MN Epilepsy Group®
Focused expertise. Comprehensive care.

REFRACTORY STATUS EPILEPTICUS

James White, MD
Minnesota Epilepsy Group

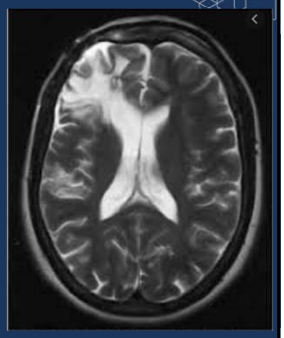
PATIENT EXAMPLE

- 42 yo male with PMH significant for epilepsy and traumatic brain injury.
- Patient's seizures began at age 32 years of age following head trauma. The patient was involved in a motorcycle accident.
- The patient's main seizure type:
  - Difficult to describe aura- then loss of contact. Would then progress to bilateral tonic clonic jerking.
- The patient worked in construction.

MN EpilepsyGroup

PATIENT EXAMPLE

- The patient's MRI demonstrates right frontal encephalomalacia.
- His seizures have been well controlled on levetiracetam for > 5 years.



MN EpilepsyGroup

PATIENT EXAMPLE

- The patient stopped taking his levetiracetam- due to financial reasons.
- The patient was found down on the sidewalk. He was noted to have GTC seizure activity. It was unclear how long he had been having seizure activity.

MN EpilepsyGroup

PATIENT EXAMPLE

- EMS was called. The patient was treated with midazolam and intubated in the field. He was taken to ANW Hospital ED.
- In the ED:
  - The patient continued to have subtle convulsive seizure activity.
  - The patient was loaded with levetiracetam and propofol was increased.
  - Clinical seizure activity was terminated.

MN EpilepsyGroup

STILL IN STATUS EPILEPTICUS (SE)

MN EpilepsyGroup

PATIENT EXAMPLE

- The patient's seizures were very difficult to control:
  - When his sedation was reduced, he went back into status epilepticus.
  - Finally, on ICU day 9, the patient was able to come off sedation without seizure activity.
  - His AED regimen included:
    - Levetiracetam
    - Fosphenytoin
    - phenobarbital

MN EpilepsyGroup

PATIENT EXAMPLE

- Fortunately, the patient recovered and was eventually discharged home- after rehab stay.
- He felt that he had some memory impairment.
- He was able to return to work.

MN EpilepsyGroup

STATUS EPILEPTICUS: DEFINITIONS

- Status epilepticus (SE):
  - 5 minutes of seizure activity.
- Refractory SE:
  - SE persisting despite adequate administration of benzodiazepines and at least one antiepileptic drug (AED).
  - 12-43% of SE
- Super refractory SE:
  - SE that continues for 24 hours or more after the use of anesthetic therapy, including cases that recur on weaning of the anesthetic agent.
  - 15% of SE

MN EpilepsyGroup

ILLUSTRATIVE POINTS

- The patient had been seizing for potentially a long time.
  - It is harder to control seizures the longer they have been ongoing.
- His outcome was overall mostly good:
  - AED noncompliance is associated with good outcome (compared to irreversible neurological insults such as a large stroke, hypoxia, etc).
- Even though convulsions are stopped, nonconvulsive seizures and nonconvulsive status epilepticus are still common.

MN EpilepsyGroup

STATUS EPILEPTICUS: DEFINITION

- Average duration of seizure:
  - CPS: 106 seconds
  - GTC: 59.9 seconds
  - Determined in patients undergoing v-EEG monitoring.
- A GTC seizure that is greater than 5 minutes in duration is > 18 standard deviations removed from the norm.

CLASSIFICATION OF STATUS EPILEPTICUS

- Generalized convulsive status epilepticus
  - The most dangerous type.
- Focal convulsive status epilepticus
- Nonconvulsive status epilepticus

MN EpilepsyGroup

EARLY TREATMENT OF STATUS EPILEPTICUS IMPROVES OUTCOME

- Less likely to require ICU care.
- Less likely to go into RSE.
- May reduce neuronal damage/neurological deficits/mortality.

MN EpilepsyGroup

RAMPART STUDY (NEJM 2012)

- The RAMPART Study compared treatment of status in the field by paramedics:
  - midazolam IM (study drug)
  - vs lorazepam IV (gold standard)
- The hypothesis: perhaps an IM dose could be given faster than IV, and be more effective.

RAMPART STUDY

- IM midazolam demonstrated a better clinical outcome than IV lorazepam:
  - On arrival to ED, seizures were more likely terminated.
  - Lower rates of hospital admission.
- Thus- supports that faster is better.
- ** Still use iv lorazepam in the hospital setting. (RAMPART was a study for in the field treatment).

MN EpilepsyGroup

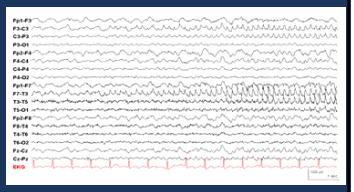
PATIENT EXAMPLE

- 69 yo female with PMH signficant for HTN. No prior history of epilepsy/seizure activity. Patient admitted due to mental status change.
- Nursing staff noted that patient's confusion intermittently became more severe:
  - She would become less responsive.
  - She was noted to have subtle stereotyped movements:
    - Slight mouth movements, repositioned herself in the chair, looked down.
  - Duration: 2-3 minutes.
  - Frequency: every few minutes.

MN EpilepsyGroup

PATIENT EXAMPLE

- Nursing staff contacted medical team- expressed concern about SE.
- Continuous v-EEG was initiated- EEG demonstrated gradually increasingly frequent seizures/ status epilepticus.



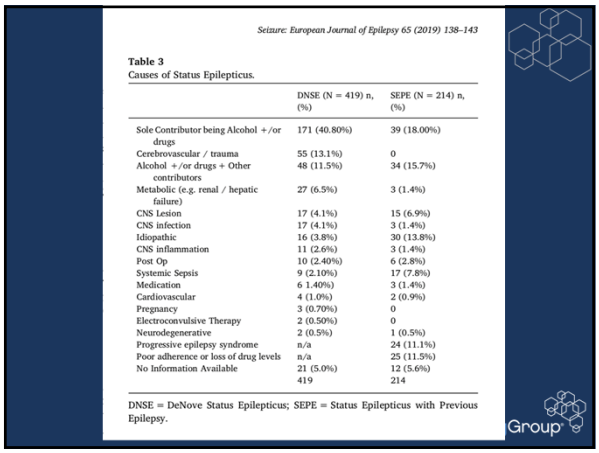
MN EpilepsyGroup

PATIENT EXAMPLE

- The patient was treated with:
  - Lorazepam
  - Levetiracetam
  - Lacosamide

- Seizures came under control.
- Patient had an excellent outcome.
- The nursing staff's identification of seizure activity was the key!

MN EpilepsyGroup



Seizure: European Journal of Epilepsy 65 (2019) 138–143

Table 3
Causes of Status Epilepticus.

	DNSE (N = 419) n, (%)	SEPE (N = 214) n, (%)
Sole Contributor being Alcohol +/or drugs	171 (40.80%)	39 (18.00%)
Cerebrovascular / trauma	55 (13.1%)	0
Alcohol +/or drugs + Other contributors	48 (11.5%)	34 (15.7%)
Metabolic (e.g. renal / hepatic failure)	27 (6.5%)	3 (1.4%)
CNS Lesion	17 (4.1%)	15 (6.9%)
CNS infection	17 (4.1%)	3 (1.4%)
Idiopathic	16 (3.8%)	30 (13.8%)
CNS inflammation	11 (2.6%)	3 (1.4%)
Post Op	10 (2.40%)	6 (2.8%)
Systemic Sepsis	9 (2.10%)	17 (7.8%)
Medication	6 1.40%)	3 (1.4%)
Cardiovascular	4 (1.0%)	2 (0.9%)
Pregnancy	3 (0.70%)	0
Electroconvulsive Therapy	2 (0.50%)	0
Neurodegenerative	2 (0.5%)	1 (0.5%)
Progressive epilepsy syndrome	n/a	24 (11.1%)
Poor adherence or loss of drug levels	n/a	25 (11.5%)
No Information Available	21 (5.0%)	12 (5.6%)
	419	214

DNSE = DeNove Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy.

Table 1 Eventual etiology of new-onset refractory status epilepticus after extensive evaluation

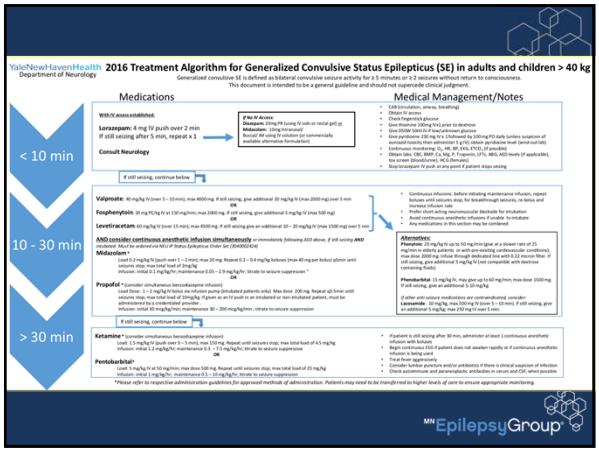
Etiology	No. (%)
Cryptogenic	67 (52)
Nonparaneoplastic autoimmune	25 (19)
Anti-NMDA receptor	7 (5)
Anti-VGKC complex	5 (4)
SREAT	5 (4)
Cerebral lupus	4 (3)
Anti-GAD65	3 (2)
Anti-striational	1 (1)
Paraneoplastic	23 (18)
Anti-NMDA receptor	9 (7)
Anti-VGKC complex	3 (2)
Anti-Hu	3 (2)
Anti-VGCC	2 (2)
Anti-CRMP5	1 (1)
Anti-Ro	1 (1)
Seronegative	4 (3)
Infection-related	10 (8)
EBV	2 (2)
VZV	2 (2)
CMV	1 (1)
WNV	1 (1)
Mycoplasma pneumoniae	2 (2)
Syphilis	1 (1)
Toxoplasma gondii	1 (1)
Others	5 (4)
SESA	2 (2)
Leptomeningeal carcinomatosis	2 (2)
Creutzfeldt-Jakob disease	1 (1)

DIAGNOSTIC PEARL

- **A significant percentage of patients with SE do not have a clear etiology when first admitted.**
- **For some patients, repeating testing 4-5 days after admission may help clarify the dx:**
  - **Repeat MRI: May show evidence for encephalitis, posterior reversible encephalopathy syndrome, anoxic brain injury/edema.**
  - **Repeat CSF: Herpes PCR can be negative in herpes encephalitis- during first 2-3 days of symptoms.**

FREQUENCY OF SZ/NCSE

ADMISSION DX	N	ANY SZ	NCSE
Epilepsy related	51	17	10
Cns infection	35	10	6
Brain tumor	43	10	5
Post neurosurg	13	3	1
Anoxia	25	5	3
SAH	108	20	14
TBI	51	9	4
Toxic-metabolic	38	7	3
Unexplained	105	17	5
ICH	45	6	4
Ischemic stroke	56	6	4
Total	570	110 (19%)	59 (10%)



PRACTICAL TIPS FOR CONVULSIVE STATUS EPILEPTICUS

- **Give benzodiazepine (proven to be one of best meds in SE):**
  - **Lorazepam 0.1mg/kg iv in divided doses.**
  - **For example, give 2 mg iv. Give more doses, up to approximately 7mg.**
- **Give second therapy:**
  - **Lorazepam wears off- so will likely want another AED on board.**
  - **Fosphenytoin, valproic acid and levetiracetam are all ok.**
- **If benzodiazepine and second therapy does not work, move quickly to:**
  - **Intubation**
  - **Anesthetic agent (propofol is often used for sedation in ICU at- so this is often the med used)**
  - **Go to anesthetic because: third medication (if not anesthetic) only has 2-3% chance of stopping seizure activity.**

Anesthetic agents for status

- Commonly used anesthetic agents for status epilepticus:
  - Propofol
  - Midazolam
- If propofol and midazolam do not work:
  - Pentobarbital
- If hypotension is an issue:
  - Consider ketamine

MN EpilepsyGroup

TREATMENT OF SE

- In refractory cases, consider:
  - Propofol, midazolam or pentobarb
- A meta analysis compared these medications in the treatment of refractory status:
  - Pentobarb seems the best for controlling seizures.
  - Pentobarb was associated with more complications:
    - Hypotension, need for pressors
  - Practical reality: Patients are often being treated with propofol for sedation in a patient on a vent. Often just titrate propofol to stop seizures—if they continue, then use pentobarbital.

MN EpilepsyGroup

ADDITIONAL TREATMENTS: NONSURGICAL

- Immunotherapy:
  - High-dose steroids
  - Iv immunoglobulin
  - Cyclophosphamide
- Ketogenic diet
- Electroconvulsive therapy

MN EpilepsyGroup

ADDITIONAL TREATMENTS: NONSURGICAL

- Therapeutic hypothermia
  - Case reports have suggested that cooling a patient to 32 degrees F could terminate refractory status.
  - One multicentered randomized clinical trial (Legriel, NEJM, 2016):
    - Compared:
      - Therapeutic hypothermia to 32-34 degree F for 24 h vs
      - Standard medical treatment
    - Rate of progression to SE in first day was lower in hypothermia group.
    - However, no difference between groups after 90 days.

MN EpilepsyGroup

ADDITIONAL TREATMENTS: SURGICAL

- Surgical resection:
  - Can be considered in patients with focal seizure onset.
  - Possibly best results if a focal lesion on MRI can be identified.

MN EpilepsyGroup

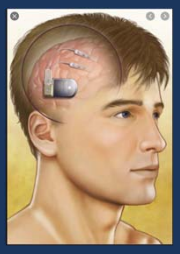
ADDITIONAL TREATMENTS: SURGICAL

- Vagal Nerve Stimulation (VNS):
  - There are several case reports and small series looking at VNS in refractory SE.
  - Systematic review of the literature (Zeiler, Epilepsy Res, 2015) identified 17 studies with 28 patients.
    - Those with generalized SE, 76% terminated
    - Those with focal SE, 25% terminated
    - Studies provided weak evidence.

MN EpilepsyGroup

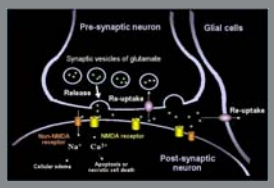
ADDITIONAL TREATMENTS: SURGICAL

- **Responsive Neurostimulation (RNS):**
  - **Case reports suggest that RNS may terminate seizures in refractory SE.**



SE AND DAMAGE TO THE BRAIN

- Mechanism has been thought to be related to:
  - Prolonged seizure activity results in massive glutaminergic receptor over activity. This results in calcium influx into neurons that triggers a cascade of processes---leading to:
    - Cell death by necrosis (excitotoxicity).
    - Triggering programmed cell death (apoptosis).



REFRACTORY SE: OUTCOME

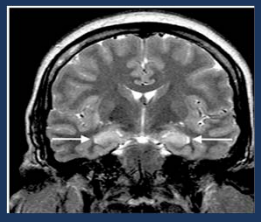
- **Refractory SE mortality rates:**
  - **11-30%**
- **Super-refractory SE mortality rates:**
  - **22-50%**
- **Both refractory and super-refractory SE are associated with significant functional decline in a high percentage of patients.**
  - **Cognitive impairment, hemiparesis, tremor, coordination issues.**

REFRACTORY SE: OUTCOME

- **Of note, there are still a proportion of patients who survive with good outcome.**
- **Good outcome associated with:**
  - **Young age**
  - **No MRI evidence of structural damage.**

MRI IN STATUS EPILEPTICUS

- **Common areas of signal change on MRI:**
  - **Mesio-limbic (hippocampal area)**
  - **pulvinar**
  - **cerebellum**
  - **basal ganglia**
- **Can be reversible or permanent damage.**



CONCLUSIONS

- **Early treatment of SE improves outcome.**
  - **There is a lot at stake!**
- **Refractory SE is relatively common in critical care settings.**
- **There are an expanding number of treatments available for SE.**


THANK YOU!
EpilepsyGroup