,
		POLG1	ataxia.

*Proportions mainly reflect adult population. There is a lack of data in pediatric population.

Abbreviations: AMPAalpha-amino-3-hydroxy-5-méthylisoazol-4-propionate; GABA; gamma aminobutyric acid; CADASIL; cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Caspr2contactin associated protein 2; CMVcytomegalovirus; CNScentral nervous system; CSFcerebrospinal fluid; EBVEpstein-Barr virus; EEGelectroencephalogram; GADglutamic acid decarboxylase; HSVherpes simplex virus; LGI1Leucine-rich glioma inactivated 1; MELASsyndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; NMDA; N-methyl-D-aspartate; PCDHprotocadherin; POLG1mitochondrial DNA polymerase gamma; SIADHsyndrome of inappropriate antidiuretic hormone secretion; SCNneuronal voltage-gated sodium channel; SEstatus epilepticus; TGthyroglobuline; TPOthyroperoxydase; VGKCvoltage gated potassium channel-complex; VZVvaricella-zoster virus; WNVWest-Nile virus.

Cryptogenic NORSE
- A Distinctive Syndrome? -

- Iizuka T et al. (Neurol Neuroimmunol Neuroinflamm 2017;4:e396: doi:10.1212/NX1.0000000000000396)
  - The Symmetric MRI lesions are usually absent at the beginning but appear after establishment of RSE, considered SE induced excitotoxic or inflammatory CNS injury → ***require urgent control of SE***



NORSE: *Treatment Algorithm*

(Sculier and Gaspard Seizure 2019;68:72-78)

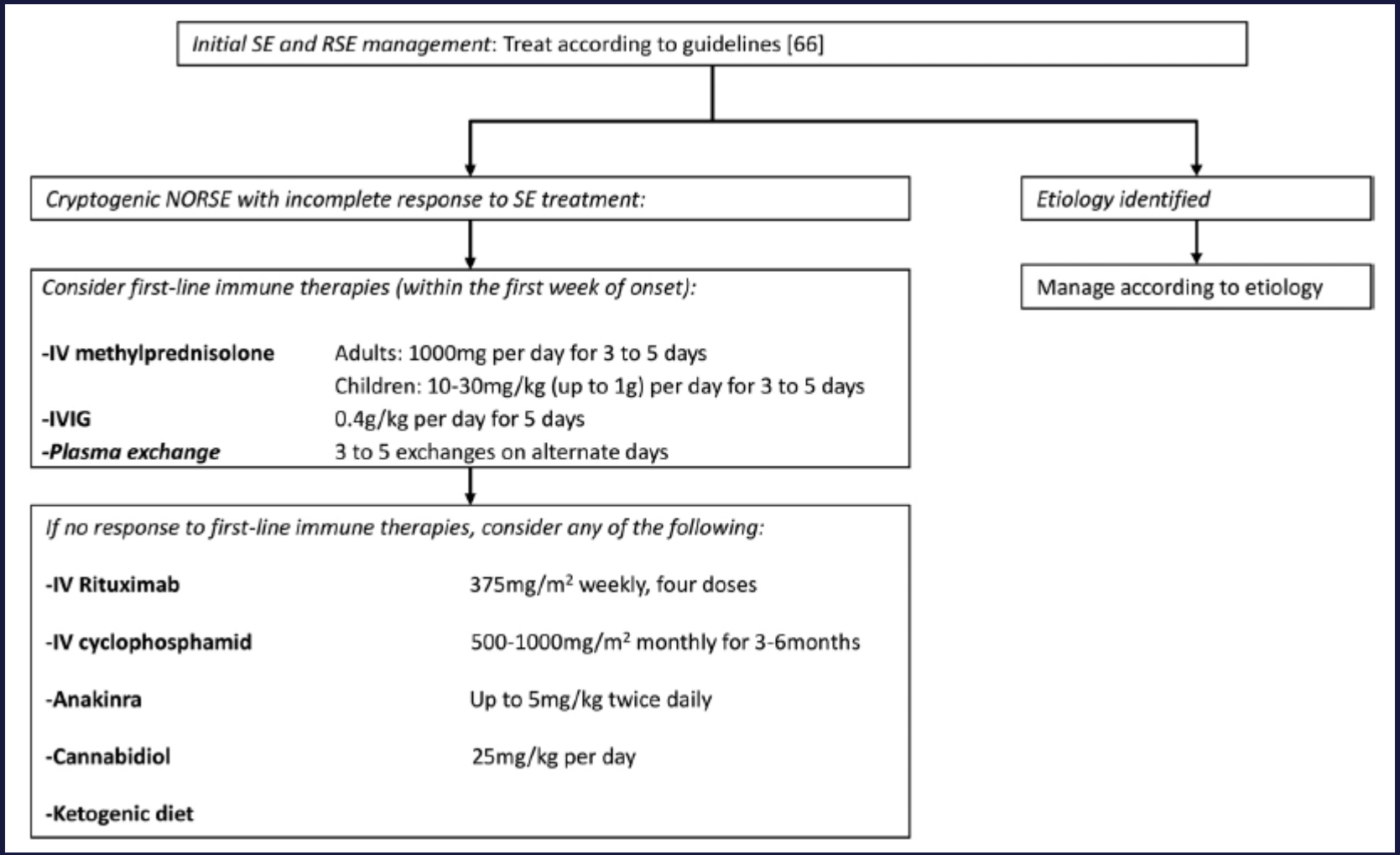


Fig. 2. NORSE treatment algorithm: Commonly used drugs in NORSE and FIRES with most frequently report ed doses (expert opinion) [66]. Adapted from Gaspard et al, 2018 [39] and van Baalen et al, 2017 [10]. IV=intravenous; IVIG=intravenous immunoglobulin; RSE: refractory status epilepticus, SE: status epilepticus.

Management of Status Epilepticus:
Treating the Seizures vs. the Etiology?

CONCLUSION

- Evaluation and management of SE are aimed at:
  - stabilization and avoidance of secondary injury,
  - rapid control of seizures,
  - rapid identification and treatment of the etiology.

- **In patients with Refractory cryptogenic SE**
  - Exhaustive search for underlying etiology is indicated
  - If the search is unrevealing, trial of immune-modulating therapy is highly indicated

Thanks for Your Attention