immediate airway intervention preventing randomization, or if the treatment team felt BVM was either required or contraindicated. Patients were selected from seven academic intensive care units in the U.S and were randomized in a 1:1 ratio to receive either bag-valve mask ventilation or no-ventilation during the interval between induction and laryngoscopy. The primary outcome was the lowest recorded oxygen saturation on continuous pulse oximetry between induction and two minutes after tracheal intubation. The secondary outcome was the number of patients who had severe hypoxemia, defined as oxygen saturation below 80% during the same time interval. Additionally, authors recorded the number of operator-reported aspiration events as well as new opacities identified on chest x-ray within 48 hours of tracheal intubation that were consistent with aspiration. Intention-to-treat as well as per-protocol analyses were performed.

This study enrolled 401 patients with 199 patients assigned to the bag-mask ventilation and 202 assigned to no ventilation. At the time of induction, the oxygen saturation was not significantly different between each group. For the primary outcome, the median lowest oxygen saturation in the bag-mask ventilation group was 96% (interquartile range, 87 to 99) compared to 93% (interquartile range, 81 to 99) in the no-ventilation group (p=0.01). For the secondary outcome, 21 patients (10.9%) in the bag-mask ventilation group had oxygen saturations less than 80% compared to 45 patients (22.8%) in the no-ventilation group (relative risk, 0.48; 95% CI, 0.30 to 0.77). With respect to the additional outcomes, the two groups did not have a significant difference in operator reported aspiration (2.5% vs. 4.0%; absolute risk difference, -1.5 percentage points; 95% CI, -4.9 to 2.0; p=0.41) or new opacity on chest XR within 48 hours of tracheal intubation that was consistent with aspiration (16.4% vs. 14.8%; absolute risk difference, 1.6 percentage points; 95% CI, -5.6 to 8.9; p=0.73). The per-protocol analysis showed similar results.

The authors have concluded that patients who receive bag-mask valve ventilation between induction and intubation maintain higher oxygen saturations and are less likely to have severe hypoxemia compared with patients who receive no-ventilation. Additionally, there does not appear to be an increased risk of aspiration with BVM, although a much larger study would be needed to definitively measure those adverse events.

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Comment: The purpose of this study was to examine the use of bag-mask ventilation in preventing hypoxemia between induction and tracheal intubation as well as to determine if there is an associated increased risk of aspiration. This trial showed that bag-mask ventilation does improve oxygen saturation between induction and intubation. The findings here suggest that there is not an increased risk for aspiration in selected critically ill patients who are ventilated with a bag-mask during induction. Understanding that we would need to have a much larger trial to definitively show that there is no increased aspiration risk, it seems that BVM during induction may be appropriate to prevent severe hypoxemia. Next steps would be to compare BVM to noninvasive ventilation, a widely used technique for oxygenation during the interval between induction and laryngoscopy.

☐ ASSOCIATION OF ANTIBIOTIC TREATMENT WITH OUTCOMES IN PATIENTS HOSPITALIZED FOR AN ASTHMA EXACERBATION TREATED WITH SYSTEMIC CORTICOSTEROIDS.

Stefan MS, Shieh MS, Spitzer KA, et al. *JAMA Internal Medicine*. 2019;179(3):333-339

For patients admitted to the hospital for asthma exacerbation, current guidelines do not recommend treating with antibiotics; however previous studies have shown a high rate of patients being prescribed antibiotics. It is unclear how treatment with antibiotics affects outcomes for hospitalized patients treated for asthma exacerbation. The purpose of this study was to determine if there is any added benefit in early antibiotic treatment in addition to systemic steroids for patients hospitalized with asthma exacerbation.

This retrospective cohort study analyzed data from 543 acute care hospitals for asthma patients over the age of 18 who were admitted with acute asthma exacerbation between January 1, 2015, through December 31, 2016. The study compared a group of patients who received early antibiotic therapy with a "no treatment" group who did not receive early antibiotics. To be included in the "early antibiotic group," antibiotic treatment had to be started during the first 2 days of hospital admission and therapy had to be prescribed for at least 2 days. Patients who were excluded included those not treated with systemic corticosteroids at a dose equivalent to 20 mg/d of prednisone, those who had other indications for antibiotics, those who had cultures of blood or sputum collected at the time of admission, and patients transferred from another hospital. The primary outcome of this study was hospital length of stay. Additional secondary outcome measures included treatment failure within 30 days of discharge, defined as transfer to the Intensive Care Unit (ICU) after hospital day 2, in-hospital mortality, requirement of mechanical ventilation, or readmission for asthma. Other secondary outcomes were hospital costs and antibiotic adverse effects, including allergic reactions and antibiotic-associated diarrhea. Asthma patients who received early antibiotics were compared to those who did not receive antibiotics using absolute standardized differences. Differences greater than 10% were considered meaningful. Additionally, to compare the effect of antibiotics on length of stay, cost, and treatment failure, a multivariate predictive model was developed and propensity scores were used to match similar patients in each treatment group in order to account for potential confounding.

Of the 19,811 patients included in the study, 8,788 (44.4%) were treated with early antibiotic therapy. Of all patients who met inclusion criteria, treatment failure was noted in 470 (5.4%) of the early antibiotic treatment group and in 634 (5.8%) of the patients who did not receive early antibiotic therapy. Using propensity matching scores, 6833 patients in the early antibiotic group were matched with similar patients who did not receive early antibiotic treatment. The median (IQR) length of stay for patients who received early antibiotic therapy was 4 (3-5) days compared to 3 (2-4) days for patients in the group that did not get early antibiotics ($p < 0.001$) with a length of stay ratio of 1.29 (95% CI, 1.27-1.31). Early antibiotic therapy was also associated with increased hospital costs (median [IQR] cost, $4776 [$3219-$7373] vs $3641 [$2346-$5942];

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).