**Factors associated with failure of first and second line antiepileptic treatment in status epilepticus**

**ABSTRACT**

Background: Currently, there is ongoing work to identify factors associated with refractory status epilepticus in children and adults.

Objective: Our objective was to identify factors associated with failure of first and second-line treatment for status epilepticus.

Methods: We conducted a secondary analysis from a multicenter, double-blind, randomized, response-adaptive trial of patients aged 2 years or older who sought care from any of the 58 participating hospital emergency departments across the United States for generalized status epilepticus that persisted despite an adequate dose of first-line benzodiazepines. Patients were stratified by age group (<18 years, 18-65 years, and > 65 years) and randomly assigned in a response-adaptive manner to receive levetiracetam, fosphenytoin, or valproate for second-line therapy. For the present analysis, we compared characteristics of patients with successful response to study drug versus patients with failure to respond. We compared demographics (age, gender, ethnicity), past medical history, underlying causes for the seizures, pre-existing seizures, having home anti-epileptic medications, and the duration of seizures.

Results: Between Nov 3, 2015 and Dec 29, 2018, we enrolled 462 unique patients with 478 total events, including 225 children < 18 years old, 186 adults up to 65 years, and 51 adults older than 65 years.  XXX patients responded to 2nd-line antiepileptic treatments with one of the study medications.   *[More to write after we have the results.]*

Discussion: *[To be written based on the findings.]*

**BACKGROUND**

Seizures affect 3 million adults and roughly half a million of children in a census done in 2015. *[Zack MM, Kobau R. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy — United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66:821–825. DOI:* [*http://dx.doi.org/10.15585/mmwr.mm6631a1]*](http://dx.doi.org/10.15585/mmwr.mm6631a1%5d) The incidence of status epilepticus ranges from 3.5 to 40 per 100,000 per year.  *[Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care. 2014; 20: 476– 83.  Betjemann JP, Josephson SA, Lowenstein DH, Burke JF. Trends in status epilepticus‐related hospitalizations and mortality: redefined in US practice over time. JAMA Neurol. 2015; 72: 650– 5.]*   It is crucial to terminate status epilepticus early as it is associated with a mortality of 3-5% and neurological sequela in 30% of the patients *[Chin RF, Neville BG, Peckham C, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006; 368(9531):222-9; Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. The Lancet. Neurology. 2006; 5(9):769-79].*  Of those with status epilepticus, 23% to 43% of them would have develop refractory status epilepticus which is associated with higher mortality rate up to 65% with up to 39% of severe neurological sequelae. *[Singh SP, Agarwal S, Faulkner M. Refractory status epilepticus. Ann Indian Acad Neurol. 201417(suppl 1);S52-S56. Sutter R, Marsch S, Fuhr P, Riegg S. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. Epilepsia. 2013;54:502-511.).*   Status epilepticus is defined as a seizure that lasts longer than 5 minutes in duration. Refractory status epilepticus is defined as status epilepticus that continues despite treatment with adequate dose of benzodiazepine and one additional antiepileptic medication. *[Glauser T, Shinnar S, Gloss D. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committed of the American Epoilepsy Society. Epilepsy Curr. 2016;16:48-61.  Brophy G, Bell R, Classen I. Neurocritical Care Society Status Epilepticus Guideline Writing Committee: Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17:3-23.)*   While benzodiazepines have been commonly used as first-line treatment in the management of status epilepticus, they fail approximately 30-40% of the time *[Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. The Cochrane database of systematic reviews. 2008]*.

Presently, there are very few studies that have identified risk factors for refractory status epilepticus which may differ from risk factors for status epilepticus. Most prior studies are retrospective studies conducted in the adult neurology intensive care unit. Risk factors identified include focal motor seizures and non-convulsive seizures at onset, stroke, encephalitis, hyponatremia, more number of home antiepileptic medications, younger age of seizure onset, high seizure frequency are associated with increased risk for refractory status epilepticus. [ref] Early recognition of patients with risk factors for RSE may allow providers to initiate modified therapy to stop these seizures in a timely manner. This study aimed to identity risk factors in patients with RSE.

**METHODS**

Study design and participants

We conducted a secondary analysis of the Established Status Epilepticus Treatment Trial (ESSET), which compared the effectiveness of three anticonvulsant medications (levetiracetam, fosphenytoin, and valproate) as second line medications to manage patients 2 years and older with benzodiazepine-refractory status epilepticus in emergency departments *[Kapur J, Elm J, Chamberlain J, Barsan W, Cloyd J, Lowenstein D, Shinnar S, Conwil R, Meinzer C, Cock H, Fountain N, Connor J, Silbergleit R. Randomized trial of three anticonvulsant medications for status epilepticus. The New England Journal of Medicine 2019].* ESETT was an investigator-initiated, multi-center, randomized, blinded, response-adaptive trial conducted at 57 hospital EDs across the United States. *[Kapur J, Elm J, Chamberlain J, Barsan W, Cloyd J, Lowenstein D, Shinnar S, Conwil R, Meinzer C, Cock H, Fountain N, Connor J, Silbergleit R. Randomized trial of three anticonvulsant medications for status epilepticus. The New England Journal of Medicine 2019]* Complete details of the parent study methods have been published previously. Briefly, patients with convulsive status epilepticus were enrolled using the Exception from Informed Consent for Emergency Research, and were randomized to receive either levetiracetam (LEV), fosphenytoin (FOS), or valproate (VAL) after failing adequate cumulative doses of benzodiazepines. Benzodiazepines may have been administered prehospital, but the last dose prior to enrollment was administered in the emergency department between 5 and 30 minutes prior to study drug. The three study drugs were identical in appearance and in volume and were administered in equal doses of mL per kg over 10 minutes.

Patients were randomly assigned, stratified by age group, in a response-adaptive manner to receive levetiracetam, fosphenytoin, or valproate as dictated in the parent study. Randomization was stratified according to age category: 2 to 17 years, 18 to 65 years, and > 65 years. The randomization was in equal allocation for the first 300 subjects. Afterwards, the target allocation ratio was updated for every additional 100 patients enrolled to allocate more patients to the treatment group most likely to be the most effective.

The primary efficacy outcome was absence of clinically apparent seizures accompanied by improving mental status at 60 minutes, without the need for additional anticonvulsant medications after study drug. Failure to meet the efficacy outcome also included the need for endotracheal intubation.

For this sub-analysis study, we compared demographics, laboratory values, past medical history, seizure classifications, home medications between patients who responded to the second-line antiepileptic treatments (valproic acid, fosphenytoin, levetiracetam) and those who failed to respond to these second-line antiepileptic treatments.

For patients who were enrolled more than once, we included only the first enrollment. We used SAS (version 9.4) and R (version 3.5.2) for all analyses.  *[Will get more input from the statisticians on this.]*

Approvals and funding

The study was approved by the Institutional Review Board (IRB) at all study sites. The trial was conducted under the exception from informed consent (FDA regulation 21 CFR50.24). All study sites were engaged in IRB approved local community consultation and public disclosure activities. The research team informed patients or legal representatives of the enrollment in the study as soon as possible, and obtained consent for continued data collection until discharge from the hospital visit.

The parent study was funded by the National Institute of Neurological Disorders and Stroke; ESETT ClinicalTrials.gov number NCT01960075. The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

**RESULTS**[[P6]](https://cumccolumbia-my.sharepoint.com/personal/myk2102_cumc_columbia_edu/Documents/ESETT/home%20AED%20for%20status%20epilepticus.5.25.20.docx#_msocom_6)

Between November 3, 2015 and December 29, 2018, there were 478 enrollments in 462 unique patients. Of the 462 unique patients, 5 were aged 1 year (who were inadvertently enrolled), 220 were aged 2-17 years, 186 were aged 18-65 years, and 51 were aged over 65 years. XXX (YY%) had a history of epilepsy. Among them, \_\_\_ patients [[P7]](https://cumccolumbia-my.sharepoint.com/personal/myk2102_cumc_columbia_edu/Documents/ESETT/home%20AED%20for%20status%20epilepticus.5.25.20.docx#_msocom_7) responded to the study medications and had cessation of seizures within 60 minutes of study medication administration. [TABLE 1]

Table 1: Demographics of patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics**[[P8]](https://cumccolumbia-my.sharepoint.com/personal/myk2102_cumc_columbia_edu/Documents/ESETT/home%20AED%20for%20status%20epilepticus.5.25.20.docx#_msocom_8) | **Overall** | **Successful Seizure Cessation Group**  **(N = zzzz)** | **Failure of Seizure Cessation Group**  **(N = yyyy)** |
| Age (years) – no (%) |  |  |  |
| Age group – no (%)     0-17y     18y - 60 y     >60 yo |  |  |  |
| Male sex – no (%) |  |  |  |
| Race – no (%)     Black     White     Other |  |  |  |
| Hispanic – no (%) |  |  |  |
| Number of home antiepileptic medications – no ( %)     1     2     3  4  5 |  |  |  |
| Years since first seizure diagnosed |  |  |  |
| Median duration of seizure at enrollment (IQR) - min |  |  |  |
| Benzodiazepines given before ED arrival – no (%) |  |  |  |

When we compared the \_\_\_ patients whose had seizure cessation after study medications to those who failed to have seizure cessation after study medications, we noted \_\_\_\_ (demographis, PMH, labs, imaging, home meds)[[P11]](https://cumccolumbia-my.sharepoint.com/personal/myk2102_cumc_columbia_edu/Documents/ESETT/home%20AED%20for%20status%20epilepticus.5.25.20.docx#_msocom_11)

**Table 2:** Past medical history and seizure types between the two groups[[P12]](https://cumccolumbia-my.sharepoint.com/personal/myk2102_cumc_columbia_edu/Documents/ESETT/home%20AED%20for%20status%20epilepticus.5.25.20.docx#_msocom_12)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Successful seizure cessation | | | Failure of seizure cessation | | |
| Past Medical History | Levetiracetam  (A) | Fosphenytoin  (B) | Valproate  © | Levetiracetam | Fosphenytoin | Valproate |
| Stroke |  |  |  |  |  |  |
| Electrolyte anomalies  -hyponatremia  -hypernatremia  -hypoglycemia  -hyperglycemia |  |  |  |  |  |  |
| Focal motor seizures  Non-convulsive seizures  Gen TC seizures |  |  |  |  |  |  |
| CNS Tumors/CNS infection |  |  |  |  |  |  |
| Unprovoked Seizures |  |  |  |  |  |  |

**Discussion**

In this large randomized, controlled clinical trial of three second-line anticonvulsants for status epilepticus, we found that X, Y, and Z were associated with failure of successful treatment.