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 underlying cause of SE
- Understand the diagnostic approaches of refractory status epilepticus
- Understand the current management strategies of New-onset refractory status epilepticus (NORSE)
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 therapeutic measures
- SE without known cause (cryptogenic SE) is frequently difficult to control with serial use of antiepileptic drugs.
- If initial diagnostic evaluation was negative and SE is refractory, a thorough diagnostic workup including CSF exam is mandatory
- Immune-related causes are the most common etiology of new-onset refractory status epilepticus (NORSE)
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**.
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
1. Why should we treat SEIZURES in SE?

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)
- 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*
  - Pre-hospital treatment by paramedics (IV or rectal valium) were associated with shorter duration of SE and lower chance of recurrent seizures in ER

<table>
<thead>
<tr>
<th>Seizure lasting for</th>
<th>10-29min(n=81)</th>
<th>≥ 30 min(n=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spont. Sz termination</td>
<td>43%</td>
<td>7%</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.6%</td>
<td>19%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Prehospital Rx (n’ = 19)*</th>
<th>No Prehospital Rx (n’ = 26)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of SE episode (min)*</td>
<td>31.7 ± 19.6</td>
<td>59.7 ± 39.0</td>
<td>.007</td>
</tr>
<tr>
<td>Recurrent Seizures in ED (%)</td>
<td>57.9</td>
<td>84.6</td>
<td>.045</td>
</tr>
<tr>
<td>Intubation Required (%)</td>
<td>31.6</td>
<td>38.5</td>
<td>.634</td>
</tr>
<tr>
<td>ICU Admission (%)</td>
<td>47.4</td>
<td>42.3</td>
<td>.736</td>
</tr>
<tr>
<td>Length of ICU Stay (days)*</td>
<td>0.9 ± 0.5</td>
<td>2.5 ± 3.2</td>
<td>.180</td>
</tr>
<tr>
<td>Length of Hospital Stay (days)*</td>
<td>2.0 ± 1.6</td>
<td>4.3 ± 5.1</td>
<td>.081</td>
</tr>
</tbody>
</table>
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 reduced 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 min 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 transition of single Sz to SE

Top: after repeated seizures, the synaptic membrane of $\text{GABA}_A$ receptors forms clathrin-coated pits, which internalise as clathrin-coated vesicles (C), inactivating the receptors because they are no longer within reach of the neurotransmitter. These vesicles develop into endosomes (E), which can deliver the receptors to lysosomes (L) where they are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane.

Bottom: by contrast, in NMDA synapses, subunits are mobilised to the synaptic membrane and assemble into additional receptors. As a result of this trafficking, the number of functional NMDA receptors per synapse increases whereas the number of functional $\text{GABA}_A$ 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 from 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

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
    - Prevention of non-convulsive seizures (NCS) by iv- AEDs was associated with lower mortality and lower volume of infarction

![Graph showing correlation between NCS and Core Infarction](image1)

![Bar chart showing lower mortality with NCS](image2)
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)
I. Why should we treat SEIZURES in SE?

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

- Clinical Studies
    - 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%)
      - intracortical 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

![Graphs showing periodic discharges and metabolic changes](image)
3. Seizures generate Systemic Complications worsening the outcome

- 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
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude RR</th>
<th>95% CI</th>
<th>Adjusted RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>4.0</td>
<td>2.2–7.1</td>
<td>3.3</td>
<td>1.8–6.1</td>
</tr>
<tr>
<td>No SE</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>By cause b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural, SE</td>
<td>6.7</td>
<td>3.0–15.0</td>
<td>7.1</td>
<td>2.9–16.9</td>
</tr>
<tr>
<td>Structural, no SE</td>
<td>2.1</td>
<td>0.96–4.6</td>
<td>2.4</td>
<td>1.1–5.5</td>
</tr>
<tr>
<td>Metabolic, SE</td>
<td>3.6</td>
<td>1.1–11.5</td>
<td>3.6</td>
<td>1.1–11.9</td>
</tr>
<tr>
<td>Metabolic, no SE</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Encephalopathic, SE</td>
<td>16.7</td>
<td>3.6–78.1</td>
<td>18.8</td>
<td>3.6–98.6</td>
</tr>
<tr>
<td>Encephalopathic, no SE</td>
<td>2.2</td>
<td>0.29–17.4</td>
<td>1.9</td>
<td>0.23–15.3</td>
</tr>
</tbody>
</table>

*Adjusted RR adjusts for cause of acute symptomatic seizure, age, and sex.

bAdjusted RR adjusts for age and sex.

RR = rate ratio; CI = confidence interval; SE = status epilepticus.
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 strategies 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.**
A Nationwide Cohort Study of 153 patients with autoimmune encephalitis (AIE) in the Netherlands (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 AEDs should be considered as add-on treatment, similar to treatment of other encephalitis symptoms.
II. Why should we treat the ETIOLOGY in 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/metabolic 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, or meningitis, thought to lead to a static lesion and associated with an increased risk of epilepsy. The time 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 insult.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No of patients(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute symptomatic</td>
<td>100 (50.0%)</td>
</tr>
<tr>
<td>Idiopathic/cryptogenic</td>
<td>27 (13.6%)</td>
</tr>
<tr>
<td>Remote symptomatic</td>
<td>39 (19.6%)</td>
</tr>
<tr>
<td>Progressive symptomatic</td>
<td>17 (8.5%)</td>
</tr>
<tr>
<td>febrile</td>
<td>16 (8.0%)</td>
</tr>
<tr>
<td>History of Epilepsy before SE</td>
<td>18 (9.0%)</td>
</tr>
</tbody>
</table>
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

**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

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J. F. Annegers et al., Epilepsia, 1995; 36:327-333
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.
NORSE: New-onset Refractory Status Epilepticus

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

**New-onset Refractory Status Epilepticus (NORSE)** is a clinical presentation of a new onset of refractory SE in previously healthy individuals without a clear acute or active structural, toxic or metabolic causes

- NORSE includes patients with viral infections and autoimmune syndromes of new 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 NORSE, but in whom the cause remains unknown after extensive workup

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

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

### NORSE: Prominent presentation features of the most frequent etiologies.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Most frequent findings</th>
<th>Clinical clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td></td>
<td>No specific findings</td>
</tr>
<tr>
<td>Inflammatory and auto-immune</td>
<td>Paraneoplastic limbic encephalitis (Anti-Hu, Ma2/Ta, -CV2/CRMP-5, -amphiphysin, -VGCC, -mGluR5)</td>
<td>Prodromal mild febrile illness in 65% of cases, Typically severe and prolonged SE</td>
</tr>
<tr>
<td>Surface-binding autoantibodies</td>
<td>Anti-NMDAr</td>
<td>Cognitive, especially memory impairment, behavioral changes, temporal lobe seizures, sleep disturbance</td>
</tr>
<tr>
<td>Anti-VGKC complex</td>
<td>Mostly young females</td>
<td><strong>Children</strong>: behavioral changes, movement disorders, <strong>EEG</strong>: extreme delta brushes (50%)</td>
</tr>
<tr>
<td>Anti-GABA(B)r</td>
<td>Limbic encephalitis</td>
<td>Most elderly males, LGI-1: limbic encephalitis, facio-brachial dystonic seizures, SIADH</td>
</tr>
<tr>
<td>Anti-GABA(A)r</td>
<td>Multifocal necrosis-related encephalitis</td>
<td>Caspr2: episodic ataxia</td>
</tr>
<tr>
<td>Anti-AMPAr</td>
<td>Prominent psychiatric symptoms, cerebellar ataxia</td>
<td><strong>Children</strong>: behavioral changes, movement disorders, <strong>EEG</strong>: extreme delta brushes (50%)</td>
</tr>
<tr>
<td>Anti-Glycine r</td>
<td>No specific features</td>
<td>No specific features</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>No specific features</td>
<td>No specific features</td>
</tr>
<tr>
<td>Steroid responsive encephalopathy with autoimmune thyroiditis</td>
<td>Rapid-onset dementia, myoclonus, stroke-like episodes, Anti-TPO, anti-TG</td>
<td>Temporal involvement</td>
</tr>
<tr>
<td>Infectious encephalitis</td>
<td>HSV 1</td>
<td>Rash, acute lower motor neuron syndrome</td>
</tr>
<tr>
<td>Enterovirus</td>
<td><strong>Immunodeficiency</strong>: Gastro-intestinal symptoms, retinitis, pneumonitis, Adenopathies, ataxia</td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>CMV</td>
<td><strong>Immunodeficiency</strong>: CNS lymphoma</td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>EBV</td>
<td><strong>Mycoplasm pneumoniae</strong></td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>VZV</td>
<td><strong>Bartonella henselae</strong></td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>Arboviruses (West Nile virus, tick-borne virus etc..)</td>
<td><strong>Arbovirus</strong>: rapid-onset meningitis, encephalitis, ataxia, <strong>EEG</strong>: paroxysmal waves</td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>Genetic disorders</td>
<td>Rare</td>
<td>Dravet syndrome, Epilepsy and mental retardation limited to female, Migraine, strokes, visual problems, cognitive deterioration</td>
</tr>
<tr>
<td>SCN1A</td>
<td></td>
<td>Elevated CSF lactate and stroke-like episodes, Occipital seizures, <strong>epilepsia partialis continua</strong>, liver failure, nystagmus, ataxia</td>
</tr>
<tr>
<td>PCDH19</td>
<td></td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>CADASIL</td>
<td></td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
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<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>MELAS</td>
<td></td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
<tr>
<td>POLG1</td>
<td></td>
<td><strong>Children</strong>: Graft-versus-host disease, skin lesion and regional adenopathy, <strong>Flu-like episode</strong>, <strong>Respiratory symptoms</strong>, <strong>EEG</strong>: extreme spikes</td>
</tr>
</tbody>
</table>

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

Abbreviations: AMPA, Alpha-amino-3-hydroxy-5-methylisoxazol-4-propionate; GABA, gamma aminobutyric acid; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Caspr2, contactin associated protein 2; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; EEG, electroencephalogram; GAD, glutamic acid decarboxylase; HSV, herpes simplex virus; LGI1, Leucine-rich glioma inactivated 1; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; NMDA, N-methyl-D-aspartate; PCDH1, protocadherin; POLG1, mitochondrial DNA polymerase gamma; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SCN, neuronal voltage-gated sodium channel; SE, status epilepticus; TG, thyroglobulin; TPO, thyroperoxidase; VGC, voltage gated potassium channel complex; VZV, varicella-zoster virus; WN, West Nile virus.
Cryptogenic NORSE - A Distinctive Syndrome?


The Symmetric MRI lesions are usually absent at the beginning but appear after establishment of RSE, considered S
E 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 reported 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.
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