SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists

Effect of cognitive prehabilitation on the incidence of postoperative delirium among older adults undergoing major noncardiac surgery: The Neurobics randomized clinical trial. JAMA Surg 2020 Nov 11 [Epub ahead of print]. PMID: 33175114.

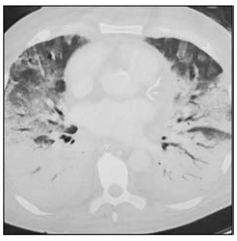
Postoperative delirium and cognitive dysfunction occur commonly in older patients. The effects of "cognitive prehabilitation" in this group are unknown. The authors performed a single-center, single-blinded randomized trial of preoperative cognitive exercises (up to 10 h using a dynamic cognitive exercise software application) in patients 60 yr and older having major noncardiac surgery with general anesthesia (minimum 72-h postoperative stay). The primary outcome was the incidence of delirium between postoperative days 0 to 7 measured by a brief Confusion Assessment Method, Memorial Delirium Assessment Scale, or medical record review. Secondary outcomes evaluated delirium characteristics. The final analysis included 125 intervention *versus* 126 control patients. In the intervention group, 97% completed a median of 5 h of training. The control group delirium rate was 23%. The intervention group delirium rate was 14% ($P = 0.08$ *vs.* control) by intention-to-treat analysis. *Post hoc* analysis after removing four patients not meeting minimum compliance yielded a delirium rate of 13% ($P = 0.04$ *vs.* control). In a multivariable regression adjusting for surgery and frailty, the relative risk was 0.58 (95% CI, 0.33 to 0.99; $P = 0.05$). Secondary analyses showed no differences in time of onset, duration, or total days of delirium. *(Article Selection: BobbieJean Sweitzer, M.D. Image: Adobe Stock.)*

Take home message: Older patients at least minimally compliant with preoperative cognitive exercises had a significantly lower incidence of postoperative delirium after major noncardiac surgery.

Alzheimer's dementia after exposure to anesthesia and surgery in the elderly: A matched natural experiment using appendicitis. Ann Surg 2020 Nov 17 [Epub ahead of print]. PMID: 33214467.

Animal and human studies have suggested a link between anesthetic exposure and pathologic findings resembling Alzheimer disease, although evidence is limited. The authors used Medicare data (2002 to 2017) to determine if patients (ages 68 to 77) undergoing appendectomy with general anesthesia had a higher rate of developing Alzheimer disease and related dementias or death during a 5- to 15-yr follow-up period compared to controls without surgery. A total of 54,996 patients without a previous diagnosis of Alzheimer disease and related dementias with appendectomy were matched with 274,980 controls. Alzheimer disease and related dementias was defined using International Classification of Diseases (ICD)-9 and ICD-10 codes. The hazard ratio for developing Alzheimer disease and related dementias alone was lower in the appendectomy group (hazard ratio 0.89 [95% CI, 0.86 to 0.92], $P < 0.0001$) *versus* control (8% *vs.* 9% at 7.5 yr, respectively). The risk of death at 7.5 yr was slightly lower in the appendectomy group compared to controls (hazard ratio 0.97 [95% CI, 0.95 to 0.99], $P = 0.002$), 22.7% *versus* 23.1%, respectively. *(Article Selection: Charles W. Emala, Sr., M.D., M.S. Image: Adobe Stock.)*

Take home message: This large retrospective observational cohort analysis failed to demonstrate any association between anesthetic exposure during appendectomy and an increased risk of subsequent Alzheimer disease or related dementias at 7.5 yr after the exposure.



Neuromuscular blockade in patients with ARDS: A rapid practice guideline. Intensive Care Med 2020; 46:1977–86. PMID: 33104824.

The benefit of neuromuscular blockade in patients with acute respiratory distress syndrome (ARDS) is debated after diverging results from clinical trials. The objective of this guideline was to provide a summary of available evidence and provide recommendations for the use of neuromuscular blocking agents in ARDS patients. Questions were addressed using the population, intervention, comparator and outcomes format, and the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach. The panel issued three statements: (1) Avoid the routine use of a neuromuscular blocking drug infusion in adults with ARDS before optimizing mechanical ventilation and assessing ARDS severity. (2) In adults with moderate or severe ARDS who tolerate ventilation using a lighter sedation strategy, avoid using a neuromuscular blocking drug infusion. If neuromuscular blockade is required to facilitate lung protective ventilation, intermittent neuromuscular blocking drug boluses with judicious deep sedation are recommended over a neuromuscular blocking drug infusion with deep sedation. (3) In adults with moderate or severe ARDS who clinicians determine require ongoing deep sedation and neuromuscular blockade to facilitate lung protective ventilation, a neuromuscular blocking drug infusion for up to 48 h is suggested over intermittent boluses. The overall certainty of the evidence was low. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

Take home message: An international working group has synthesized existing literature evidence recommending against the routine use of neuromuscular blocking drug infusion in adults with ARDS of any severity.

A multi-center analysis of cumulative inpatient opioid use in colorectal surgery patients. Am J Surg 2020; 220:1160–6. PMID: 32684292.

Understanding which patients are likely to require high doses of opioids after surgery or persistent postoperative use might help providers target opioid use reduction strategies. This observational study using data from the American College of Surgeons National Surgical Quality Improvement Program analyzed cumulative postoperative opioid usage in 1,646 patients undergoing colorectal surgery at five hospitals in Massachusetts (2015 to 2017) using the same Early Recovery After Surgery protocol. Patients receiving greater than 250 morphine milligram equivalents (highest quartile of postoperative opioid use) were compared with patients in other quartiles. When comparing these patients (410 patients) to the remainder of the cohort (1,236 patients), significant predictors of high cumulative use included age 65 yr or younger (odds ratio 0.37), emergency case status (odds ratio 1.88), inflammatory bowel diseases (odds ratio 2.42 to 2.57), postoperative complications (odds ratio 2.03), and length of stay (odds ratio 1.13). A similar rate of previous opioid use (approximately 40%) was noted in all quartiles; however, persistent use of opioids at 90 to 180 days postoperatively (overall 12.2%) was noted in the highest use quartile (19.8%, $P < 0.001$). Significant predictors of persistent opioid use included age 65 yr or younger (odds ratio 0.62), American Society of Anesthesiologists status III or higher (odds ratio 1.74), opioid naïve status (odds ratio 0.35), and top quartile of inpatient use (odds ratio 1.48). *(Article Selection: Marilyn D. Michelow, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: It may be possible to identify patients at risk for requiring high opioid doses postoperatively in hospital and following discharge after colorectal surgery. The lack of an objective measure of pain or analysis of provider prescribing patterns limits generalizability of these results.

Plasma ACE2 and risk of death or cardiometabolic diseases: A case–cohort analysis. Lancet 2020; 396:968–76. PMID: 33010842.

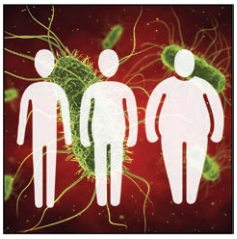
Angiotensin-converting enzyme 2 is a metalloenzyme counterbalancing the effects of the renin-angiotensin system and is a known regulator of cardiac function. This case-cohort study evaluated the relationship of circulating angiotensin-converting enzyme 2 activity to cardiovascular disease using bio-banked data from 10,753 subjects in the Prospective Urban Rural Epidemiology (PURE) study, a prospective global health study, to assess determinants of plasma angiotensin-converting enzyme 2 concentration and to measure its association with the incidence of myocardial infarction, stroke, heart failure, diabetes, and death. The strongest associations with angiotensin-converting enzyme 2 plasma concentration were male sex, geographic ancestry (east Asian), and higher body mass index, whereas there was no association between angiotensin-converting enzyme 2 plasma concentration and the use of antihypertensive medications or diuretics. Greater angiotensin-converting enzyme 2 plasma concentration was associated with greater risk of both cardiovascular and noncardiovascular death (hazard ratio 1.35 per 1 SD increase [95% CI, 1.29 to 1.43]), as well as greater incidence of myocardial infarction, stroke, heart failure, and diabetes. External validation in independent cohorts is needed to confirm the role of plasma angiotensin-converting enzyme 2 concentration as a biomarker for cardiovascular disease. *(Article Selection: Meghan E. Prin, M.D., M.S. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Angiotensin-converting enzyme 2 plasma concentration surpasses clinical risk factors in predicting myocardial infarction, heart failure, stroke, and death.

Enhanced recovery protocols reduce mortality across eight surgical specialties at academic and university-affiliated community hospitals. Ann Surg 2020 Nov 18 [Epub ahead of print]. PMID: 33214486.

Enhanced recovery protocols may improve surgical outcomes. However, many are complex to implement or have studied limited cohorts undergoing a narrow range of procedures. The authors report a propensity-matched, retrospective case-control analysis of 3,367 patient pairs comparing outcomes with 12 months before (control group) and after the implementation of a "simplified" enhanced recovery protocol incorporating seven key clinical domains (minimally invasive approaches, pre/intra/postoperative multimodal analgesia, nausea and vomiting prophylaxis, early diet, ambulation and urinary catheter removal) implemented in five academic and community hospitals within a single healthcare system (2014 to 2017). Elective major orthopedic, abdominal, and urologic surgical procedures were included. Compared to control, lesser mortality was observed from 30 days (0.2% *vs.* control 0.6%, $P = 0.002$) to 2 yr after surgery (3.9% *vs.* control 5.1%, $P < 0.001$), shorter length of hospital stay (3.9 *vs.* 4.8 days, $P < 0.001$) with no difference in 30-day readmission. Cardiovascular and respiratory complications were significantly less ($P < 0.02$) with the exception of venous thromboembolism. Compliance with the enhanced recovery program guidelines was generally above 70%. *(Article Selection: J. David Clark, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

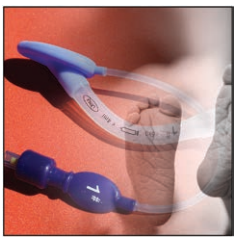
Take home message: A simplified standardized enhanced recovery protocol implemented across a range of surgical procedures in a single healthcare system was associated with a variety of improved outcomes.



Body mass index and risk of dying from a bloodstream infection: A Mendelian randomization study. PLoS Med 2020; 17:e1003413. PMID: 33196656.

Observational studies of sepsis have found a reduced risk of mortality among patients with elevated body mass index (BMI), consistent with the "obesity paradox" noted in other diseases, which may result from selection bias, reverse causation, or confounding. Studies of the general population have reported elevated BMI a risk factor for sepsis and associated mortality. To address this contradiction, the authors employed a Mendelian randomization approach mimicking a randomized study using genetic data as instruments for exposures. A population cohort of 55,908 patients (1995 to 2017 from a cross-sectional survey study in Norway) was studied to assess the incidence and mortality from blood stream infections, correlating this risk with genetically predicted BMI (based on a genetic risk score calculated based on 939 of 941 near-independent single nucleotide polymorphisms identified as related to BMI in a meta-analysis of approximately 700,000 individuals), independent of lifestyle factors. A genetically predicted BMI of 30 kg/m^2, compared with 25 kg/m^2, had a hazard ratio of 1.78 (95% CI, 1.4 to 2.27; $P < 0.001$) for developing a blood stream infection and 2.56 (95% CI, 1.31 to 4.99; $P < 0.006$) for associated mortality. Among patients with sepsis, BMI higher than 30 kg/m^2 had a hazard ratio of 2.34 (95% CI, 1.11 to 4.94; $P < 0.025$) for death. *(Article Selection: Marilyn D. Michelow, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Higher genetically predicted BMI is associated with greater risk of developing and dying from blood stream infections, contradicting the so-called "obesity paradox" of a protective effect.



A randomized trial of laryngeal mask airway in neonatal resuscitation. N Engl J Med 2020; 383:2138–47. PMID: 33252870.

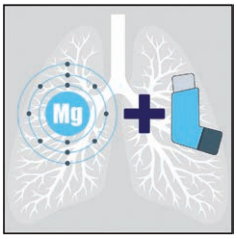
Ventilation with a laryngeal mask airway is seen as an attractive alternative to face-mask ventilation during neonatal resuscitation. However, it remains unclear whether its use improves outcome in neonates with asphyxia. In this phase 3, open-label, superiority trial in Uganda, the authors randomly assigned neonates requiring positive-pressure ventilation by a trained midwife to either laryngeal mask airway or face-mask ventilation. The primary outcome was a composite of death within 7 days or intensive care unit admission with moderate-to-severe hypoxic-ischemic encephalopathy within the first 5 days. The primary outcome occurred in 27% in the laryngeal mask airway group *versus* 24% in the face-mask group (adjusted relative risk 1.16 [95% CI, 0.90 to 1.51]). Death within 7 days occurred in 22% *versus* 18% (adjusted relative risk 1.21 [95% CI, 0.90 to 1.63]), while admission to the neonatal intensive care unit occurred in 11% *versus* 10%, respectively (adjusted relative risk 1.27 [95% CI, 0.84 to 1.93]). Safety assessment was based on clinical and video observations; no significant differences were noted. *(Article Selection: David Faraoni, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In neonates with asphyxia, ventilation with laryngeal mask airway was safe in the hands of midwives but not superior to face-mask ventilation in relation to early mortality or incidence of hypoxic–ischemic encephalopathy.

Conservative and liberal attitudes drive polarized neural responses to political content. Proc Natl Acad Sci USA 2020; 117:27731–9. PMID: 33082227.

Cognitive biases relating to interpretation of political information influenced by previous beliefs can contribute to political polarization so prevalent today. The authors investigated neural mechanisms underlying biased processing of political content using functional magnetic resonance imaging with semantic content analyses. American participants with conservative-leaning or liberal-leaning immigration attitudes underwent scanning while they watched contemporary video content related to U.S. immigration policy. Evidence of "neural polarization" (activity in the brain that diverges between people who hold liberal *versus* conservative political attitudes) was observed in the dorsomedial prefrontal cortex, a brain region associated with the interpretation of narrative content. Neural polarization intensified in the presence of risk-related and moral-emotional language, suggesting that these features are most likely to drive political divergent interpretations. Subjects whose dorsomedial prefrontal cortex activity closely matched that of average conservative or liberal participants were more likely to change their attitudes in the direction of that respective group's position. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Preexisting political attitudes bias information processing in the brain, the type of language most likely to drive polarized neural responses, and the consequences of biased processing for attitude change.



Effect of nebulized magnesium vs placebo added to albuterol on hospitalization among children with refractory acute asthma treated in the emergency department: A randomized clinical trial. JAMA 2020; 324:2038–47. PMID: 33231663.

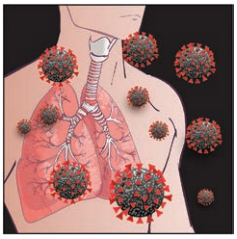
In treating children with severe acute asthma, intravenous magnesium can reduce rates of hospitalization, but clinicians are reluctant to use it due to its invasive nature and association with hypotension. Delivery by nebulization is a more targeted, less invasive approach, although data on its use are sparse. The authors report a randomized, double-blind, parallel-group clinical trial in 7 pediatric emergency departments in Canada. Children aged 2 to 17 yr with moderate to severe asthma receiving 1 h of evidence-based standardized initial care (oral corticosteroid and three albuterol and ipratropium treatments) were randomized to receive three additional nebulized albuterol treatments with either magnesium sulfate (600 mg, n = 410) or 5.5% saline (n = 408). The primary outcome was the rate of hospitalization within 24 h of randomization. Secondary outcomes included the Pediatric Respiratory Assessment Measure score, respiratory rate, oxygen saturation, and blood pressure at 60, 120, 180, and 240 min, and further albuterol treatments within 240 min. Hospitalization occurred in 44% of treated patients *versus* 48% of placebo (difference –4.2%, $P = 0.26$). There were no significant differences between groups for the secondary endpoints or in the incidence of serious adverse events. *(Article Selection: David Faraoni, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Among children with refractory acute asthma in the emergency department, after initial standardized evidence-based therapy, the combination of nebulized magnesium and albuterol did not significantly decrease the rate of hospitalization compared with placebo and albuterol.

Association between patient frailty and postoperative mortality across multiple noncardiac surgical specialties. JAMA Surg 2021; 156:e205152. PMID: 33206156.

There is increasing recognition that frailty is an important contributor to postoperative mortality in noncardiac surgery. This national cohort study using data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) and the associated Veterans Affairs counterpart (VASQIP) evaluated the impact of frailty on 30-day and 180-day mortality (VASQIP only) across nine surgical specialties in more than 2.7 million patients (2010 to 2014). Patients were retrospectively categorized into robust, normal, frail, and very frail groups using the Risk Analysis Index. Surgical stress and intensity were categorized into low, moderate, and high, based on the Operative Stress Score. Overall, the 30-day mortality was 1.0% in VASQIP and 1.2% in NSQIP while 180-day mortality was 3.4%. Frailty was a consistent independent risk factor for mortality across ranges of surgical intensity. Very frail patients having a low-stress procedure in a low-intensity specialty had a 30-day mortality of 14.6% in NSQIP and 9.6% in VASQIP with a 180-day mortality of more than 25%. A nonstepwise association was noted between moderate- and high-intensity specialties such that the former had higher mortality than the latter, suggesting lack of recognition or appreciation of frailty during preoperative screening. *(Article Selection: Jamie W. Sleigh, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Preoperative frailty is an important association of postoperative mortality across all studied surgical subspecialties regardless of case mix and should be incorporated into all surgical decision-making processes.



Evaluation of the incidence and potential mechanisms of tracheal complications in patients with COVID-19. JAMA Otolaryngol Head Neck Surg 2021; 147:70–6. PMID: 33211087.

Anecdotal reports suggest that COVID-19 patients with respiratory failure requiring mechanical ventilation are at increased risk for tracheal damage (full-thickness tracheal lesions or tracheoesophageal fistula) and associated sequelae (pneumomediastinum, pneumothorax, and subcutaneous emphysema). This retrospective study compared associations between tracheal damage (detected by bronchoscopy or computed tomography imaging) and associated seqeulae in 30 adult patients with COVID-19 respiratory failure mechanically ventilated for 14 days or more at a tertiary hospital intensive care unit to 45 historical controls (2019 time frame) requiring tracheostomy matched for age and sex (mean ± SD, 69 ± 9 yr for COVID-19 group *vs.* 68 ± 14 yr in the control group with a male preponderance). The duration of ventilation was similar, although COVID-19 patients all underwent prone ventilation and received systemic steroids *versus* only 11% and 31% of control patients, respectively. Full-thickness tracheal lesions were present in 33% of COVID-19 patients *versus* 2.2% in the control group (odds ratio 38.4 [95% CI, 4.7 to 316.9]). Tracheoesophageal fistulas were detected in 13% of COVID-19 patients *versus* 0% in the control group. Pneumomediastinum, pneumothorax, and subcutaneous emphysema were observed in 20%, 33%, and 43% of COVID-19 patients with tracheal complications *versus* 0% in COVID-19 patients without tracheal damage or in the control group. *(Article Selection: Meghan E. Prin, M.D., M.S. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: This study demonstrates a higher incidence of tracheal damage with related clinical complications in COVID-19 patients treated with prolonged mechanical ventilation compared to non-COVID-19 historical controls.