OR, 1.30; 95%CI, 1.28-1.33). Rate of treatment failure between the two groups was not statistically significant with 373 (5.5%) of patients treated with early antibiotics having treatment failure compared to 388 (5.7%) in the non-antibiotic group ($p = 0.58$) with an odds ratio of 0.95 (95% CI, 0.82-1.11). Risk of antibiotic-related diarrhea between the groups was not significant in the propensity score-matched data (OR, 1.34; 95% CI, 0.99-1.83), however it was noted to be higher overall in the early antibiotic group prior to propensity score matching (OR, 1.6; 95% CI, 1.2-1.9). In one analysis that excluded patients treated with antibiotics after day 2, patients in the early antibiotic group were 2.6 times more likely to develop diarrhea compared to patients who did not receive antibiotics (OR 2.6; 95% CI, 1.7-3.9).

The authors concluded that early antibiotic therapy in the first 2 days of hospital admission was associated with increased hospital length of stay, increased hospital costs and increased risk of antibiotic-associated diarrhea. They determined that there was no benefit to using antibiotics in treatment of asthma exacerbation, unless otherwise clinically indicated by a concurrent infectious process. The authors also raised concerns about inappropriate antibiotic use and the possible public health implications of poor antimicrobial stewardship leading to increased prevalence of antibiotic resistant infections. The study was limited by the lack of certain data points including spirometry tests, specific symptoms experienced by each patient, and baseline pulmonary function tests (PFTs) to quantify severity of asthma, but overall had extensive statistical analysis to decrease confounding variables related to increased treatment in patients with more severe asthma. The study also had a limited population due to only including events that happened while patients were admitted to the hospital as well as not including patients with 30-day readmissions to a hospital different than their original admission.

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Comment: This study highlights the lack of data supporting antibiotic use in treatment of acute asthma exacerbation. Even though current guidelines advise against antibiotic use, they are still routinely given in the absence of other infectious process. This is imperative for emergency medicine physicians to consider when starting the initial workup and treatment of asthma exacerbations prior to admission to the hospital. With the emphasis on emergency department protocols for early antibiotic initiation in sepsis, it is important to consider uncomplicated asthma exacerbation when patients with history of asthma present with tachypnea, tachycardia, and respiratory distress instead of assuming infectious process is present.

☐ THROMBOLYSIS GUIDED BY PERFUSION IMAGING UP TO 9 HOURS AFTER ONSET OF STROKE.

Ma H, Campbell BCV, Parsons MW, Churilov L, et al.
N Engl J Med 2019;380:1795-1803

Guidelines currently limit time to initiate thrombolytic therapy in acute stroke to 4.5 hours after symptom onset. In contrast, endovascular thrombectomy has been shown to improve outcomes in patients with salvageable brain tissue on imaging studies up to 24 hours after the onset of symptoms. The use of tissue viability as the guide to thrombectomy has also led to better outcomes compared to selection based on time of onset. This study hypothesized that extending the time window for thrombolytic therapy to 9 hours after onset of symptoms in patients with a small core of infarction and a larger area of hypoperfusion would be beneficial.

This study was a phase 3, investigator-initiated, multicenter, randomized, placebo-controlled trial that randomized patients with symptoms of acute stroke to one of two groups: alteplase versus a placebo. Patients in the alteplase group were treated with 0.9 mg per kg with a maximum dose of 90 mg. Ten percent of the dose was given as a bolus with the remaining 90% infused intravenously over one hour. Patients in the placebo group received a matching placebo infused in the same manner. Symptom onset was required to be within 4.5 to 9 hours of presentation or present upon awakening with the onset time considered to be from the midpoint of sleep. Inclusion criteria included age 18 years or older, a modified Rankin score <2 before enrollment, a stroke with a National Institutes of Health Stroke Scale (NIHSS) of 4-26 upon presentation, and salvageable tissue on a perfusion scan with either computed tomography (CT) perfusion or perfusion-diffusion MRI. Patient candidacy for potential endovascular thrombectomy was an exclusion criterion. A modified Rankin score of 0 or 1 at 90 days was the primary outcome. Secondary outcomes included modified Rankin score at 90 days and a score of 0-2 on the modified Rankin scale which indicates functional independence. Tertiary outcomes included major neurological improvement (NIHSS score of 0 or 1 and/or a score reduction of 8 or greater) and partial or complete recanalization of the occluded artery at 24 hours. Death at 90 days and symptomatic intracerebral hemorrhage were safety outcomes. Investigators calculated that the study needed 400 participants to achieve 80% power to detect a difference of 15% between groups, with an allowance for 90 patients to be lost to follow-up, and still achieve a p value of .05. During this trial, it was prespecified that during statistical analysis of all clinical outcomes, the primary analysis would be adjusted for age, NIHSS score at baseline, time to intervention, geographic region, and presence of large-vessel occlusion; unadjusted results were reported as well.

Between August 2010 and June 2018, there were 225 patients with symptoms of acute stroke randomized to one of two groups: 113 received alteplase and 112 received a placebo. The data and safety monitoring board recommended the trial be stopped early after results of the WAKE-UP trial were published in May 2018. Patients in the placebo group were on average younger, had a lower NIHSS score, and had a smaller irreversibly damaged core than patients in the alteplase group. Of the patients included in the study, 25% received their assigned therapy 6-9 hours after symptom onset, 10% in the 4.5-6 hour window, and 65% of patients woke up with stroke-like symptoms. The primary outcome was achieved in 35.4% of patients in the alteplase group and 29.5% in the placebo group (adjusted risk ratio (ARR), 1.44; 95% confidence interval (CI), 1.01 to 2.06; p= 0.04). There was no significant difference for the primary outcome between groups in the unadjusted analysis. There was no statistically significant difference for modified Rankin score at 90 days between the two groups (common odds ratio, 1.55; 95% CI, 0.96 to 2.49).

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