Functional independence as determined by a modified Rankin score of 0-2 was achieved in 49.6% of patients in the alteplase group and 42.9% in the placebo group (ARR, 1.36; 95% CI, 1.06 to 1.76). Recanalization at 24 hours occurred in 67.3% and 39.4% in the alteplase group and placebo group, respectively (ARR 1.68; 95% CI, 1.29 to 2.19). Early major neurologic improvement was also statistically significant with 23.9% of patients in the alteplase group and 9.8% of patients in the placebo group experiencing major improvement (ARR 1.68, 95% CI, 1.29 to 2.19). Although 6.2% of patients in the alteplase group and 0.9% of patients in the placebo group experienced symptomatic intracranial hemorrhage, this was not statistically significant (ARR 7.22, 95% CI, 0.97 to 53.54; P=.053). Additionally, there was no statistical significance in deaths between the two groups.

The authors concluded that the use of alteplase between 4.5 and 9 hours for acute ischemic stroke with salvageable tissue on perfusion imaging led to a higher percentage of patients with a modified Rankin score of 0 or 1. Unadjusted analysis of data for recanalization, reperfusion, and early major neurologic improvement also proved to be statistically significant. There was no significant difference in functional outcomes between the two groups. Rates of intracerebral hemorrhage were higher in the therapy group versus the placebo group, but these differences were not statistically significant. Limitations of this study include lack of statistical significance in the unadjusted analysis of the primary outcome and lack of a significant difference in functional outcomes between the two groups. These nonsignificant findings could be related to being underpowered, as the trial was stopped early. Overall, the authors felt that additional studies are required to determine if there is benefit to an extended window for intravascular thrombolysis in the setting of acute stroke.

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Comment: This study attempts to give new insight into the appropriate timing for alteplase administration in acute ischemic stroke. These data suggest that the potential treatment window is more based on imaging findings that suggest reversible ischemia rather than last known well time. They did find significant improvements in the treatment group. However, the study was stopped early which significantly limits the applicability. Rates of intracranial hemorrhage were higher in the alteplase group, although not significant, but we suspect this is due to being underpowered. We would be reluctant to change practice at this time without more conclusive data on the safety of this approach for ischemic stroke patients.

☐ LEVETIRACETAM VERSUS PHENYTOIN FOR SECOND-LINE TREATMENT OF CONVULSIVE STATUS EPILEPTICUS IN CHILDREN (CONSEPT): AN OPEN-LABEL, MULTICENTRE, RANDOMISED CONTROLLED TRIAL.

Dalziel SR, Borland ML, Furyk J, et al. *The Lancet.* 2019; 393:2135-2145

Current literature supports benzodiazepines as first-line treatment in pediatric convulsive status epilepticus, but low quality evidence exists to support current guideline recommendations of phenytoin and fosphenytoin as second-line agents. Additionally, current evidence suggests increased risk of adverse events with phenytoin and there have been cases of fatal loading dose errors. Levetiracetam has emerged as a popular option due to its favorable safety profile. This study examined the comparative efficacy of levetiracetam and phenytoin as second-line agents for the treatment of pediatric convulsive status epilepticus. In particular, it sought to provide further evidence of the superiority of levetiracetam compared to phenytoin based on previous retrospective data.

The study was a multicenter, open-label, randomized controlled trial (RCT) conducted at 13 emergency departments in Australia and New Zealand. Study participants were children 3 months to 16 years of age presenting with persistent convulsive status epilepticus following two doses of benzodiazepines. Subjects underwent computer-generated randomization and an independent pharmacist placed treatment assignments into sequential, opaque, sealed envelopes which were opened at the time of study enrollment. The phenytoin arm received 20mg/kg intravenous (IV) or intraosseous (IO) phenytoin over a period of 20 minutes while the levetiracetam arm received 40mg/kg IV or IO levetiracetam over 5 minutes. The study sites allowed retrospective consent, so parental consent was obtained after random assignment and treatment. The primary outcome was seizure cessation 5 minutes after completion of the infusion. If seizure activity persisted, clinicians could administer the other study agent. For the primary outcome, videos were recorded when possible which were reviewed by two emergency physicians and one neurologist at study completion. They were masked to treatment allocation and confirmed or refuted seizure cessation by consensus agreement. Secondary outcomes included seizure activity at 2 hours, additional rescue medications, rates of rapid sequence intubation, ICU admission, adverse events and seizure recurrence at follow-up.

Of the 639 total children presenting with convulsive status epilepticus, 234 were enrolled in the study. However, consent was declined for one study participant, resulting in 114 children in the phenytoin group and 119 children in the levetiracetam group. Seizure cessation at 5 minutes post infusion occurred in 60% of phenytoin recipients and 50% of levetiracetam recipients with an overall risk difference -9.2% (95% CI -21.9 to 3.5; p=0.16) in the intention-to-treat population, -9.7% (95% CI -23.6 to 4.2; p = 0.18) in the modified intention-to-treat population, and -9.9% (95% CI -22.8 to 2.9; p = 0.13) in the per-protocol population. Rates of seizure control per the video analysis reviewers were 63% and 49% in the phenytoin and levetiracetam groups, respectively. Cessation of seizure activity at 2 hours was also similar between groups at 54% in the phenytoin group and 51% in the levetiracetam group (difference -3.1% [95% CI -15.9 to 9.7]; p = 0.63). The alternative study agent was given in 37% of patients in the phenytoin group and 40% of patients in the levetiracetam group. In patients who received one or both drugs, rates of seizure control at 2 hours was 78% and 72% for the phenytoin group and levetiracetam group, respectively. The phenytoin group had a median time to seizure cessation of 22 min compared to 17 min in the levetiracetam group (difference -5.0 [95% CI -13.5 to 3.5]; p = 0.25). Seizure

activity at 1 month follow up was also similar between groups. Study groups had similar rates and lengths of ICU admission, as well as hospital length of stay. Additionally, adverse events rates at 2h, during admission and at 1 month follow-up were similar.

The authors concluded the study showed no evidence for superior efficacy of levetiracetam compared to phenytoin and that both agents appear effective in treating convulsive status epilepticus in pediatric populations. Given that > 70% of cases resolved within 2 hours in patients who received one or both drugs, it appears that rates of intubation could be significantly reduced by giving the alternative 2nd line agent. The authors acknowledged this was a superiority trial, so levetiracetam cannot be considered statistically equivalent to phenytoin. Furthermore, they recognized that the different infusion times could bias the results in favor of phenytoin due to the occurrence of natural seizure decay or onset of benzodiazepine effect. The results cannot be generalized to patients who regularly take levetiracetam or phenytoin since these populations were excluded from the study. There is potential for physician bias since they were not masked to the assigned therapy, but they did use video analysis to mitigate this possibility. Additionally, EEG was not used and patients with non-epileptic events may have been included.

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Comment: Overall, this randomized controlled trial suggests it is reasonable to choose either phenytoin or levetiracetam as a 2nd line agent, followed by adding the other agent if seizures persist. This can likely prevent unnecessary intubations as patients who received both drugs had high rates of seizure cessation and stabilization. It is important to note that children already on one of these agents were excluded. Additionally, this trial was open label so there added risk of bias. Although both agents appear effective, further studies are needed to demonstrate equivalent therapeutic benefit.

☐ COMPARISON OF THE EFFICACY OF A BOUGIE AND STYLET IN PATIENTS WITH ENDOTRACHEAL INTUBATION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

Sheu YJ, Yu SW, Huang TW, et al. *Journal of Trauma and Acute Care Surgery.* 2019;86(5):902–908

Endotracheal intubation (ETI) is a common procedure in the emergency department, one in which fist-attempt success is vital to preventing peri-intubation adverse events. Endotracheal intubation is often performed with assistance from either a flexible bougie or malleable stylet placed into the endotracheal tube. A recent article in the Journal of the American Medical Association found that the bougie had a higher first-attempt success rate. This meta-analysis took this recent study and compared it to other randomized controlled trials evaluating first-attempt success, intubation duration, and safety of using a bougie versus using a stylet.

This meta-analysis collected data from randomized controlled trials (RCT) performed prior to October 2018 using search databases including PubMed, Embase, and the Cochrane Library. The RCTs comparing the success rates of stylet and bougie were included in this analysis and had to clearly list inclusion and exclusion criteria, as well as first attempt success rates, intubation technique, and duration of intubation. The intubation attempts had to be performed on living patients, as data pertaining to manikins and cadavers were excluded. Data pertaining to the analysis from the prior RCTs was collected by two of the study authors, with disagreements and inconsistencies reviewed by a third author. The authors used the Cochrane Risk of Bias tool to evaluate the quality of the studies, assigning a grade for the overall risk of bias to each study. The data were stratified by study design, population characteristics of the patients studied, inclusion and exclusion criteria, and outcomes regarding duration of intubation, first attempt success rate, and complications. The primary outcome of the meta-analysis was first attempt intubation success rate, and secondary outcomes were intubation duration and esophageal intubation rate. The analysis used a confidence interval of 95% and significance was indicated by $p<0.05$.

The initial search process yielded 370 studies. After removal of duplicate and ineligible studies as well as studies meeting exclusion criteria, 5 trials remained that were eligible for inclusion. Of these five trials representing 1038 patients, three were performed in the preoperative setting, one performed in the emergency department, and one performed in the pre-hospital environment. The distribution of the need for intubation was 633 (60.98%) for medical issues in the emergency department, 230 (22.16%) for elective surgeries, 124 (11.95%) secondary to trauma which were performed in the emergency department, and 51 (4.91%) patients in a pre-hospital setting for which data could not be obtained. Four of the five trials used an identical stylet (one trial used a stylet manufactured to 60 degrees), and the specific technique for using the bougie differed slightly due to different manufacturers of the bougie. The five studies all used modified Mallampati scores (four classifications) and two different systems for laryngeal grades (Cormack and Lehane, Cook's) to predict the ease of intubation. Issues regarding methodological quality were reported from the individual studies and included deviation from initial intended intervention (early termination of using the bougie secondary to unfamiliarity by the performing clinician), as well as concerns about the randomization process and bias in the measurement of outcomes.

For the primary outcome of first-pass intubation rate, there was no difference between bougie or stylet (RR, 1.03; 95% CI, 0.85–1.24). The definition of the duration of intubation, or time it took to secure the airway, varied slightly in all five of the trials', but overall there was no difference between bougie or stylet (mean difference in seconds, 6.01; 95% CI, −0.07 to 12.09). Esophageal intubation rate was reported in four of the trials and there was also no difference found for this outcome (RR, 0.59; 95% CI, 0.13–2.59). Numerous other complications and their rates were reported between the five trials including dental trauma, witnessed aspiration, iatrogenic bleeding, hypoxemia, and pneumothorax, but there was no significant difference in rates between the two methods, and there was no overall statistical difference in complications between the two methods (RR, 1.03; 95% CI, 0.75-1.42).