National Institute of Neurological Disorders and Stroke

NIH CounterACT Program

Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes

February 28 - March 1, 2023

Clinical Unmet Needs in Refractory Status Epilepticus, Including SRSE and NORSE

Lawrence J. Hirsch, MD, Yale University

Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes

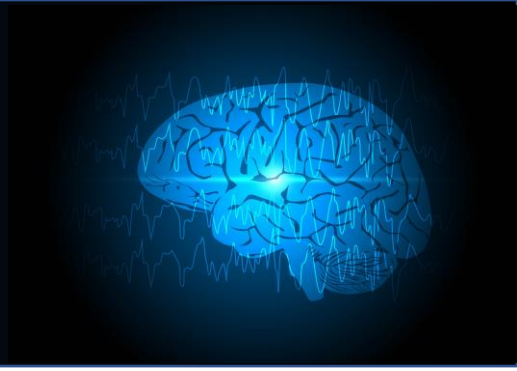
Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of NIH.

Disclosures

This certifies that I, Lawrence J. Hirsch, MD, have financial relationships that are potentially relevant to the subject matter of the presentation (next slide).

Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes: DISCLOSURES



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Consultant

- Ceribell; Eisai; Marinus; Neuropace; UCB; Neurelis; Rafa; Gilead; Vial Health Technology

Honoraria for speaking

- Neuropace; Natus; UCB

Royalties

- Wolters Kluwer for UpToDate sections on EEG, NCSE, imaging in epilepsy
- Wiley for the Atlas of EEG in Critical Care (Hirsch and Brenner 1st ed; Hirsch, Fong and Brenner, 2nd ed, 2023)

Sample case to guide us

Young unidentified female found convulsing on a jogging path in the park. 911 called by a passer by.

Case, continued

- EMS: IM midaz administered
- Arrival to ED: on and off convulsive movements, not awake
- Loaded w/ levetiracetam, jerking stops, not waking up

Definitions (ILAE plus)

- SE: 5 min if bilat convulsive, otherwise 10 mins* (ILAE)
  - Or back to back seizures w/out return to baseline
  - *or >20% of any hour for nonconvulsive ictal activity (ACNS 2021)
- Established SE: failed benzo
- Refractory SE: failed at least 2 meds
- Super refractory SE: failed 24h of anesth
- Prolonged SE/prolonged SRE: >1 week of SE or RSE

Seizure burden is independently associated with short-term outcome in critically ill children

Payne ET, … Hahn C. Brain 2014

- N=259 PICU patients undergoing CEEG
- Outcome: neurological decline (on Peds Cerebral performance Category score, PCPC)
- Seizures in 36%
- Neurological decline in 67%
- If maximum hourly seizure burden was >20% (12 min), marked rise of chance and severity of neurological decline (but not mortality)

Seizure burden is independently associated with short-term outcome in critically ill children

Payne ET, … Hahn C. Brain 2014

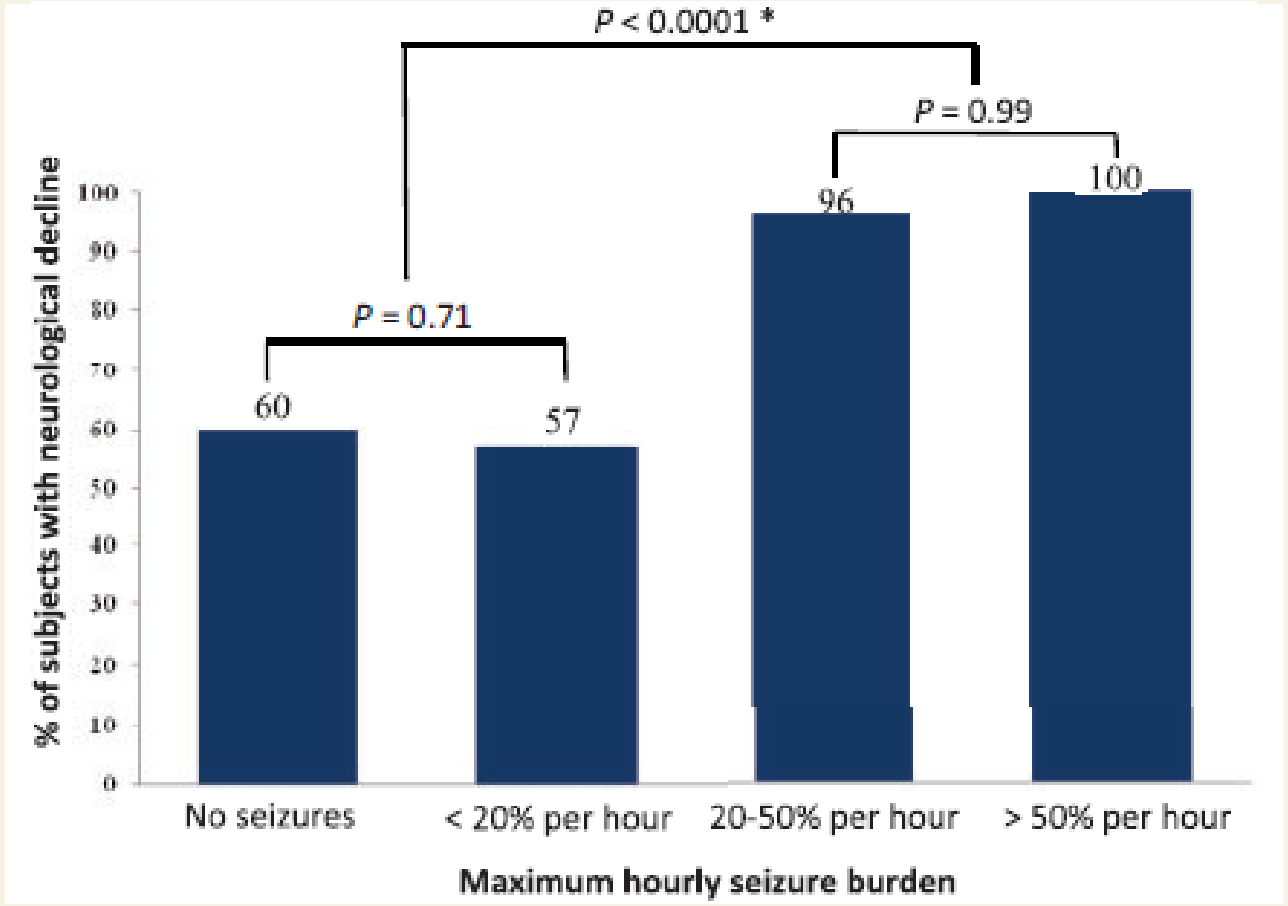


Figure 1 Maximum hourly seizure burden of 20% (12 min) is associated with neurological decline.Comparisons performed using Fisher's exact test. The single subject with a seizure burden

What we do know

- Benzos > placebo on way to hospital for convulsive SE (Alldredge et al, NEJM 2001)
- LRZ > PHT (VA Status study, Treiman et al 1998)
- IM midaz > IV loraz (if no IV in place already) (RAMPART, Silbergleit et al 2012)
- For benzo-refractory SE: VPA=fosPHT=LEV (ESETT, Kapur et al, 2019)
  - 45-47% success

What we do not know

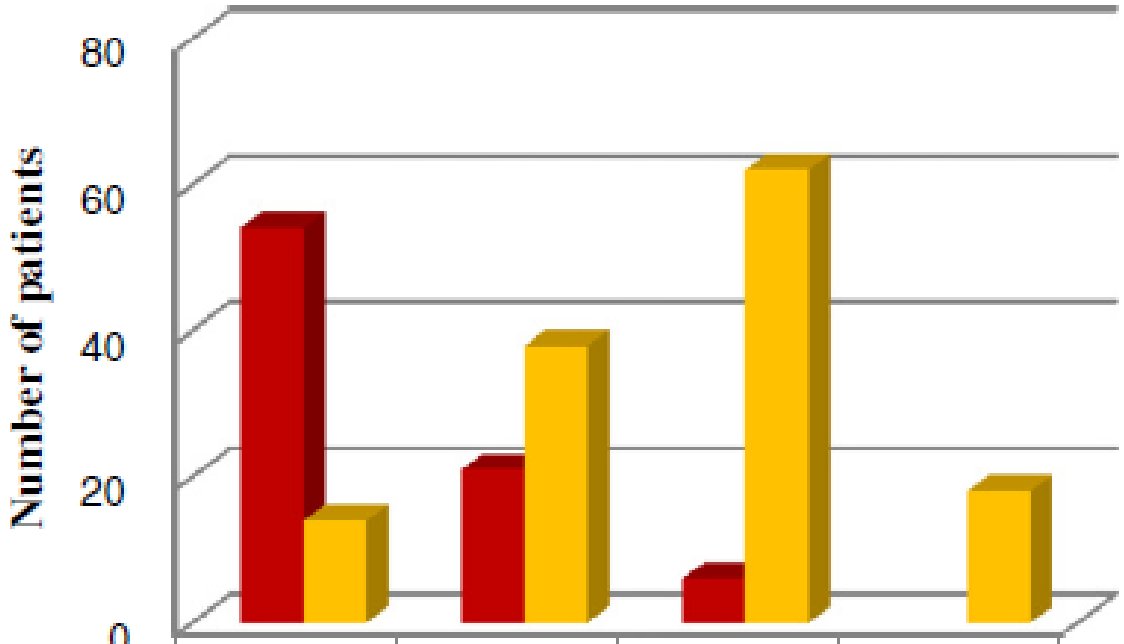
- Is intranasal as good or better than IM for benzos?
- How do brivaracetam and lacosamide compare to the 3 ESETT meds?
  - For refractory nonconvulsive seizures (not SE):
    - Lacos non-inferior to fosPHT (TRENDS, Husain et al, 2018)
- Is there a role for ketamine? At what stage?
- Other neuroprotective agents?
- Which is better, serial administration, or cocktails?
- If we need anesthesia, which agent? To what endpoint?

Case of the unidentified jogger, cont’d

- In ED, unresponsive, no longer having any movements
- All labs, head CT, tox screen negative/normal
- Given 250 mg IV pyridoxine
  - Does B6 defic play a role in benzo-refractory SE?

Pyridoxine deficiency in adult SE

Dave HN et al, Epil Behav 2015



	0 to 5	5+ to 10	10+ to 50	> 50
NCSE	54	21	6	
Outpatients	14	38	62	18

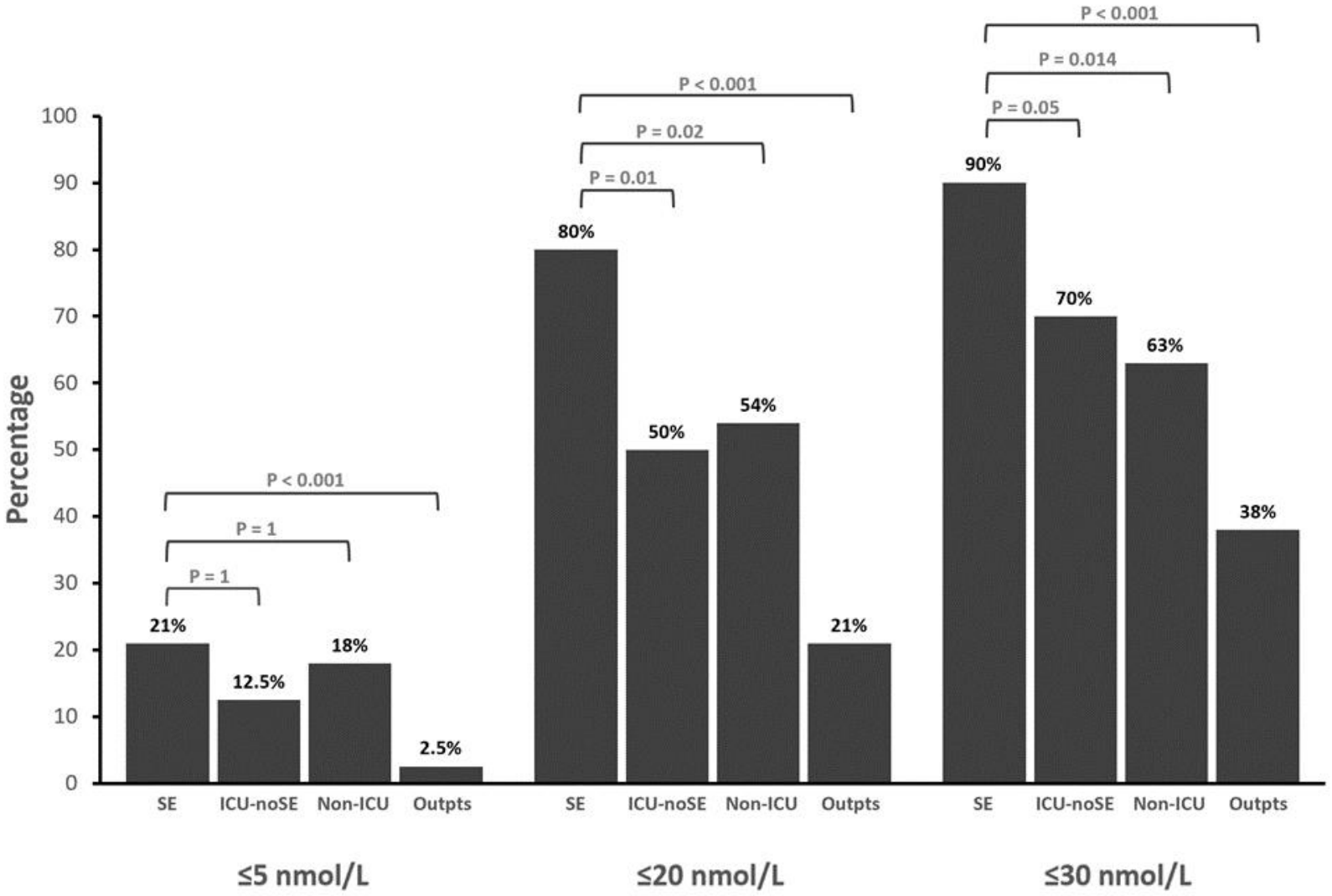
Fig. 1. Pyridoxine blood level (ng/ml) in patients with SE (n = 81) versus outpatients (n = 132).

- 94% of SE patients were deficient (≤10 ng/mL = 40 nmol/L), vs. 39% of outpatients
- Pyridox was undetectable in 14% of SE patients

Pyridox in Established SE:

Rubinos C et al, neurocrit care 2023

- 293 patients with pyridox levels:
  - 52 Established SE
  - 40 ICU non-SE
  - 44 non-ICU
  - 157 outpatients

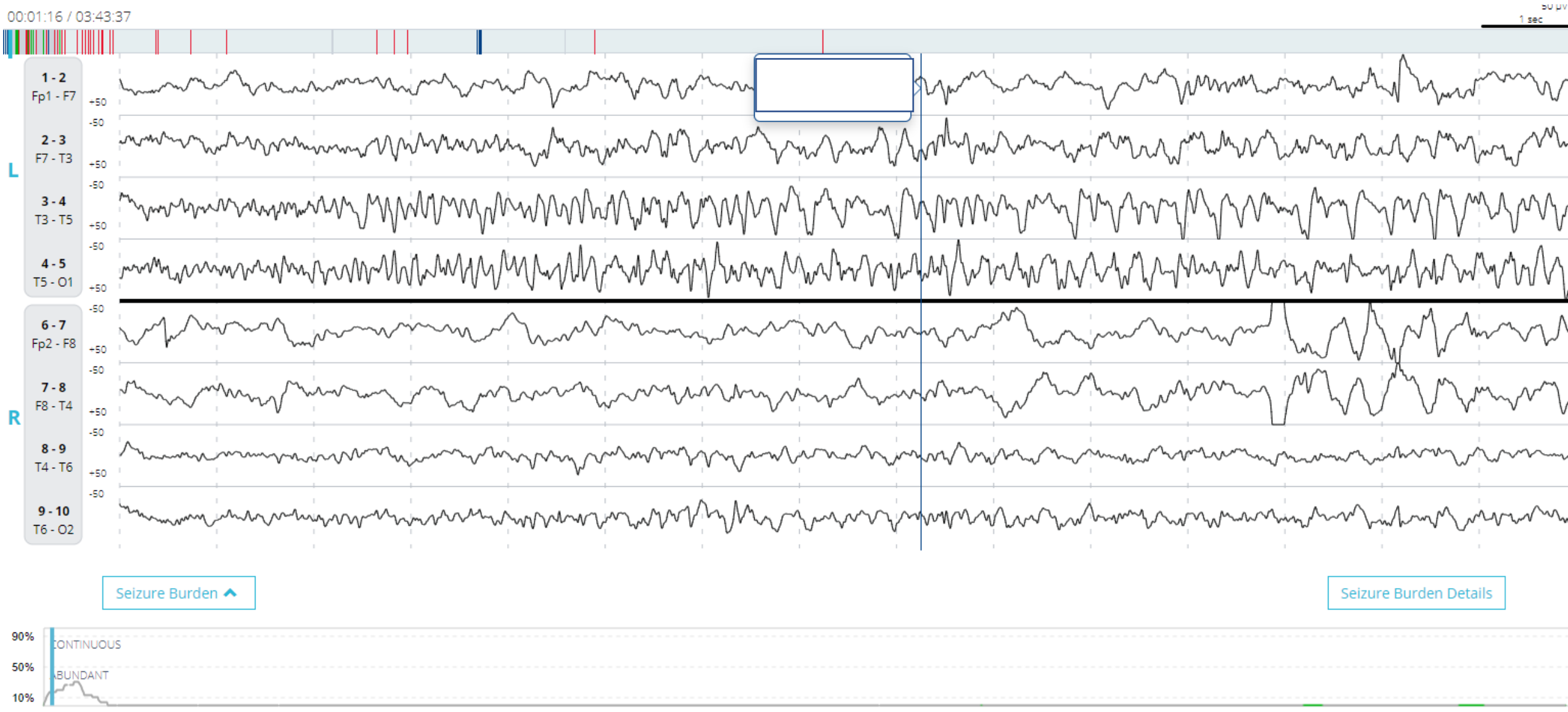


Case of the unidentified jogger, cont'd

- Rapid response EEG done: shows frequent 1-2 minute seizures from either temporal lobe with seizure burden of 40%; no clinical correlate (except unresponsiveness throughout)
- VPA load given, seizure burden down to 15%, still unresponsive
  - Abundant LPDs between seizures, 1.5 Hz
  - Occasional BIPDs

- Anesthesia? More anti-seizure meds? Is the ictal activity causing harm? How about the periodic discharges?

Rapid-response EEG



Adverse physiologic effects of nonconvulsive seizures

- Increased CBF and ICP
- Increased lactate
- Increased glutamate (6 fold)
- Increased glycerol (membrane breakdown)
- Increased neuron specific enolase
- Increased edema/mass effect on serial scans
- Increased peri-injury depolarizations

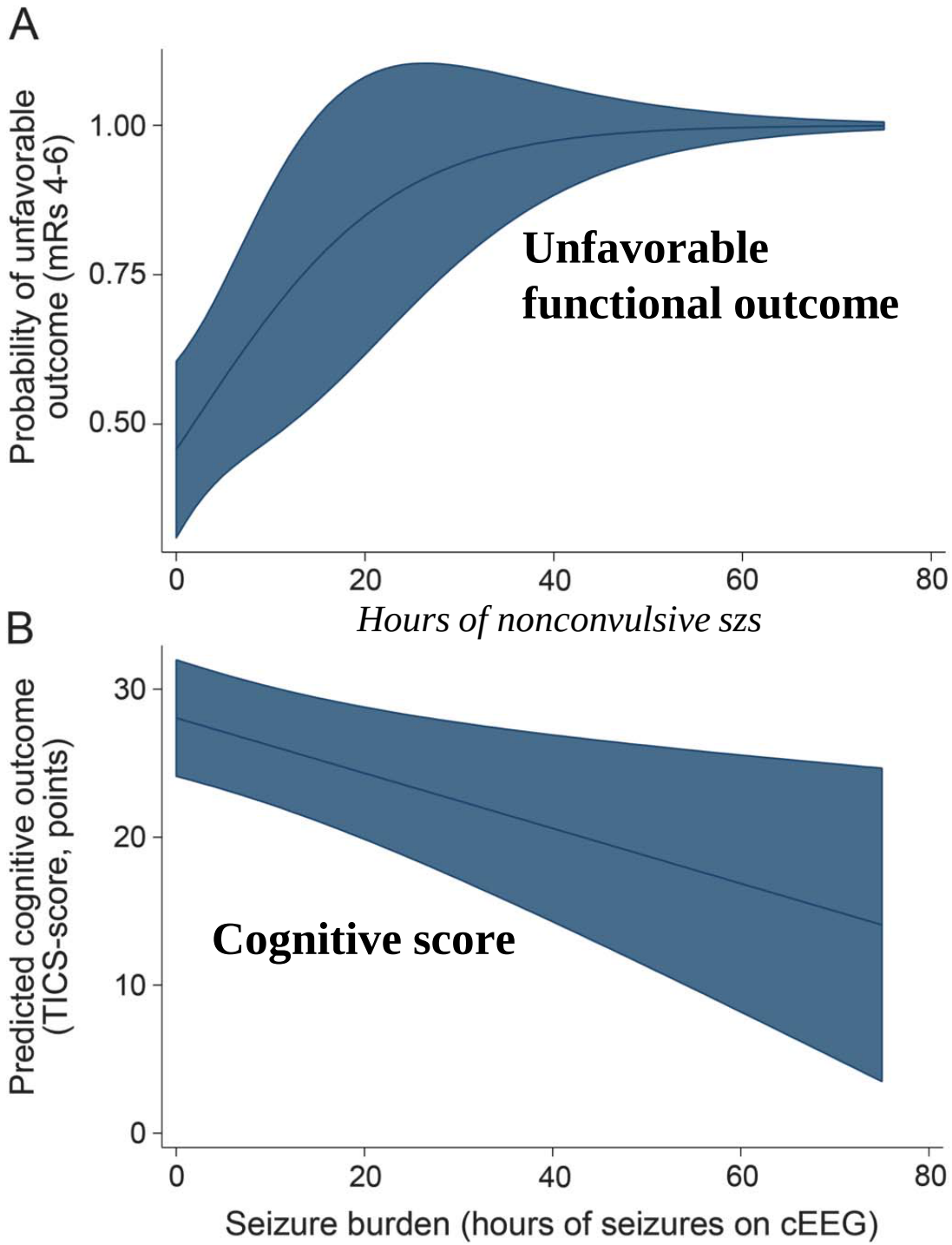
Seizure burden in SAH associated with functional and cognitive outcome

De Marchis GM et al, Neurology 2016

- 402 consecutive adult patients with SAH undergoing continuous EEG from 1996-2013
- Seizures in 50 patients (12%)
  - 46/50 were in NCSE
  - All seizures were nonconvulsive
  - Median seizure burden was 6 hours

Seizure burden in SAH associated with functional and cognitive outcome at 3 months

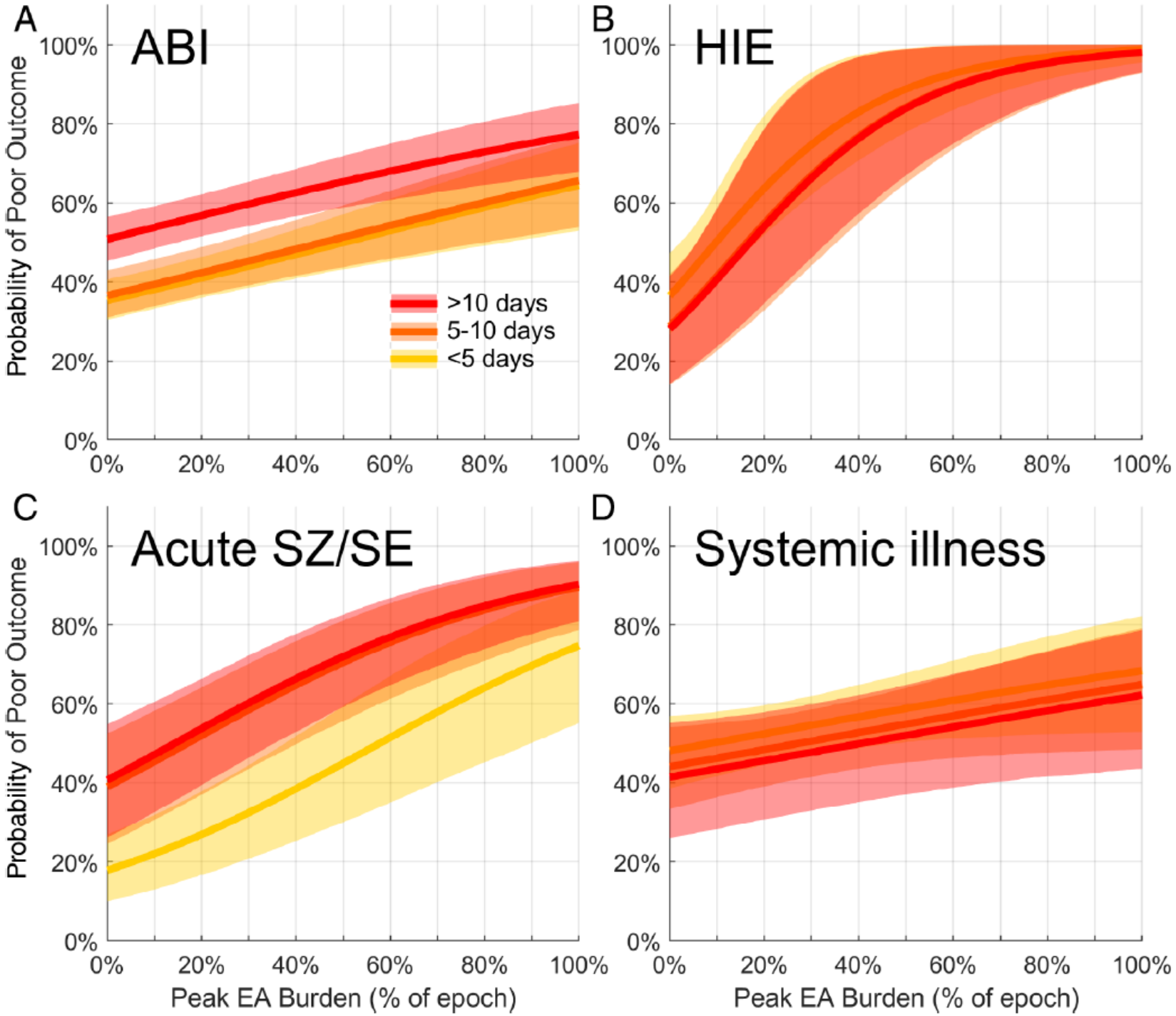
De Marchis GM et al, Neurology 2016



Automated calculation of seizure and epileptiform pattern burden and its association with outcome

Zafar SF et al, Annals Neurol 2021

- Automated detection of highly epileptiform patterns, including seizures, in 1967 patients undergoing cEEG
  - Excluded sporadic epileptiform discharges
- Peak (max 12-hr) epileptiform burden was a strong independent predictor of outcome ($p<0.0001$), in a clear dose-dependent manner.
  - Also: age, Apache-II, sz on presentation [protective], HIE
  - Increase of “epileptiform” burden from 0 to 100% increased the chance of poor outcome by 35% after accounting for confounders.



Automated calculation of seizure/epileptiform pattern burden and its association with outcome

Zafar SF et al, Annals Neurol 2021

- Peak 12-hour burden and association w/ poor outcome

JAMA Neurology | Original Investigation

Electroencephalographic Periodic Discharges and Frequency-Dependent Brain Tissue Hypoxia in Acute Brain Injury

Jens Witsch, MD; Hans-Peter Frey, PhD; J. Michael Schmidt, PhD; Angela Velazquez, MD; Cristina M. Falo, PhD; Michael Reznik, MD; David Roh, MD; Sachin Agarwal, MD; Soojin Park, MD; E. Sander Connolly, MD; Jan Claassen, MD, PhD

2017

- 90 comatose SAH patients
- Invasive multimodality monitoring including depth electrode in most
- 36% had PDs on depth and scalp EEG, 23% on depth only
- 31% had seizures, but 2/3 of these were only visible on depth, not scalp

JAMA Neurology | Original Investigation

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2017

- RESULTS:
- Increasing frequency of PDs (from 0.5 Hz to 3.0 Hz) was assoc'd with increasing CBF, but dropping tissue oxygen, reaching hypoxic levels when PDs >2.0 Hz.

JAMA Neurology | Original Investigation

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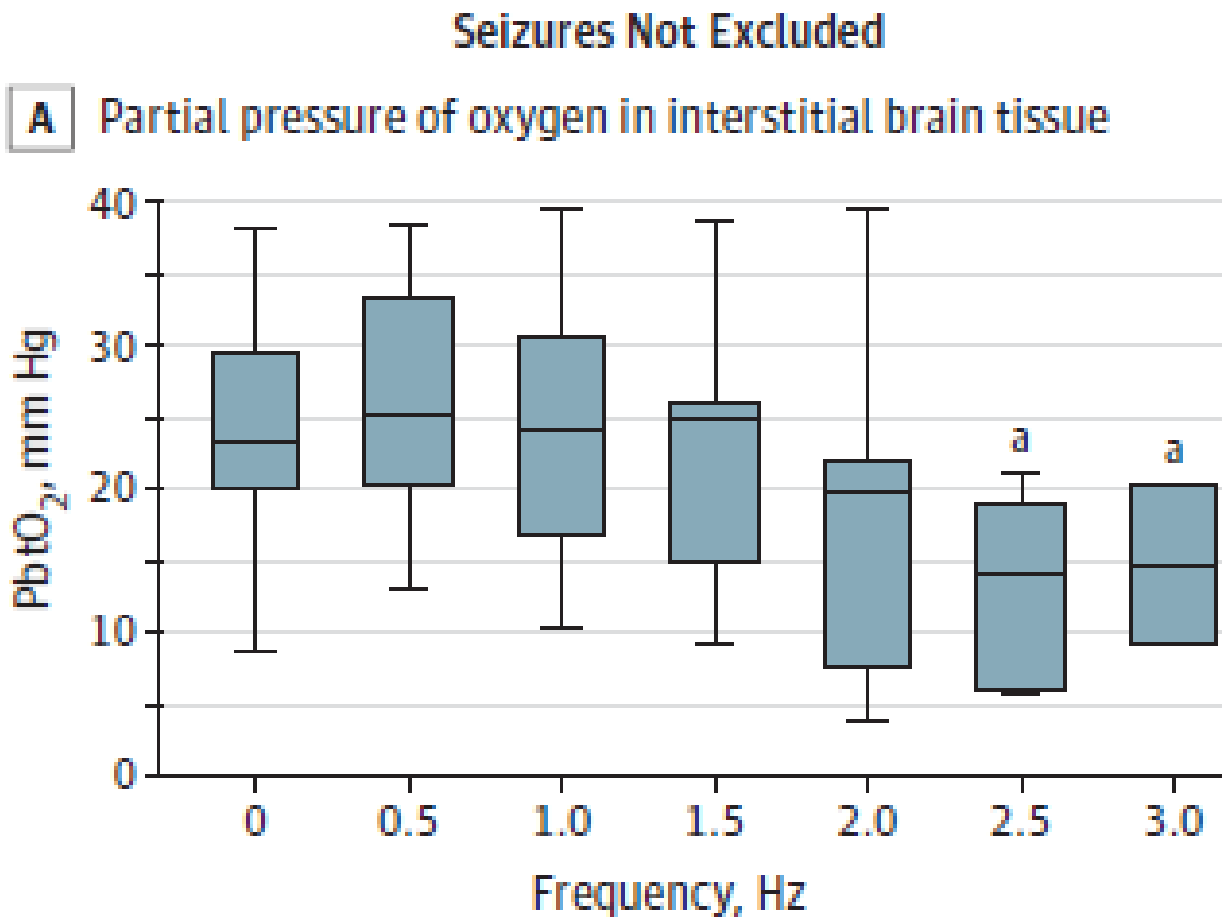
2017



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2017; Columbia Univ

- CONCLUSIONS
- On average, in comatose SAH patients, the brain can compensate for increased metab demand via increasing CBF up to about 2 Hz, but not faster than that.

- Relevant with no acute brain injury?

Consensus Definition of NORSE

Hirsch LJ et al, Epilepsia 2018

- *New-Onset Refractory Status Epilepticus:* ***A clinical presentation****, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause.*
  - Includes viral infections and autoimmune syndromes –these may present as NORSE
  - Typically presents as super-refractory status epilepticus (SRSE), but this is not required for the diagnosis of NORSE.
  - Subgroup: Cryptogenic after extensive workup; referred to as “cryptogenic NORSE” or “NORSE of unknown etiology”.

Consensus Definition of FIRES

Hirsch LJ et al, Epilepsia 2018

- FIRES: **Febrile infection-related epilepsy syndrome**: a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24h prior to onset of refractory status epilepticus.
  - No age cutoff: can be infant, child or adult.
  - Can be with or without fever at the time of onset of SE (about 50% have fever in prior literature)

Case of the unidentified jogger, cont'd

- MRI negative
- LP: 10 wbc's, prot 50, all other studies neg
  - Elevated IL-6, IL-8: should this guide therapy?
- Seizures worsened, required anesthesia for 3 weeks
- Day 3: Given IV steroids, then IVIG course
- After 2 weeks, given tocilizumab
- Multiple medical complications (pneumonia, DVT, ileus, UTI, C. diff)
- Awoke, followed some commands, but cognitively limited

- Sent to rehab after 2 months, on 5 anti-seizure meds, very poor memory, intermittent agitation, 1-2 subtle nonconvulsive seizures per day

More knowledge gaps

- What caused this (esp cryptogenic NORSE)? IL-1, IL-6, IL-8 implicated
  - Does prior fever/infection matter?
  - Is this different in children than adults?
- What is the role of inflammation in RSE (even with clear cause) and can it be treated? How long does the inflammation last?
- Prognosis? Seizures, cognitive, behavioral/mood

Wu J et al, 92 cases of pediatric NORSE

Epil & Behav 2021 (China)

- Single center over 10 yrs
- 90% qualified as FIRES as well as NORSE
  - No diffs found in clin hx, diagnostic testing or outcomes between FIRES and non-FIRES
- 68.5% cryptogenic
- 26% viral
  - 9 HSV, 5 Japanese enceph, 4 EBV, 4 Coxsackie, 2 Mycoplasma
- 3 autoimmune: 2 NMDA, 1 CASPR-2
- Median duration of SE: 8 days; 44% SRSE

Wu J et al, Epil Behav 2021: FIRES vs non-FIRES (all pediatric)

Table 2
Comparison of characteristics between patients in the FIRES group and those in the non-FIRES group.

Characteristic	FIRES ($N = 82$) No. of patients (%) or median (IQR)	Non-FIRES ($N = 10$) No. of patients (%) or median (IQR)	P
Duration of SE (d)	8 (4, 17)	9.5 (3, 19)	0.821
SRSE	36 (43.9)	3 (30.0)	0.509
EEG characteristics			
Interictal discharge on EEG	65 (72.3)	7 (70.0)	0.449
Electrographic seizures	44 (53.7)	4 (40.0)	0.511
NCSE	20 (24.4)	1 (10.0)	0.445
Neuroimaging findings			
Diffuse cortical edema	36 (43.9)	2 (20.0)	0.181
Abnormality Location			0.234
Multifocal abnormality	51 (62.2)	4 (40.0)	
Focal abnormality	7 (8.5)	1 (10.0)	
No (normal MRI/CT)	22 (26.8)	5 (50.0)	
Prognosis			0.509
Good	46 (56.1)	7 (70.0)	
Poor	36 (43.9)	3 (30.0)	

Wu J et al, 92 cases of pediatric NORSE: Outcomes Epil & Behav 2021 (China)

- 22.8% mortality
- Overall outcome: Good in 53 (56%; 23 back to baseline, 30 "mild" neurological morbidity"); Poor in 39 (42%)
  - Poor outcome in 44% FIRES, 30% non-FIRES, not signif
- Predictors of poor outcome: SRSE, electrographic szs, NCSE, diffuse cortical edema, multifocal abnormality on imaging.
  - No obvious relation to etiology or treatment
- Among 71 survivors, outcome was poor at discharge, but 68.5% had fair-good outcome at last f/u
- Epilepsy: 15 intractable, 27 on AEDs

Predicting outcome: Status Epilepticus Scales

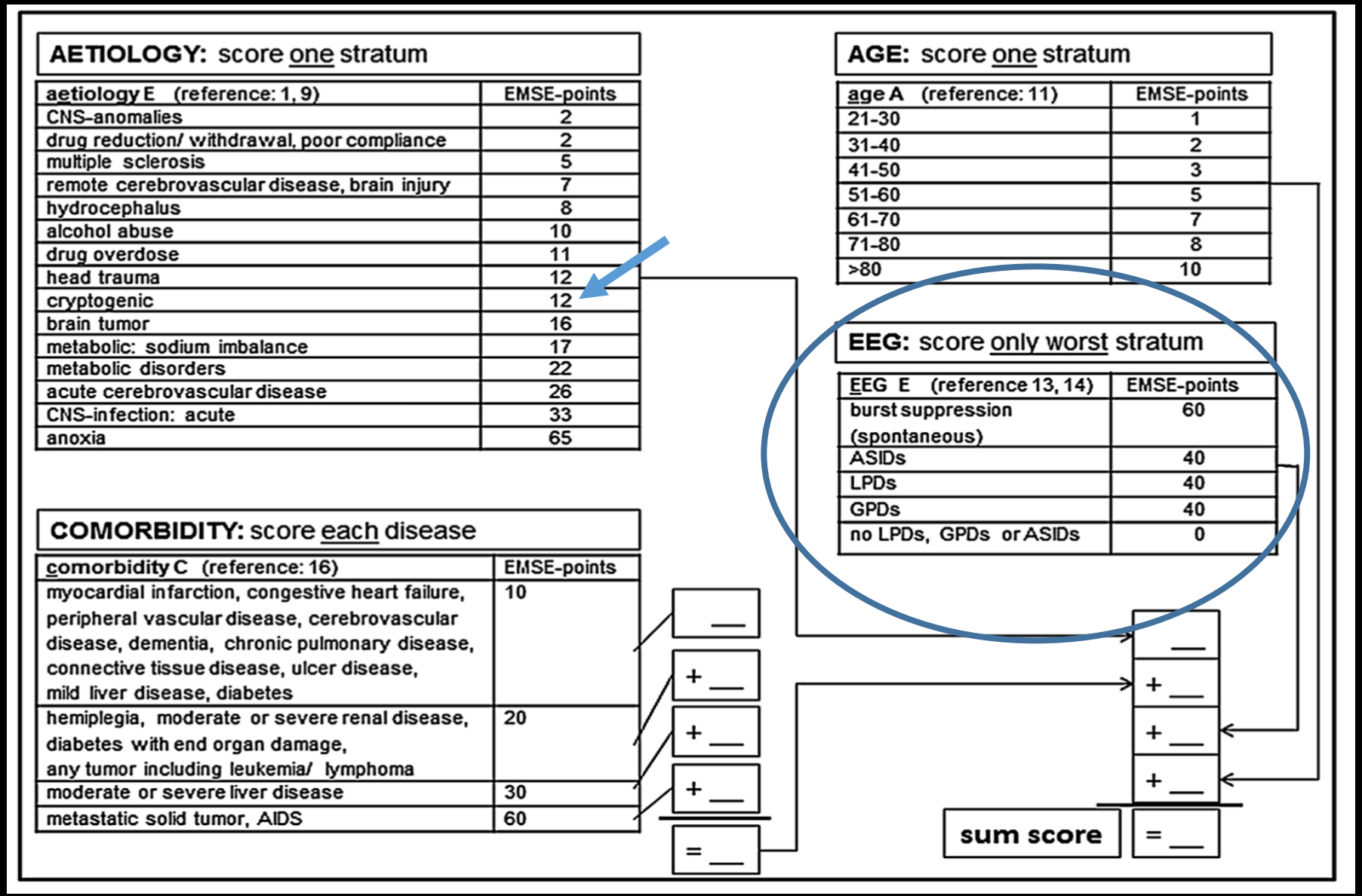
Status Epilepticus Severity Score (STESS), *Rossetti et al 2006*

Modified STESS (STESS + baseline mRS), *Gonzalez-Cuevas et al, 2016*

Epidemiology based Mortality score in Status Epilepticus (EMSE), *Leitinger et al 2015*

Encephalitis - Nonconvulsive Status Epilepticus - Diazepam Resistance Image abnormalities - Tracheal Intubation (END-IT) score, *Gao et al, 2016*

EMSE: Epidemiology based Mortality score in Status Epilepticus



AETIOLOGY: score one stratum

aetiology E (reference: 1, 9)	EMSE-points
CNS-anomalies	2
drug reduction/ withdrawal, poor compliance	2
multiple sclerosis	5
remote cerebrovascular disease, brain injury	7
hydrocephalus	8
alcohol abuse	10
drug overdose	11
head trauma	12
cryptogenic	12
brain tumor	16
metabolic: sodium imbalance	17
metabolic disorders	22
acute cerebrovascular disease	26
CNS-infection: acute	33
anoxia	65

AGE: score one stratum

age A (reference: 11)	EMSE-points
21-30	1
31-40	2
41-50	3
51-60	5
61-70	7
71-80	8
>80	10

EEG: score only worst stratum

EEG E (reference 13, 14)	EMSE-points
burst suppression (spontaneous)	60
ASIDs	40
LPDs	40
GPDs	40
no LPDs, GPDs or ASIDs	0

COMORBIDITY: score each disease

comorbidity C (reference: 16)	EMSE-points
myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes	10
hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor including leukemia/ lymphoma	20
moderate or severe liver disease	30
metastatic solid tumor, AIDS	60

sum score

Leitinger et al NCC, 2015

Scale comparison for predicting 3 mo poor functional outcome (Yuan F et al, Epilepsia 2018)

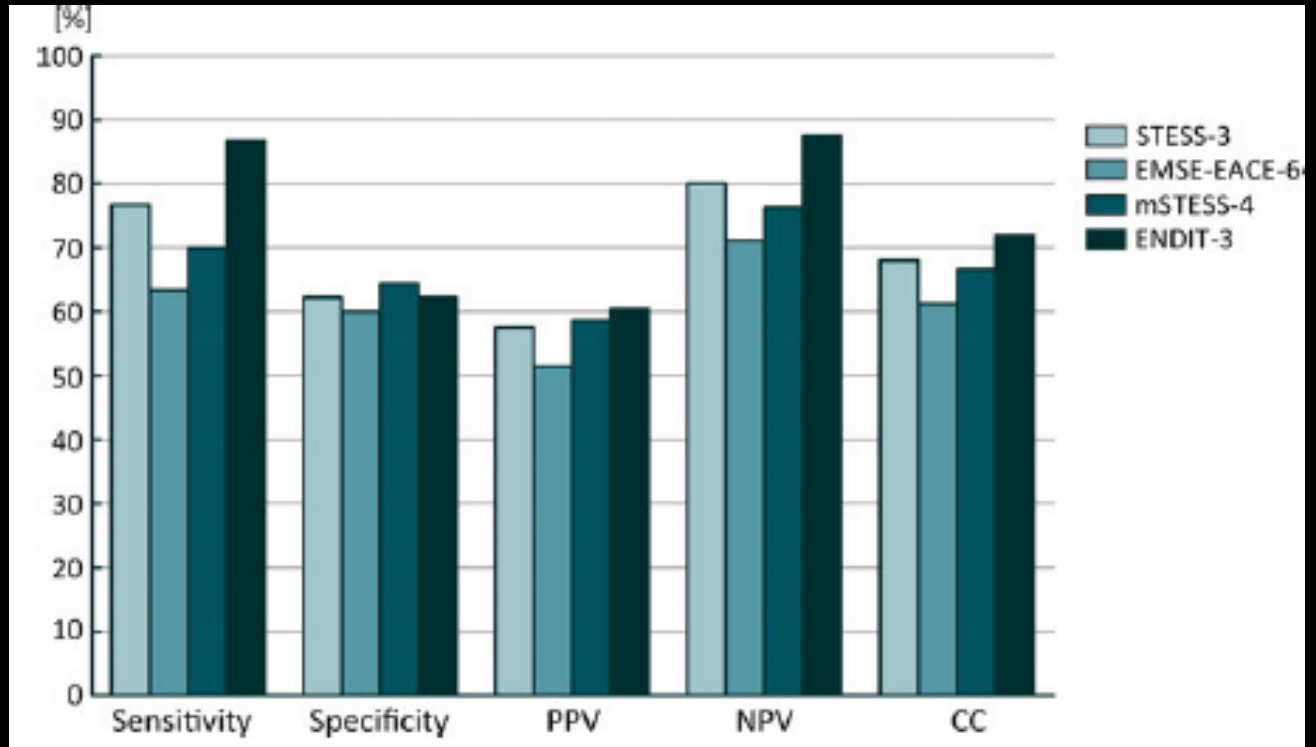


FIGURE 2 Comparisons of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and number of correctly classified (CC) patients toward 3-month poor functional outcome between STESS-3, EMSE-EACE-64, mSTESS, and END-IT

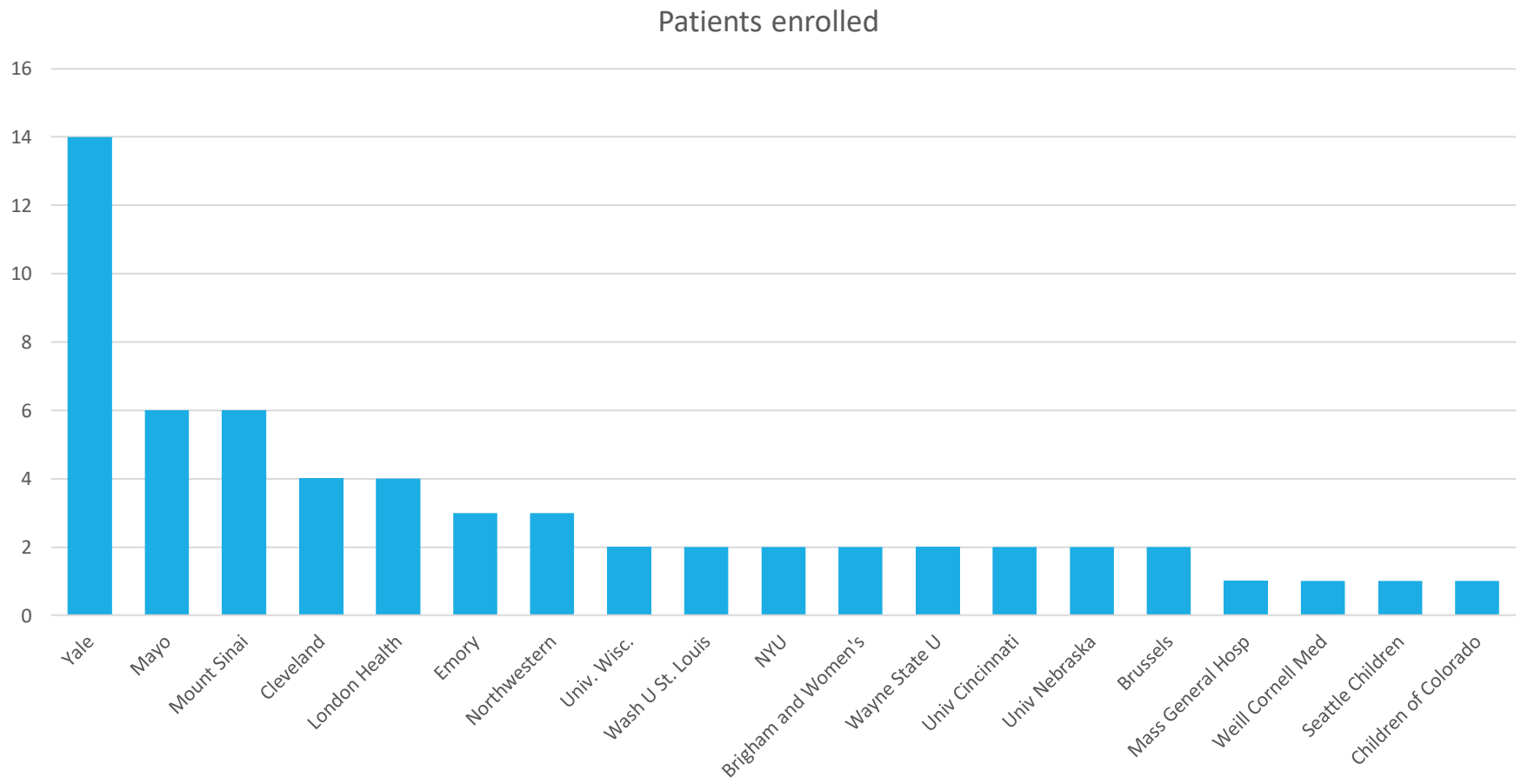
Updated 10/10/2022

NORSE/FIRES Prospective Observational Multicenter study: PRELIM, UNPUBLISHED

Participating sites: 25

Patients enrolled: 64

41% qualified as FIRES as well (6/7 peds cases)



NORSE/FIRES Prospective Observational Multicenter study: Prelim data, unpublished

Final etiology:

Information was recorded for 54 patients

43 patients (80%) qualify as cryptogenic

6 patients: NDMA-R encephalitis
2 patients: GAD encephalitis
1 patient each: lupus cerebritis, CNS lymphoma, acute necrotizing encephalopathy of childhood (RANBP2 gene)

Pediatric patients: 6 patients -> all cryptogenic

Updated 10/10/2022

NORSE/FIRES biorepository: Prelim data, unpublished

- Full CSF results of 46 patients are available of which 13 patients had > 10 WBCs/µL

- Relevant antibodies included NMDA-R in 6 patients (2 in CSF and serum, 4 in CSF only) and GAD in 2 patients (1 in CSF, 1 unknown)
- In the 7 pediatric cases, no antibodies or other evidence of etiology found

- No positive PCRs or cultures identified in CSF for possible causative infectious agents

Updated 10/10/2022

NORSE/FIRES Prospective Observational Multicenter study: Prelim data, unpublished

Immune therapy was given to 41 patients / 52 (missing information for 8 patients):

- 39 patients received steroids
- 32 patients received IVIG
- 20 patients had plasma exchange
- 13 patients received rituximab
- 7 patients received anakinra
- 5 patients received tocilizumab

First immune therapy started on average 6 days after SE onset (range 0 - 29 days)

Updated 10/10/2022

NORSE/FIRES Prospective Observational Multicenter study: Prelim data, unpublished

Outcome at discharge:

27% (14 out of 51) expired during hospitalization
4% (2 out of 51): vegetative state
47% (24 out of 51): severe disability, based on Glasgow Outcome Scale-extended (GOS-E)
22% (11/51) moderate disability or better

Longer term follow-up:

- 12 months: 15 patients evaluated
  - Severe disability: 6
  - Moderate disability: 0
  - Lower disability or normal: 9

NORSE/FIRES BIOREPOSITORY AT YALE

www.norseinstitute.org

EST. DECEMBER 2022

Thanks to Nora and Raymond Wong

Standard testing to be done on all patients

Blood/serum *(n=100)*

- **Autoantibody testing:** M. Wilson, UCSF
- **Genetics:** whole genome sequencing (Yale Center for Genomic Analysis; they will store results in shareable manner as well)
- **Cytokine analysis**
- **Single cell RNA sequencing on PBMCs** when feasible, for 10 cases for now

CSF *(n=100)*

- **Autoantibody testing:** M. Wilson, UCSF
- **Metagenomics** for non-human genetic material (ie, infections): M. Wilson, UCSF
- **Cytokine analysis**
- **Single cell RNA sequencing** for 5 cases, for now

Brain biopsy *(n=3/yr including some existing samples) or autopsy (3-5/yr)*

- **Single cell RNA sequencing** on 5-10 cases for now

Other: nasopharyngeal swabs, saliva, urine, stool: Just storing for now

Including Long-term outcomes

YALE UNIVERSITY
THE SCHOOL OF MEDICINE

Overproduction of pro-inflammatory cytokines in patients with New-Onset Refractory Status Epilepticus (NORSE) predicts outcome

Annals of Neurology 2023

Hanin A et al

Next 5 slides courtesy of:

Aurélie HANIN, PharmD, PhD

Neurology and Immunobiology Department, Yale School of Medicine, New Haven

Institut du Cerveau, ICM, Unité d'Epilepsie, Hôpital Pitié-Salpêtrière, Paris

Methods

61 patients with NORSE (including 4 pediatric patients)
51 out of 61 with cryptogenic NORSE

Compared to **37 patients with other forms of RSE** (previous epilepsy n=16; etiology found in the first 72 hours n=21)

Compared to **52 control patients** with or without previous epilepsy

12 cytokines/chemokines measured in serum and CSF samples (for some patients)

Multiplexed fluorescent bead-based immunoassay detection (BD Biosciences)

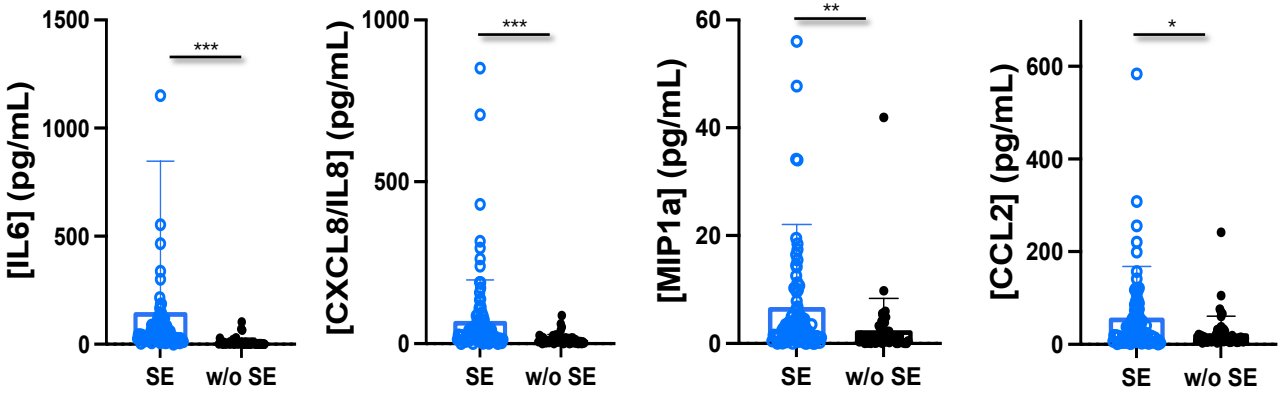
Hanin A et al, Annals Neurol 2023

Patients w/SE vs w/o SE

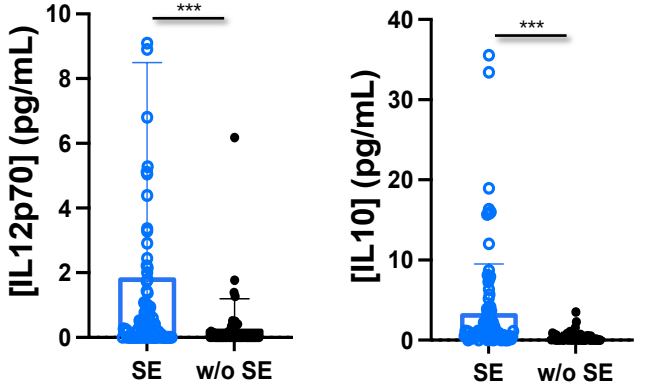
Hanin A et al, Annals Neurol 2023

- **Serum**

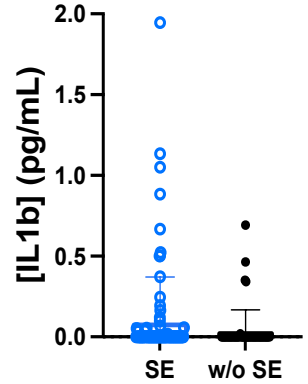
↗ innate immunity pro-inflammatory cytokines



↗ T-cells associated cytokines

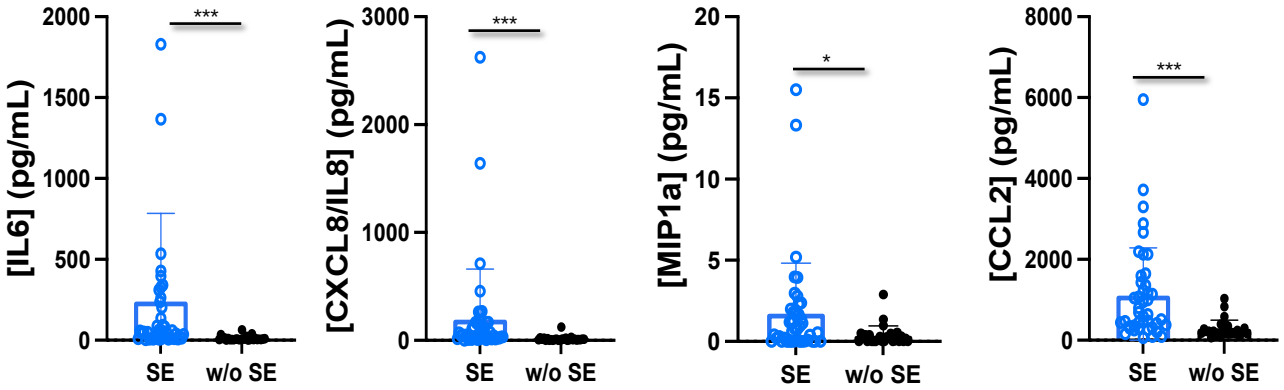


No diff for IL-1ß

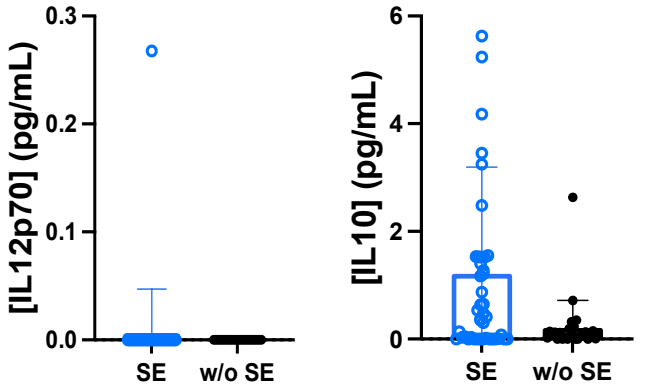


- **CSF**

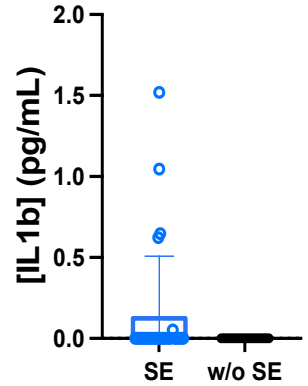
↗ innate immunity pro-inflammatory cytokines



No diff for T-cells associated cytokines



No diff for IL-1ß

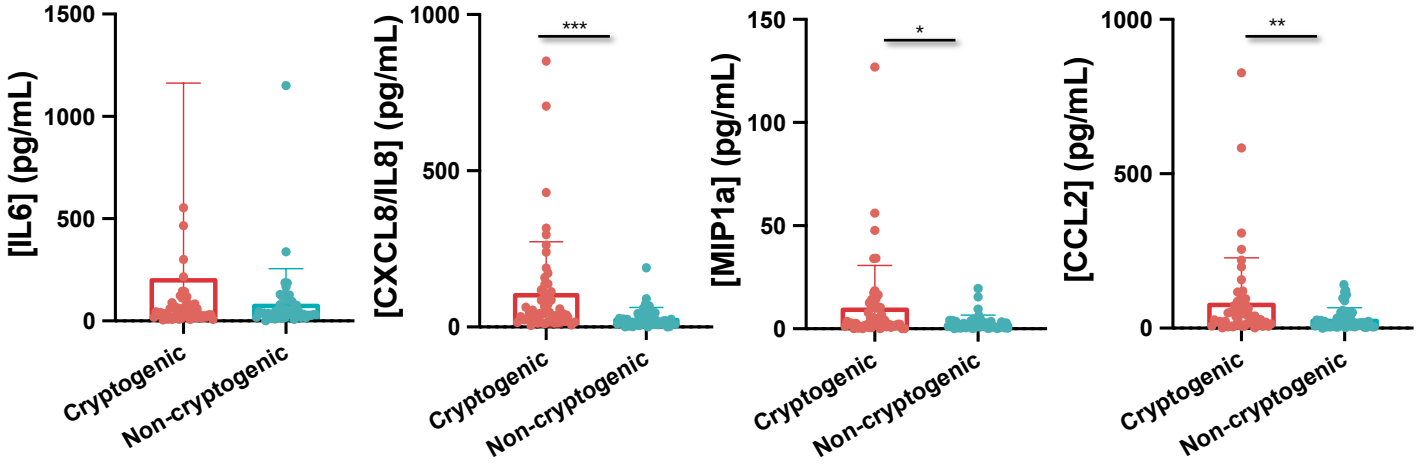


Patients w/ cryptogenic NORSE vs non-cryptogenic RSE

51 cryptogenic NORSE vs 47 non-cryptogenic RSE
(10 known-etiology *NORSE + 37 others RSE)*

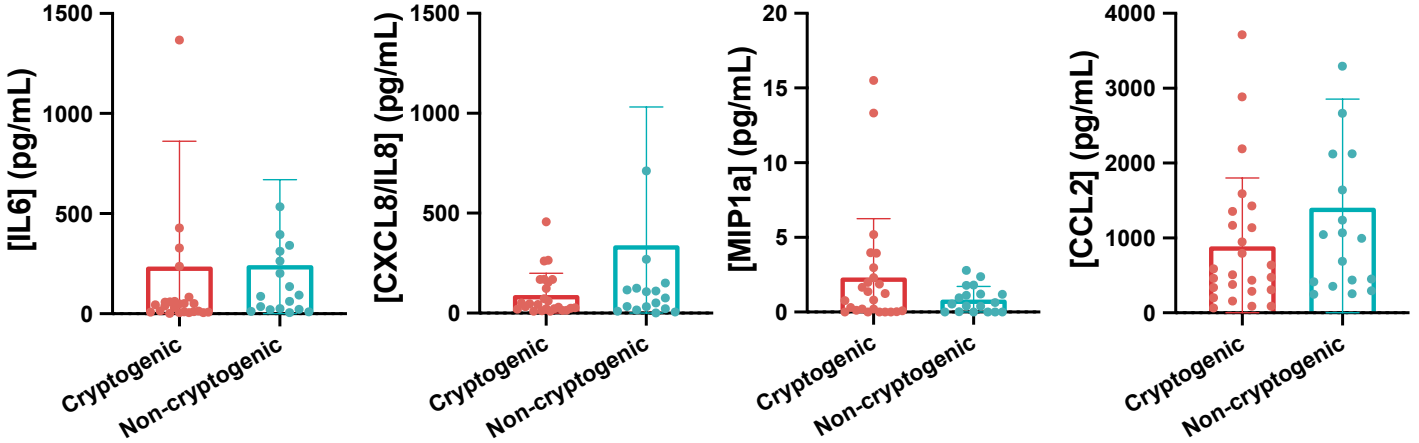
- **Serum**

↗ innate immunity pro-inflammatory cytokines



- **CSF**

No diff for innate immunity pro-inflammatory cytokines



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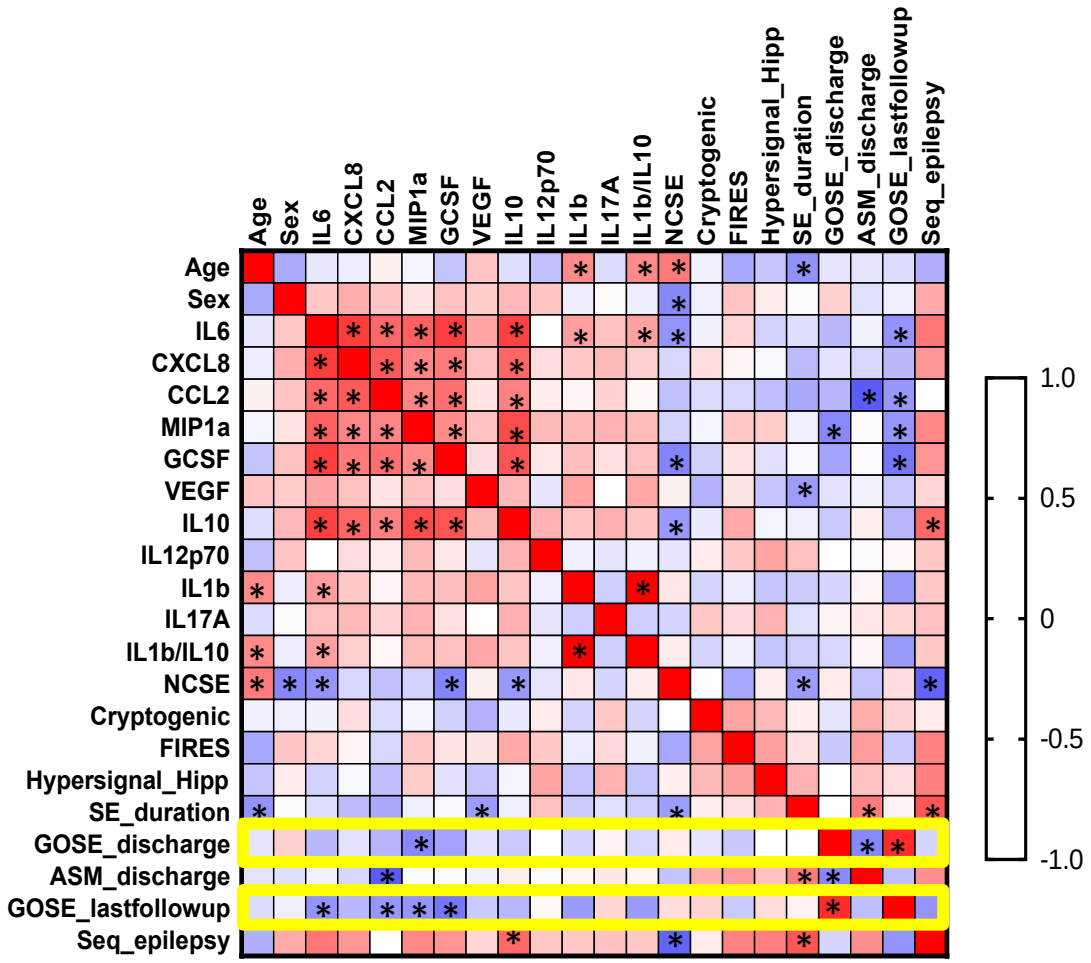
Correlation of cytokine levels and clinical data



Among the 61 patients with NORSE,
FIRES n=24 (39%), including 21 adults
Etiology found for n=10 (16%)
22% expired during hospitalization - 57% with severe disability
After several months: 36% expired, 16% fully dependent, 14% moderate disability; 34% lower disability or full recovery

- ↗ serum IL-6, IL-8, CCL2, MIP-1a --> worse outcome at discharge
- ↗ serum IL-6, IL-8, CCL2 --> worse outcome several months after SE ended

- ↗ CSF MIP-1a --> worse outcome at discharge
- ↗ CSF IL-6, CCL2 and MIP-1a --> worse outcome several months after SE ended

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Conclusion & Future directions related to cytokine results

Conclusion

- **Significant differences in serum and CSF cytokine/chemokine profiles between patients w/ SE and patients w/o SE**
  - Explained by activated glial cells and blood-brain barrier leakage or by the production by peripheral leukocytes *(Ravizza et al. 2008; Cusick et al. 2017)*

- **Elevation of serum innate immunity pro-inflammatory cytokines in patients w/ cryptogenic NORSE compared to non-cryptogenic RSE**

- **Innate immunity pro-inflammatory cytokines in serum and CSF predict NORSE outcome both at short- and long-term**
  → Involvement of peripheral inflammation in NORSE pathophysiology or consequences
  → Importance of utilizing specific anti-inflammatory interventions (e.g., anti CXCL8/IL-8 therapy, reparixin) *(Di Sapia et al. 2021)*

Perspectives

→ **Prospective analysis** of cytokine/chemokine profiles for new patients enrolled in the biorepository (results within few days)
→ **Evaluation of serial serum cytokine levels** according to the treatments used and patient's clinical condition

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Does race/ethnicity/gender affect incidence or outcome of SE?

- Gender
  - Outcome worse in males. N=34,000 cases of new onset SE. (Choi SA, Neurology 2022)
  - Outcome worse in females. N=11,500 cases of generalized convulsive SE. (Koubeissi M, Neurology 2007)
  - Incidence of post-isch stroke convulsive SE higher in females. N=718,000. (Bateman BT, Ncrit Care 2007)

- Socioeconomic factors
  - Outcome worse for lower status. N=34,000 cases of new onset SE. (Choi SA, Neurology 2022)
  - Outcome in children worse for lower status, independent of ethnicity. N=176. (Chin RFM, Epilepsia 2009)

Does race/ethnicity/gender affect incidence or outcome of SE?

- Race/ethnicity
  - Incidence of SE after stroke (all kinds) is higher in African Americans (Wang H, Seizure 2021): systematic review.
  - Incidence of SE in anti-NMDAR encephalitis higher in Hispanics (Gofshteyn JS, Epil Disord 2020)
  - Incidence of SE after subdural hematoma higher in Blacks. N=29,000. (Brown SC, Neurol 2020)
  - Incidence of SE higher in Maori and Pacific Islanders (compare to Europeans and Asians/other) in New Zealand. N=367. (Bergin PS, Epilepsia 2019)
  - Incidence of SE higher in Blacks (compared to whites and other). N=760,000. [but lower mortality] (Dham BS Ncrit Care 2014; and a few others)
  - Outcome better in Blacks N=760,000. [but higher incidence] (Dham BS, Ncrit Care 2014)
  - Incidence of convulsive SE higher in Asian children. UK study, N=176 (Chin RFM, Epilepsia 2009)
  - Incidence of post-isch stroke convulsive SE higher in African Americans, and post-ICH incidence higher in African Americans and Hispanics (Bateman BT, Ncrit Care 2007)

Other knowledge gaps

Does race/ethnicity/gender affect response to specific treatments?

Are there other ways to practice personalized medicine? (e.g., cytokine profile)

Are there useful biomarkers of seizure-induced neuronal injury?

Can we prevent recurrence of SE?

- Seizure detection devices
- Seizure forecasting/prediction/early identification
- Ultra-long term EEG systems (implanted)
- Rescue meds and other responsive treatment, including closed loop/automated

Can we (and are we ready to) run clinical trials to answer some of these clinical knowledge gaps?

THANK YOU!!

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YALE