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## Emergency Medicine Journal Club

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## Emergency Medicine Journal Club

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### Abstract

In this column, we provide a brief review of important papers recently published that relate to the field of Emergency Medicine. The goal is to provide the busy clinician a bullet-like summary of the study, focusing on the research question, methods, results, limitations and bottom line interpretation.

### Keywords

emergency medicine, evidence based medicine, journal club, review

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### Conflict of Interest Statement

We, the authors, have no conflicts of interest to disclose.

## REVIEW

## Emergency Medicine Journal Club

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## Abstract

In this column, we provide a brief review of important papers recently published that relate to the field of Emergency Medicine. The goal is to provide the busy clinician a bullet-like summary of the study, focusing on the research question, methods, results, limitations and bottom line interpretation.

**Keywords:** Emergency medicine, Evidence based medicine, Journal club, Review

## 1. Topic: Pulmonary embolism, decision rules

**Question:** To exclude pulmonary embolism without imaging in PERC-positive patients, is a combined YEARS and age-adjusted D-dimer approach non-inferior to age-adjusted D-dimer alone?

**Study:** Freund Y et al. Effect of a diagnostic strategy using an elevated and age-adjusted D-dimer threshold on thromboembolic events in emergency department patients with suspected pulmonary embolism: a randomized clinical trial. *JAMA*. 2021; 326(21):2141–2149. <https://doi.org/10.1001/jama.2021.20750>.

**Methods:** Multicenter, prospective, cluster randomized, crossover, noninferiority trial of low to intermediate risk patients for pulmonary embolism (PE) by clinician gestalt across 18 emergency departments in France and Spain from 2019 to 2020. The control arm used age-adjusted D-dimer alone (threshold = age  $\times$  10 ng/mL if age  $\geq$  50, 500 ng/mL otherwise), with positive patients receiving chest imaging (CT angiogram or VQ scintigraphy). The intervention arm first evaluated YEARS score (0–3, 1 point each for PE most likely, hemoptysis, or signs of DVT); if YEARS was positive, age-adjusted D-dimer threshold was used, if 0, threshold was set to 1000 ng/mL (see flowchart below created for this review, not from the original paper). Patients at high risk, at low risk who were also PERC negative, who had obvious alternate diagnoses, were pregnant, or

who were on anticoagulation were excluded. Participating EDs were randomized to use the intervention or control approach for all appropriate patients for 4 months, then switched to the alternate approach after a 2 month washout period. Patients were followed up after 3 months to identify diagnostic failures.

**Results:** 1414 patients were enrolled, 726 in the intervention arm, 688 in the control arm and analyzed as-enrolled. An additional analysis was performed after excluding 39 patients for protocol deviations and 67 incorrectly-enrolled patients in a per-protocol analysis. PE was diagnosed in the ED in 100 patients, 7.4% and 6.7% of the intervention and control groups, respectively. Up to 9 PEs were missed in the as-enrolled group (3 in intervention arm, 6 in control arm), including 5 deaths due to unknown cause, a failure rate of 0.15% and 0.80% in the intervention and control groups respectively. No PEs were missed in patients with YEARS score 0 in the intervention arm, the only group whose management was different between intervention and control. Chest imaging was 14.3% less in the intervention group (1 in 7 patients). For another, more detailed summary, see the analysis in RebelEM.

**Limitations:** European setting may be different from American patients and practice; protocol relied on emergency physician gestalt which may not be generalizable to residents, non-EM physicians, or non-physicians; pregnant patients were excluded;

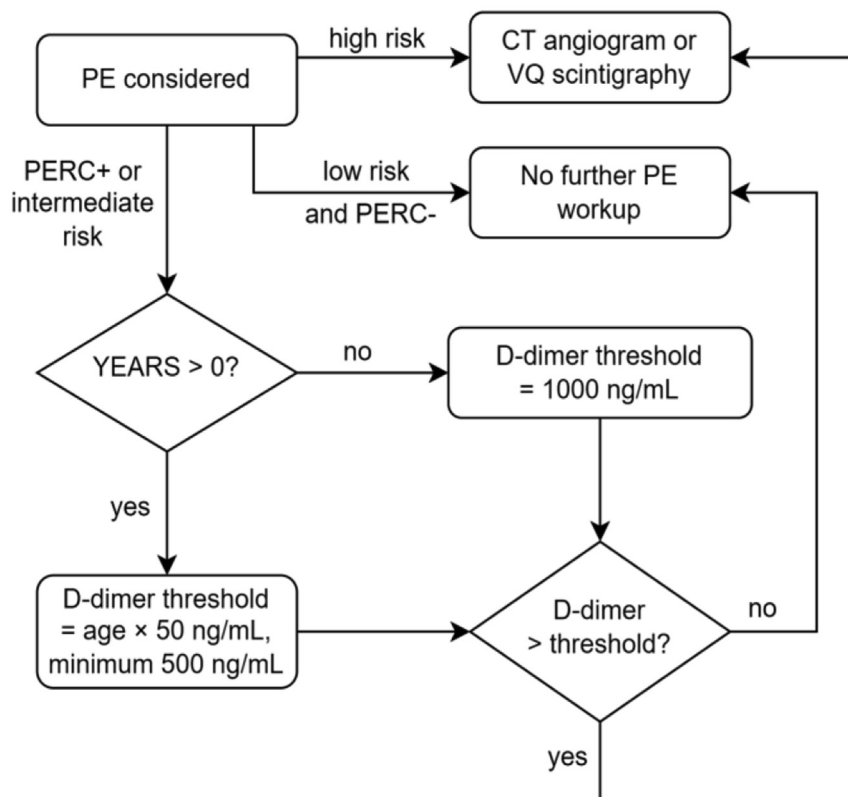
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randomization occurred at the center and not patient level; some selection bias likely; moderate number of protocol errors (7.5% of all patients), unclear handling of intermediate-probability VQ scans.

**Bottom Line:** In this well-designed study, combining the YEARS score and age-adjusted D-dimer to exclude PE without imaging was non-inferior to age-adjusted D-dimer alone and reduced need for chest imaging.

## 2. Topic: Nephrology, bias, health equity

**Question:** Should calculations of estimated glomerular filtration rate (eGFR) exclude race, and if so, how should eGFR be calculated?

**Study:** Delgado C, Baweja M, Crews DC et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis.* 2022; 79(2):268–288.e1. <https://doi.org/10.1053/j.ajkd.2021.08.003>.

**Methods:** Evidence-based review by expert task force convened by the National Kidney Foundation and American Society of Nephrology. Evidence was reviewed over 10 months and incorporated feedback from patients, clinicians, health equity

experts, and reviews of interim reports. For background, standard eGFR calculations include a race coefficient that increases the eGFR for a given creatinine in Black patients, including the standard CKD-EPI and earlier MDRD equations. The race coefficient is especially concerning given the long history of racism in medicine and present reality that Black patients have longer delays, worse outcomes, and face more barriers in nearly all aspects of medicine, including nephrology care.

**Results:** 26 eGFR calculations were reviewed, including those which are based on cystatin C,  $\beta_2$  microglobulin, and other non-creatinine filtration markers. Non-creatinine markers were excluded after review due to feasibility and implementation concerns. Calculations were compared based on accuracy of predicting measured GFR and examined for bias. The task force found that current research demonstrates that cohorting patients into Black and non-Black populations poorly reflects underlying biologic reality and inserts racial bias into major medical decisions. They found that the race coefficient fails to resolve discrepancies between eGFR and measured GFR, and increasing the eGFR for a given creatinine means that Black patients are less likely to have early diagnosis of chronic kidney disease, referral for dialysis, or referral for

transplant. Of all the considered approaches, the task force determined that the best option was the CKD-EPI<sub>Cr</sub>\_R equation, identical to the currently used CKD-EPI equation but without the race coefficient.

**Limitations:** No current eGFR calculation is known to be accurate in all groups and easily implementable, CKD-EPI<sub>Cr</sub>\_R is the task force's conclusion as to the least worst option, sharing its inaccuracies equally across ethnic groups. Usual caveats regarding the limitations of estimates apply. In particular, all eGFR calculations presume stable renal function, which is definitionally not the case in emergency patients with acutely abnormal renal function.

**Bottom Line:** Race should not factor into eGFR calculations. Calculations of eGFR are already imperfect due to the complexities of kidney filtration; the race coefficient failed to resolve these imperfections and introduced new, racially biased errors. CKD-EPI without the race coefficient is the current best estimate available by expert consensus. Other approaches, such as using cystatin C, can be more accurate but are not available in the emergency medicine context. Within Rochester Regional Health, GFR calculations will use the new equation beginning March 1, 2022.

### 3. Topic: Abdominal pain

**Question:** What are the long-term outcomes of appendicitis treated with antibiotics vs surgical management?

**Study:** Antibiotics versus Appendectomy for Acute Appendicitis - Longer-Term Outcomes. *N Engl J Med.* 2021 Dec 16; 385(25):2395–2397.

**Methods:** This is a follow-up letter describing long-term outcomes of up to four years for patients with appendicitis treated with antibiotics alone. The letter updates data from the Comparison of Outcomes of Antibiotic Drugs and Appendectomy trial (CODA) which initially showed that treatment of appendicitis with antibiotics was non-inferior to surgery at 30 days.

**Results:** In the antibiotics groups, the percentage of patients who underwent subsequent appendectomy was 40% (95% CI, 36–44%) at 1 year and 46% (95% CI, 42–49%) at 2 years. The percentage was 49% (95% CI, 44–53%) at 3 and 4 years, according to limited longer-term follow-up. By two years, 14% of patients had required a second course of antibiotics. Patients with an appendicolith were more likely to require appendectomy, especially in the short term.

**Limitations:** A large number of patients were lost to follow-up, calling into question the reliability of the long-term results.

**Bottom Line:** In a group of adults treated with antibiotics, 49% of patients required appendectomy at four years. These results suggest antibiotic management may be reasonable in select patients with appendicitis, but providers should consider patient specific factors and utilize shared decision making when determining which patients are best suited for antibiotic management.

### 4. Topic: Radiology/Neurology

**Question:** Is it possible to rule out aneurysmal subarachnoid hemorrhage (aSAH) using multislice CT scanning (MSCT) out to 24 h after headache onset?

**Study:** Vincent A et al. Sensitivity of modern multislice CT for subarachnoid haemorrhage at incremental timepoints after headache onset: a 10-year analysis. *Emerg Med J.* 2021 Nov 24; *emermed-2020-211,068.*

**Methods:** Retrospective analysis of data from a single hospital in Christchurch New Zealand for patients diagnosed with SAH between 2008 and 2017. 347 patients met inclusion criteria. 260 had aSAH and of those, 97.3% had a positive MSCT. Time to MSCT was defined as the duration of headache onset to CT.

**Results:** Sensitivity for detection of aSAH decreased over time: at 6, 12, 24, 48, 72 and 96 h post headache onset the sensitivity was 100% (98.0–100%), 100% (98.2–100%), 100% (98.3–100%), 99.6% (97.6–100%), 99.6% (97.6–100%), and 98.7% (96.4–99.7%), respectively.

**Limitations:** Authors relied on the final diagnosis of SAH as inclusion criteria and patients with SAH may have been missed if they were not eventually diagnosed with SAH on the initial encounter or follow up. Authors believe this is unlikely as they cross checked mortality data and there is only one hospital in this metropolitan area. Additionally, this is retrospective data.

**Bottom Line:** This study adds to the growing data supporting a longer time window to rule out aSAH based on trained radiologist interpretation of modern generation CT scans. Debate will continue as to whether LP or CT angiogram should be performed to definitively exclude aneurysmal hemorrhage in high risk cases, and it is clear that sensitivity of plain CT decreases over time.

## 5. Topic: Hematology

**Question:** What are some strategies to manage anemic patients in the Emergency Department who cannot receive blood transfusions?

**Study:** Johnson-Arbor K et al. Bloodless Management of the Anemic Patient in the Emergency Department. *Ann Emerg Med* 2022 Jan; 79(1):48–57. doi: 10.1016/j.annemergmed.2021.06.015.

**Methods:** Review article of the ED management of anemia in those that cannot receive blood transfusions due to religious reasons, blood scarcity, or autoimmune hemolysis.

### Recommendations:

1. **Reduce Unnecessary Blood loss.** They recommend using small vacutainers, limited to only the essential labs. Avoid ordering hold tubes. Additionally, if the patient has active bleeding they emphasize immediate control of bleeding whether that means early surgical or procedural intervention (ie EGD), and rapid correction of coagulopathy. Use of recombinant factor VII (derived from hamster serum), along with bleeding control, has been used in patients who cannot receive blood products. TXA has been used to control bleeding in a variety of conditions, with varying levels of efficacy. Also consider autologous autotransfusion if the means of doing so are available at your facility.
2. **Enhance Red Cell Production.** Consider early administration of erythropoietin, or other similar products to enhance marrow production of RBCs.
3. **Increase O<sub>2</sub> Carrying Capacity of Blood.** Consider administration of synthetic hemoglobin products, or transfer to a facility with hyperbarics to increase the patient's oxygen carrying capacity.
4. **Interpersonal Interactions.** The authors caution providers to avoid chastizing their patients over religious decisions to not receive blood products, and to obtain an ethics consult should they care for an unresponsive/incapacitated patient who would otherwise not receive blood products if they were capable of making decisions.
5. **Consider developing hospital guidelines for dealing with bloodless patients.** This may facilitate them receiving alternative treatments, and streamline their care.

**Bottom Line:** Anemic patients who cannot receive blood products are clinically challenging to manage, and the authors summarize a number of ways in

which providers can provide care beyond blood transfusion.

## 6. Topic: Pediatrics

**Question:** Does IV magnesium worsen outcomes in pediatric asthma?

**Study:** Arnold D et al. Prospective Observational Study of Clinical Outcomes After Intravenous Magnesium for Moderate and Severe Acute Asthma Exacerbations in Children

**Methods:** Secondary analysis of prospective observational data from children 5 to 17 with moderate to severe asthma exacerbations. Outcomes measured were change in Acute Asthma Intensity Research Score, hospitalizations, and time to spacing to 4 h for albuterol treatments.

**Results:** Among 301 children, median age was 8.1 (6.4–10.2) years, and 84 received IV-Mg (28%). In a propensity score covariate-adjusted multivariable linear regression model, IV-Mg treatment was associated with a 2-h increase in the Acute Asthma Intensity Research Score ( $\beta$ -coefficient = 0.98; 95% confidence interval [CI], 0.20–1.77), indicating increased exacerbation severity. Three additional PS-based models yielded similar results. Participants receiving IV-Mg had 5.8-fold (95% CI, 2.8–11.9) and 6.8-fold (95% CI, 3.6–12.9) greater odds of hospitalization in PS-based multivariable regression models. Among hospitalized participants, there was no difference in time to albuterol of every 4 h or more in a PS covariate-adjusted Cox proportional hazards model (hazard ratio = 1.2; 95% CI, 0.8–1.8).

**Limitations:** Secondary analyses are prone to bias, and the patients were not randomized to IV magnesium. It could be that the receivers of IV magnesium were a sicker cohort that was not detected due to unmeasured variables in the propensity score models.

**Bottom Line:** IV magnesium was associated with worsening asthma severity, however there were several trial limitations and more information on the topic is needed.

## 7. Topic: Resuscitation, airway

**Question:** Does use of a bougie increase the likelihood of first pass intubation success compared to stylet?

**Study:** Driver BE, Semler MW, Self WH et al. Effect of use of a bougie vs endotracheal tube with stylet on successful intubation on the first attempt among critically ill patients undergoing tracheal intubation: a randomized clinical trial. *JAMA*. 2021;

326(24):2488–2497. <https://doi.org/10.1001/jama.2021.22002>.

**Methods:** Multicenter, randomized, prospective clinical trial. Patients were eligible if intubation with a Macintosh or Miller blade was planned by the clinician and were not pregnant, incarcerated, or requiring immediate intubation without time for randomization. Clinicians could exclude patients if they felt that either of a bougie or stylet was required or contraindicated. Medications, such as paralytic and sedative choice, were chosen by the intubator as they felt appropriate. The primary outcome was first-pass success; secondary outcome was incidence of SpO<sub>2</sub> < 80%.

**Results:** 1102 patients out of 1558 screened were included across 7 emergency departments and 8 intensive care units at 11 hospitals in the United States. A video laryngoscope was used for a majority of patients (75.7% in bougie patients, 73.8% with stylet patients). Successful first-pass intubation occurred in 80.4% of bougie patients and 83.0% of stylet patients. Hypoxia occurred in 11.0% of bougie patients and 8.8% of stylet patients. For additional analysis in print and podcast form, see RebelEM.

**Limitations:** Clinicians could override randomization, acutely decompensating patients were excluded, low baseline first-pass success rate, low intubator experience with bougies (median of 10 prior uses) and low experience overall (median of 60 prior intubations), video laryngoscopy was used a majority of the time limiting generalizability to direct laryngoscopy, most intubators were residents, only 62.9% were emergency physicians.

**Bottom Line:** Routine use of a bougie did not significantly change first-pass intubation success. However, the study has significant limitations reducing its generalizability, particularly to direct laryngoscopy where bougies are frequently used, and to acutely decompensating patients who were excluded.

## 8. Topic: Neurology, regional anesthesia

**Question:** Are peripheral nerve blocks effective for primary headaches?

**Study:** Patel D, Yadav K, Taljaard M, Shorr R, Perry JJ. Effectiveness of peripheral nerve blocks for the treatment of primary headache disorders: a systematic review and meta-analysis [published online ahead of print, 2021 Oct 28]. *Ann Emerg Med.* 2021; S0196-0644(21)00794–0. <https://doi.org/10.1016/j.annemergmed.2021.08.007>. Associated editorial: Friedman BW. Peripheral nerve blocks for headache: a precise approach to pain management in the emergency department [published online

ahead of print, 2021 Dec 21]. *Ann Emerg Med.* 2021; S0196-0644(21)01461-X.

**Methods:** Meta-analysis of randomized controlled trials for primary headache (migraine, tension, or cluster headaches). Included regional anesthesia techniques were sphenopalatine ganglion blocks and greater occipital nerve blocks using either lidocaine or bupivacaine. Studies compared regional anesthesia to placebo or standard medication therapy (dopamine antagonists, non-steroidal anti-inflammatories, or triptans).

**Results:** 11 studies were included; 10 were double-blinded, 1 was single-blinded. Sphenopalatine ganglion blocks were mostly delivered via intranasal droplets, but some were using a commercial device specific for this purpose. Greater occipital nerve blocks were performed using a standard syringe and small gauge needle. Pain scores were overall significantly lower in the treatment arms at 1, 5, 15, and 30 min intervals compared to placebo; inconsistency of time point measurement precluded comparison to standard treatment across studies. Risk of bias was low to moderate overall; repeat analysis after excluding high risk of bias studies did not meaningfully change results. No serious adverse events occurred; the most common events were injection site pain and dizziness. Only 2 studies evaluated repeat visits to the ED, one of which found higher occurrence in the regional anesthesia group, the other had no repeat visits.

**Limitations:** Analysis was only able to draw conclusions when compared to placebo, not standard treatment, duration of effect past 30 min was not evaluated, limited number of studies overall, heterogeneity of studies limits conclusions.

**Bottom Line:** Regional anesthesia may be effective for treatment of primary headaches. However, its efficacy compared to standard treatment approaches remains unclear.

## 9. Topic: Resuscitation

**Question:** Is there a lower incidence of acute kidney injury or death in critically ill adults treated with balanced multielectrolyte solution (BMES) vs. normal saline?

**Study:** Finfer S et al. PLUS Study Investigators and Australian New Zealand Intensive Care Society Clinical Trials Group. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. *N Engl J Med.* 2022 Mar 3; 386(9):815–826. <https://doi.org/10.1056/NEJMoa2114464>. Epub 2022 Jan 18.

**Methods:** Double-blind randomized study. Critically ill ICU patients were randomized to receive BMES (Plasma-Lyte 148) or 0.9% normal saline.



Primary outcome was death from any cause within 90 days. Secondary outcomes included receipt of new renal-replacement therapy and the maximum increase in creatinine level during ICU stay.

**Results:** 5037 patients in Australia and New Zealand were included. Death occurred in 530 of 2433 patients (21.8%) in the BMES group and in 530 of 2413 patients (22.0%) in the saline group. There was no statistical difference in creatinine increase between groups. No difference in adverse and serious adverse events was noted. Median amount of fluid given was 3.9 L. About 30% of patients were admitted to ICU from the ED, while the remainder came from the hospital floor or surgery. Just over 40% of patients had sepsis.

**Limitations:** These were ICU patients with only 30% or so admitted from the ED. Many patients received fluids prior to admission to ICU and 5% of the BMES group received >500 mL saline prior to randomization. Over half of the patients in the BMES group received greater than 500 cc of saline due to medication infusions. The large amount of saline administered to patients in the BMES group may have attenuated the benefit of BMES.

**Bottom Line:** There was no difference in the outcomes of death or kidney injury between patients given BMES when compared to normal saline. Results are consistent with those from the recent BASICS trial. There is likely no significant benefit to balanced crystalloids when compared to normal saline, and no compelling reason to choose balanced fluids for most patients undergoing resuscitation in the ED.

## 10. Topic: Cardiology/Resuscitation

**Question:** Does the timing of ECG acquisition affect the diagnostic accuracy of ECG for STEMI in patients with return of spontaneous circulation (ROSC) following out-of-hospital cardiac arrest (OHCA)?

**Study:** Baldi E, Association of Timing of Electrocardiogram Acquisition After Return of Spontaneous Circulation With Coronary Angiography Findings in Patients With Out-of-Hospital Cardiac Arrest. *JAMA NetwOpen*. 2021 Jan 4; 4(1):e2032875. <https://doi.org/10.1001/jamanetworkopen.2020.32875>.

**Methods:** Retrospective, multicenter cohort study conducted in 3 centers in Europe of adult patients with OHCA due to a medical cause and ROSC achieved in the emergency department. Only patients who had both a post-ROSC ECG and angiography performed were included. Two cardiologists blinded to the angiography results and

ECG timing independently evaluated the ECGs for STEMI criteria. Patients with an ECG demonstrating STEMI and an obstructive coronary lesion requiring percutaneous coronary angioplasty (PTCA) were classified as true positives, with those without an obstructive lesion requiring intervention were classified as negatives.

**Results:** 370 of 586 eligible patients were included. Median age was 62 years. The percentage of false-positive ECG findings was significantly higher in the group with an ECG obtained in 7 min or less (18.5%) as compared to those who received an ECG later after ROSC (7.2% at 8–33 min and 5.8% at time >33 min).

**Limitations:** Retrospective study with small sample size. Outcome was not the identification of an obstructive culprit lesion, but rather the performance of angioplasty. There could have been confounders which led to the delay of timing of post-ROSC ECG in some cases and it is unclear why >33 min elapsed after ROSC prior to obtaining an ECG in many patients. A large number of patients never had a post-ROSC ECG performed and were excluded.

**Bottom Line:** There may be a benefit in waiting several minutes after ROSC to obtain an ECG or obtaining serial ECGs in certain patients with ROSC. ST changes consistent with STEMI may be due to global ischemia or other metabolic derangements in the period immediately following ROSC and may not be indicative of a coronary lesion amenable to angioplasty. It would be wise to discuss all these cases with the interventionalist before determining whether or not the patient requires immediate angiography if early ST changes consistent with STEMI normalize post ROSC.

## 11. Topic: ENT

**Question:** Is topical tranexamic acid (TXA) effective for the management of epistaxis?

**Study:** Janapala RN et al. Efficacy of topical tranexamic acid in epistaxis: A systematic review and meta-analysis. *Am J Emerg Med*. 2022 Jan; 51:169–175.

**Methods:** Systematic review and meta-analysis searching PubMed and Scopus databases for randomized controlled and observational studies on TXA for the management of epistaxis. Primary outcome was cessation of bleeding at the first assessment. Secondary outcomes included rebleeding at 24–72 h and again at 7–8 days. Random effects model was used to calculate odds ratio.



**Results:** There were eight studies in the analysis, including seven randomized trials and one retrospective study including 1299 patients. 596 (46%) received TXA while 703 (54%) received control treatment (placebo, lidocaine plus vasoconstrictors or local anesthetics). Patients who were treated with TXA were 3.5 times (OR 3.5, 95% CI 1.3–9.7) more likely to achieve bleeding cessation at the first assessment. Patients treated with TXA had 63% (OR 0.37, 95% CI 0.20–0.66) less likelihood of returning due to rebleeding at 24–72 h.

**Limitations:** Cochrane bias tool rated 4 of the studies as possibly suffering from bias. They did not include many studies that compared txa to placebo and it is possible that TXA offers an overall low treatment effect. Most studies were not double blinded, potentially introducing bias. Not all studies had robust demographic information such as the presence of anticoagulation or hypertension.

**Bottom Line:** This meta analysis suggests TXA is superior to other topical pharmacotherapy in the management of epistaxis, but more study is needed to see whether topical therapy in general should be attempted over other management strategies such as cautery, packing, or balloon tamponade.

## 12. Topic: Musculoskeletal

**Question:** Are muscle relaxants effective in the management of acute low back pain?

**Study:** Abril L et al. The Relative Efficacy of Seven Skeletal Muscle Relaxants. An Analysis of Data From Randomized Studies. *J Emerg Med.* 2022 Jan 20:S0736-4679(21)00839–8.

**Methods:** Planned analysis of 4 randomized, double blind, placebo-controlled trials comparing naproxen + placebo to various muscle relaxants, including tizanidine, cyclobenzaprine, baclofen, metaxalone, diazepam, methocarbamol, and orphenadrine. Primary outcome was change of Roland–Morris Disability Questionnaire (RMDQ) at 1 week.

**Results:** Mean improvement in RMDQ per group was placebo 10.5 (95% confidence interval [CI] 9.5–11.5), baclofen 10.6 (95% CI 8.6–12.7), metaxalone 10.3 (95% CI 8.1–12.4), tizanidine 11.5 (95% CI 9.5–13.4), diazepam 11.1 (95% CI 9–13.2), orphenadrine 9.5 (95% CI 7.4–11.5), methocarbamol 8.1 (95% CI 6.1–10.1), and cyclobenzaprine 10.1 (95% CI 8.3–12). The between-group differences were not statistically significantly different.

**Limitations:** Unlike typical meta-analysis, this study did not undergo systematic review of databases and thus the studies selected may suffer from selection bias. With that said, the quality of all

studies selected was high. Additionally these studies were conducted in 2 ERs in the Bronx, and may not be generalizable to other populations. Older adults were excluded from the studies.

**Bottom Line:** This is pretty good evidence that muscle relaxants are of limited to no benefit in the management of low back pain.

## 13. Topic: Evidence-based medicine

**Question:** How many unbiased, high-quality meta-analyses address issues of clinical importance in emergency medicine?

**Study:** Parish AJ, Yuan DMK, Raggi JR, Omotoso OO, West JR, Ioannidis JPA. An umbrella review of effect size, bias, and power across meta-analyses in emergency medicine. *Acad Emerg Med.* 2021; 28(12):1379–1388. doi:10.1111/acem.14312.

**Methods:** Meta-analysis of meta-analyses (umbrella review) germane to emergency medicine via comprehensive journal and database search from 1990 to 2020. Data was analyzed at the levels of the individual studies and the meta-analysis summaries. Bias, quality, and power were analyzed using standardized tools such as funnel plots, Cohen's d, and GRADE analyses. Studies were separated by those which measured mortality versus other clinical outcomes.

**Results:** 431 meta-analyses of 3129 individual studies across 350 topics were included. 39.0% of meta-analyses and 28.4% of individual studies were statistically significant. Of the statistically significant results, only 9.5% of meta-analyses and 14.5% of individual studies favored the control intervention. 41.3% of meta-analyses reported small effect sizes. 50.0% were rated low quality evidence by GRADE, only 11.1% were rated high quality. Only 18.0% of studies were adequately powered. No meta-analyses that measured a mortality outcome were composed of randomized controlled trials, adequately powered, statistically significant, and showed no evidence of bias.

**Limitations:** Significant abstraction was required for the appropriate analyses and may introduce bias; some interventions (such as insulin for diabetic ketoacidosis or defibrillation for ventricular fibrillation) are so dramatically beneficial that randomized controlled trials are inappropriate and these interventions would not be captured; analysis only assessed primary outcomes.

**Bottom Line:** As in many fields, few emergency medicine interventions have high-quality, unbiased evidence supporting them. Care must be taken to understand systemic sources of bias that exist beyond methods and framing of individual papers,

especially with new evidence. This is especially true given the pressure to publish positive, financially lucrative, and otherwise personally or institutionally beneficial results.

#### 14. Topic: Infectious disease/Bias

**Question:** Is there evidence of racial bias resulting in delays in diagnosis of appendicitis in children?

**Study:** Goyal MK, Chamberlain JM, Webb M et al. Racial and ethnic disparities in the delayed diagnosis of appendicitis among children. *Acad Emerg Med.* 2021; 28(9):949–956. <https://doi.org/10.1111/acem.14142>.

**Methods:** Multicenter retrospective cohort study of children diagnosed with appendicitis identified via the PECARN Registry, which tracks 7 pediatric emergency departments in the United States, from 2014 to 2018. Children were identified via ICD codes for appendicitis and were eligible if ethnicity data was coded and patients did not leave prior to completion of evaluation. Primary outcomes were perforation (identified by ICD code), delayed diagnosis by bounceback visits with subsequent appendicitis diagnosis, and whether diagnostic imaging was used in the prior visit in cases of delayed diagnosis.

**Results:** 7298 children were eligible for inclusion. 35.2% of children had perforation, with non-Hispanic Black patients having a higher ratio than non-Hispanic White patients (36.5% versus 34.9%, aOR = 1.21, CI > 1). 2.8% of patients had a related emergency visit in the previous 7 days, with children of minority ethnicity having higher rates (4.7% for non-Hispanic Black, OR = 2.45; 4.0% for Hispanic, OR = 2.07). Non-Hispanic Black patients with delayed diagnosis had a lower likelihood of imaging at initial presentation (28.6% versus 35.9% for non-Hispanic White patients).

**Limitations:** Cases were identified by ICD codes which may miss some cases, many variables were analyzed and multiple models were run which increases risk of statistical bias.

**Bottom Line:** Racial bias leads to delayed diagnosis and missed diagnosis of appendicitis in children. This adds to the growing literature demonstrating how racial and other forms of bias permeate medicine and cause harm.

#### 15. Topic: Treatment modalities

**Question:** Should antibiotics be prescribed for mild acute diverticulitis (AD)?

**Study:** Mora-López L et al. DINAMO-study Group. Efficacy and Safety of Nonantibiotic

Outpatient Treatment in Mild Acute Diverticulitis (DINAMO-study): A Multicentre, Randomised, Open-label, Noninferiority Trial. *Ann Surg.* 2021 Nov 1; 274(5):e435-e442.

**Methods:** Prospective, multicenter, open-label, noninferiority, randomized controlled trial of ED patients with acute diverticulitis conducted at 15 hospitals in Spain. Adult patients between the ages of 18 and 90 were included. Patients were excluded if they had significant comorbidities, immunosuppression, a previous episode of AD in the past 3 months, recent antibiotic treatment, poor symptom control in the ED, or met SIRS criteria. Patients were only included if they met the Neff 0 criteria for mild, uncomplicated diverticulitis. All patients received a CT scan prior to enrollment and were then randomized to antibiotics (ATB), or no ATB. Primary endpoint was hospital admission. Secondary endpoints included ED revisits, pain control, and emergency surgery. NSAIDs were prescribed to all patients for pain control.

**Results:** 480 patients met inclusion criteria. No significant difference in the primary or any of the secondary outcomes was observed. Hospitalization rates were 14/238 (5.8%) in the ATB-Group and 8/242 (3.3%) in the Non-ATB-Group [mean difference 2.58%, 95% confidence interval (CI) 6.32 to -1.17]. Revisits were: 16/238 (6.7%) in the ATB-Group and 17/242 (7%) in the Non-ATB-Group 4.83. Poor pain control at 2 days follow-up was 13/230 (5.7%) in the ATB-Group and 5/221 (2.3%) in the Non-ATB-Group.

**Limitations:** There was no placebo used and both clinicians and patients were aware of group randomization. Many exclusion criteria mean results are not generalizable to a large number of patients we see with acute diverticulitis.

**Bottom Line:** This is another in a series of studies supporting outpatient treatment of uncomplicated diverticulitis without antibiotics. UpToDate recently changed their guidance on this subject to recommend against prescribing antibiotics for outpatient treatment of uncomplicated diverticulitis. It is important to consider local practice patterns and to carefully screen patients for exclusion criteria before utilizing this approach. This may be a good area for shared decision making with patients.

#### 16. Topic: COVID-19

**Question:** Is there a benefit to antiplatelet agents in the treatment of critically ill patients with COVID-19?

**Study:** REMAP-CAP Writing Committee for the REMAP-CAP Investigators, Bradbury CA et al.

Effect of Antiplatelet Therapy on Survival and Organ Support-Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. *JAMA*. 2022 Apr 5; 327(13):1247–1259. doi: 10.1001/jama.2022.2910.

**Methods:** This was an adaptive platform trial testing multiple interventions. Patients were randomized to receive either open-label aspirin, a P2Y12 inhibitor, or no antiplatelet therapy. Interventions were continued in the hospital for a maximum of 14 days and were in addition to anticoagulation thromboprophylaxis. The primary endpoint was organ support-free days (days alive and free of intensive care unit-based respiratory or cardiovascular organ support) within 21 days. There were 13 secondary outcomes, including survival to discharge and major bleeding to 14 days.

**Results:** 1557 critically ill patients with COVID-19 were included, 1549 of whom completed the trial. The median for organ support-free days was 7 in both the antiplatelet and control groups (median-adjusted OR, 1.02 [95% credible interval {CrI}, 0.86–1.23]; 95.7% posterior probability of futility). The proportions of patients surviving to hospital discharge were 71.5% (723/1011) and 67.9% (354/521) in the antiplatelet and control groups, respectively (median-adjusted OR, 1.27 [95% CrI, 0.99–1.62]; adjusted absolute difference, 5% [95% CrI, –0.2%–9.5%]; 97% posterior probability of efficacy). Among survivors, the median for organ support-free days was 14 in both groups. Major bleeding occurred in 2.1% and 0.4% of patients in the antiplatelet and control groups (adjusted OR, 2.97 [95% CrI, 1.23–8.28]).

**Limitations:** Open-label trial. The multiple secondary outcomes limit the ability to make definitive conclusions for many of these outcomes, due to under-powering. Patients received varying types of antiplatelet agents, resulting in substantial heterogeneity and limiting the ability to draw conclusions definitively for any one antiplatelet agent.

**Bottom Line:** There was no benefit for the addition of anti-platelet agents to the treatment of critically ill patients with COVID-19, and there was an increased risk of bleeding in the group treated with antiplatelet drugs.

## 17. Topic: Neurology

**Question:** Is recent DOAC use associated with an increased risk of intracranial hemorrhage prior to alteplase administration in acute stroke?

**Study:** Kam W et al. Association of Recent Use of Non-Vitamin K Antagonist Oral Anticoagulants With Intracranial Hemorrhage Among Patients

With Acute Ischemic Stroke Treated With Alteplase. *JAMA*. 2022 Feb 22; 327(8):760–771.

**Methods:** Retrospective cohort study of 163,038 patients who received intravenous alteplase for acute stroke. 2207 were taking NOACs in the week prior to receiving alteplase and 160,831 did not. Primary outcome was symptomatic intracranial hemorrhage within 36 h of alteplase administration. Secondary outcomes included mortality and functional outcomes.

**Results:** Of 163,038 patients treated with intravenous alteplase 2207 (1.4%) were taking NOACs and 160,831 (98.6%) were not taking anticoagulants prior to their stroke. The unadjusted rate of symptomatic intracranial hemorrhage was 3.7% (95% CI, 2.9%–4.5%) for patients taking NOACs vs 3.2% (95% CI, 3.1%–3.3%) for patients not taking anticoagulants. After adjusting for baseline clinical factors, the risk of symptomatic intracranial hemorrhage was not significantly different between groups (adjusted odds ratio [OR], 0.88 [95% CI, 0.70 to 1.10]; adjusted risk difference [RD], –0.51% [95% CI, –1.36%–0.34%]). There were no significant differences in the secondary safety outcomes, including inpatient mortality (6.3% for patients taking NOACs vs 4.9% for patients not taking anticoagulants; adjusted OR, 0.84 [95% CI, 0.69 to 1.01]; adjusted RD, –1.20% [95% CI, –2.39% to –0%]). Of the secondary functional outcomes, 4 of 7 showed significant differences in favor of the NOAC group after adjustment, including the proportion of patients discharged home (45.9% vs 53.6% for patients not taking anticoagulants; adjusted OR, 1.17 [95% CI, 1.06 to 1.29]; adjusted RD, 3.84% [95% CI, 1.46%–6.22%]).

**Limitations:** Retrospective study. Differences in baseline characteristics in DOAC vs no DOAC groups introduces confounding. There could be selection bias in which patients taking DOACs received alteplase. Could it be only patients that forgot to take their last dose of DOAC were ones that were offered TPA? We don't know.

**Bottom Line:** This is some evidence that taking DOACs prior to TPA might not be the contraindication we've previously thought it to be, but more evidence is needed for major practice change.

## 18. Topic: Cardiology

**Question:** Can the Modified Sgarbossa Criteria be used to detect myocardial infarction (MI) in ventricular paced rhythms with high accuracy?

**Study:** Dodd KW et al. Electrocardiographic Diagnosis of Acute Coronary Occlusion Myocardial Infarction in Ventricular Paced Rhythm Using the

Modified Sgarbossa Criteria. *Ann Emerg Med.* 2021 Oct; 78(4):517–529.

**Methods:** Retrospective case control study of patients presenting to 16 international cardiac care centers between Jan 2008–2018. There were two control groups, one of “non-occlusion MI-angio group” who had presumed type I MI but did not meet STEMI criteria and “no occlusion MI group” which consisted of randomly selected ED patients without occlusion MI.

**Results:** There were 59 occlusion myocardial infarction, 90 non-occlusion myocardial infarction-angio, and 102 no occlusion myocardial infarction subjects. For the diagnosis of occlusion myocardial infarction, the Modified Sgarbossa Criteria (MSC) were more sensitive than the original Sgarbossa criteria (sensitivity 81% [95% confidence interval [CI] 69 to 90] versus 56% [95% CI 42 to 69]). For the no occlusion myocardial infarction control group of ED patients, additional test characteristics of MSC and original Sgarbossa criteria, respectively, were as follows: specificity 96% (95% CI 90 to 99) versus 97% (95% CI 92 to 99); negative likelihood ratio (LR) 0.19 (95% CI 0.11 to 0.33) versus 0.45 (95% CI 0.34 to 0.65); and positive LR 21 (95% CI 7.9 to 55) versus 19 (95% CI 6.1 to 59). For the non-occlusion myocardial infarction angio

control group, additional test characteristics of MSC and original Sgarbossa criteria, respectively, were as follows: specificity 84% (95% CI 76 to 91) versus 90% (95% CI 82 to 95); negative LR 0.22 (95% CI 0.13 to 0.38) versus 0.49 (95% CI 0.35 to 0.66); and positive LR 5.2 (95% CI 3.2 to 8.6) versus 5.6 (95% CI 2.9 to 11).

**Limitations:** The study was retrospective given the low prevalence of patients with both a ventricular paced rhythm AND occlusion MI. Additionally given the difficulty in finding subjects, the results had very wide confidence intervals that were nearly overlapping. The trend favoring modified sgarbossa across all groups is pretty convincing however. Differences in single-versus biventricular pacing in the no occlusion/occlusion groups possibly introduces bias.

**Bottom Line:** Although this study has flaws, it is pretty decent evidence that Modified Sgarbossa has reasonable test characteristics and outperforms traditional Sgarbossa in evaluating for MI in ventricular paced rhythms.

#### Conflict of interest

We, the authors, have no conflicts of interest to disclose.