

# SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

# ANESTHESIOLOGY

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## Key Papers from the Most Recent Literature Relevant to Anesthesiologists



### Neurodevelopmental outcome at 5 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): An international, multicentre, randomised, controlled equivalence trial. *Lancet* 2019; 393:664–77.

Treatment with general anesthetics is associated with learning and memory impairments in animals. The purpose of the GAS trial was to determine whether general anesthesia in early infancy affects neurodevelopmental outcomes in humans. More than 4,000 infants scheduled for inguinal herniorrhaphy in seven countries were screened for age, birth at gestational age greater than or equal to 26 weeks, neurologic injury risk factors, and previous anesthesia exposure. Of these, 722 were randomized to receive either an awake-regional anesthetic or sevoflurane-based general anesthetic. The assessors who tested neurodevelopmental outcomes were blinded to group allocation. The primary outcome measure was full-scale intelligence quotient on the Wechsler Preschool and Primary Scale of Intelligence, third edition, at 5 yr of age. Assessors obtained primary outcome data from 205 children in the awake-regional group and 242 in the general group. The *Lancet* reported that the median duration of general anesthesia was 54 min (interquartile range, 41 to 70). The mean full-scale intelligence quotient score was 99.08 (SD 18.35) in the awake-regional anesthesia group and 98.97 (SD 19.66) in the general anesthesia group, with a difference in means (awake-regional anesthesia minus general anesthesia) of 0.23 (95% CI, -2.59 to 3.06). Both the intention-to-treat analysis and the per-protocol analysis yielded similar results. (Article Selection: Laszlo Vutskits. Image: C. Brodoway, A. I. duPont Hospital for Children.)

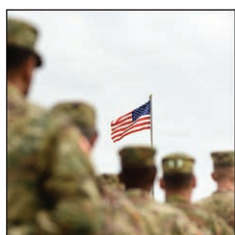
**Take home message:** There were no differences in neurodevelopmental outcomes at 5 yr of age between infants having inguinal herniorrhaphy with general anesthesia when compared to awake-regional anesthesia in this international study.



### Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: The ENGAGES randomized clinical trial. *JAMA* 2019; 321:473–83.

There is significant interest in whether electroencephalography-guided anesthetic administration can decrease the risk of postoperative delirium in older surgical patients. This study randomized older patients undergoing major surgery at a single institution to receive electroencephalography-guided anesthetic administration ( $n = 614$ ) or usual anesthetic care ( $n = 618$ ) and stratified them by cardiac *versus* noncardiac surgery and history of a recent fall. Delirium was assessed on postoperative days 1 to 5 using the Confusion Assessment Method and was identified in 157 of 604 patients (26%) in the guided group and 140 of 609 patients (23%) in the control group (difference, 3% [95% CI, -2 to 8];  $P = 0.22$ ). Patients in the intervention group had significantly lower median end-tidal volatile anesthetic concentrations than those in the control group (0.69 vs. 0.80 minimum alveolar concentration) and their median cumulative time with electroencephalography suppression was less (7 vs. 13 min). In the intervention group, 124 patients (20%) experienced serious adverse events, whereas 130 in the control group did (21%). Thirty-day mortality was 4 patients (1%) in the electroencephalography-guided group and 19 (3%) in the control group ( $P = 0.004$ ). (Article Selection: Martin J. London. Image: J. P. Rathmell.)

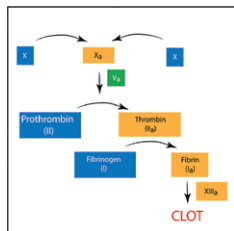
**Take home message:** Electroencephalography-guided anesthetic management in older patients having major surgical procedures may not be associated with a decrease in the incidence of postoperative delirium.



### Association between predeployment optimism and onset of postdeployment pain in US Army soldiers. *JAMA Netw Open* 2019; 2:e188076.

Pain following deployment of U.S. army soldiers is a major health concern. This prospective cohort study examined whether there was an association between predeployment optimism and postdeployment onset of new pain among 20,734 soldiers. Slightly more than one third of soldiers (37%) reported new pain in at least one new body part after deployment. Of these, 25% reported new back pain, 23% reported new joint pain, and 12% reported new frequent headaches. The authors found that each 1-unit increase in optimism was associated with 11% lower odds of reporting new postdeployment pain. This was true even after adjusting for demographic, military, and combat factors (odds ratio [OR], 0.89; 95% CI, 0.86 to 0.93). Soldiers with low optimism were 35% (OR, 1.35; 95% CI, 1.21 to 1.50) more likely to report new pain than high-optimism soldiers, who had the lowest odds of new pain. (Article Selection: J. David Clark. Image: ©gettyimages.)

**Take home message:** Predeployment optimism may be associated with lower odds of reporting new pain after deployment in soldiers.

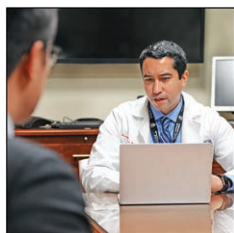


## Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* 2019; 380:1326–35.

The risk of hemorrhage is elevated among patients taking factor Xa inhibitors. This study evaluated the effects of andexanet alfa (a modified inactive form of human factor Xa) in 352 patients with major bleeding within 18 h of receiving a factor Xa inhibitor. Each patient (mean age 77 yr) received a bolus of andexanet alfa, followed by a 2-h infusion. The primary outcomes included the percent change in anti-factor Xa activity after andexanet alfa treatment and the percentage of patients with excellent or good hemostatic efficacy 12 h after the infusion. Andexanet alfa efficacy was assessed in patients who had confirmed bleeding and baseline anti-factor Xa activity of at least 75 ng/ml. Two thirds ( $n = 227$ , 64%) of these

patients had an intracranial hemorrhage and one quarter had gastrointestinal bleeding ( $n = 90$ , 26%). In patients who had received apixaban, the median anti-factor Xa activity decreased from 150 ng/ml at baseline to 11 ng/ml after the andexanet alfa bolus (92% reduction; 95% CI, 91 to 93); in patients who had received rivaroxaban, the median value decreased from 212 ng/ml to 14 ng/ml (92% reduction; 95% CI, 88 to 94). Slightly more than 80% of evaluable patients achieved excellent or good hemostasis ( $n = 204$ , 82%). The authors found that reduction in anti-factor Xa activity was modestly helpful in predicting which patients would develop intracranial hemorrhage. (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** Among patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet alfa reduced anti-factor Xa activity, with improved hemostatic efficacy 12 h later.



## Shifting and sharing: Academic physicians' strategies for navigating underperformance and failure. *Acad Med* 2018; 93:1713–8.

The ability to deal with periods of professional underperformance is important for patient care. This study explored physicians' strategies for coping with periods of professional underperformance and even failure. The goal was to examine physicians' qualities of insight and resilience to learn strategies to support both learners and practitioners. The authors interviewed 28 academic physicians about their experiences with professional underperformance or failure, using constructivist grounded theory to inform their data collection and analysis. They found that interviewees focused on topics ranging from interpersonal conflict and work-life imbalance to patient errors and academic failures. They found that responding physicians sometimes coped by focusing on an aspect of their identity where they felt successful instead of on their failures. At times, the physicians deflected blame for performance gaps, even as they admitted that insight develops by acknowledging and reflecting on error. More often, the authors found that interviewees seemed to accept personal responsibility while simultaneously sharing accountability for underperformance or failure with external forces, even though they perceived learners who used these strategies to be less insightful. This so-called shifting and sharing may actually be beneficial, despite educators' perceptions that this practice equates with avoiding personal responsibility. (Article Selection: Cathleen L. Peterson-Layne. Image: J. P. Rathmell.)

**Take home message:** This study suggests that there may be protective and functional value to distributing responsibility for underperformance and failure. However, this strategy confronts educator assumptions that learners who deflect are avoiding personal responsibility.



## Understanding links among opioid use, overdose, and suicide. *N Engl J Med* 2019; 380:71–9.

Rates of suicide and unintentional overdose in the United States have climbed dramatically during the past 20 yr. This review article examines the vital role opioid use plays in fueling both of these public health problems and possible interventions. Although opioid use and abuse is multifactorial, the review highlights several pathways that can increase patients' vulnerabilities to overdose and/or suicide. These include unmanaged or poorly managed pain, medical system-based drivers of opioid prescribing, and large-scale supply and demand issues. Preferred solutions include pain management programs, expanded access to mental health services, and increased access to medication-assisted treatment for opioid use disorders.

Additionally, the review highlights the need for further research in the area of whether opioid tapering is a useful strategy to decrease overdose and suicide risks and the need for improved protocols to reduce opioid withdrawal and the efficacy of alternative pain management. (Article Selection: J. David Clark. Image: ©gettyimages.)

**Take home message:** This review article describes the relationship between opioid use overdose and suicide risk.



### Use of prescription opioids and initiation of fatal 2-vehicle crashes. *JAMA Netw Open* 2019; 2:e188081.

The role of prescription opioids in fatal automobile crashes remains unknown. This pair-matched study assessed the association between driver use of prescription opioids and the risk of a fatal two-vehicle automobile crash between January 1, 1993, and December 31, 2016, and compared them with alcohol-related automobile crashes. The study included 36,642 drivers involved in 18,321 fatal two-vehicle crashes. Drivers who caused the crashes were more likely to test positive for prescription opioids than those who tested negative (918 [5%] vs. 549 [3%];  $P < 0.001$ ). The same was true of alcohol (blood alcohol level greater than or equal to 0.01 g/dl, 5,258 [29%] vs. 1,815 [10%];  $P < 0.001$ ) and the use of both substances (1% vs. 0.3%;  $P < 0.001$ ). The adjusted odds ratio of crash initiation was 2.18 (95% CI, 1.91 to 2.48) for drivers testing positive for prescription opioids compared to drivers testing negative. The odds ratio increased with blood alcohol levels (blood alcohol levels 0.01 to 0.07 g/dl: adjusted odds ratio, 1.97; 95% CI, 1.75 to 2.22; blood alcohol levels greater than or equal to 0.08 g/dl: adjusted odds ratio, 8.20; 95% CI, 7.42 to 9.07; compared to blood alcohol levels less than 0.01 g/dl). Interestingly, there was no significant interaction between the combination of both prescription opioid and alcohol use on fatal automobile crashes. (Article Selection: J. David Clark. Image: ©gettyimages.)

**Take home message:** Use of prescription opioids may be associated with causation of fatal two-vehicle crashes independent of alcohol use; use of ethanol with or without opioids may be associated with causation of fatal two-vehicle crashes.



### Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: The DEXACET randomized clinical trial. *JAMA* 2019; 321:686–96.

Both sedatives and opioids have been associated with the development of postoperative delirium. This study evaluated whether the administration of postoperative intravenous acetaminophen combined with sedation using either intravenous propofol or dexmedetomidine decreased the risk of postoperative delirium in older patients undergoing cardiac surgery. One hundred twenty patients were randomized to one of four groups receiving postoperative analgesia with intravenous acetaminophen or placebo every 6 h and postoperative sedation with dexmedetomidine or propofol starting at chest closure and continuing for up to 6 h. The primary outcome was incidence of postoperative delirium assessed using the Confusion Assessment Method. The acetaminophen group had a significant difference in delirium (10% vs. 28% in the placebo group; difference, –18% [95% CI, –32 to –5];  $P = 0.01$ ; hazard ratio (HR), 2.8 [95% CI, 1.1 to 7.8]). In contrast, there was no significant difference in delirium among patients randomized to dexmedetomidine when compared to propofol for sedation (17% vs. 21%;  $P = 0.54$ ; HR, 0.8 [95% CI, 0.4 to 1.9]). However, the need for breakthrough analgesia was significantly lower in patients receiving dexmedetomidine for sedation (median, 329 vs. 398  $\mu$ g; difference, –69 [95% CI, –155 to –4];  $P = 0.04$ ). (Article Selection: Deborah J. Culley. Image: ©gettyimages.)

**Take home message:** Acetaminophen, combined with intravenous propofol or dexmedetomidine for sedation, was associated with lower rates of delirium after cardiac surgery.

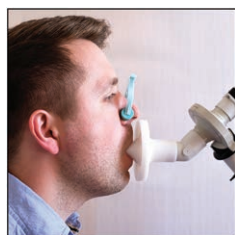


### Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med* 2019; 380:425–36.

Intravenous antibiotics are often utilized to treat bone or joint infections occurring after surgery. This study investigated whether oral antibiotic therapy was noninferior to intravenous antibiotic therapy for the management of postoperative orthopedic infections. Adult patients with bone or joint infections following orthopedic surgery at 26 centers in the United Kingdom were randomized to receive either intravenous or oral antibiotics for the first 6 weeks of therapy. Follow-up oral antibiotics were permitted in both groups and the primary endpoint was treatment failure within 1 yr after randomization, with a noninferiority margin of 7.5 percentage points. There was no difference in treatment failure between the two groups.

In the intravenous antibiotic group, 74 of 506 (15%) patients had treatment failure, whereas 67 of 509 (13%) patients in the oral antibiotic group had treatment failure. The intention-to-treat analysis showed a difference in the risk of definitive treatment failure (oral group vs. intravenous group) of –1.4% (90% CI, –5 to 2; 95% CI, –6 to 3), suggesting noninferiority between intravenous and oral antibiotic administration. Similarly, there were no between-group differences in the incidence of serious adverse events (146 of 527 participants [27.7%] in the intravenous antibiotic group and 138 of 527 [26.2%] in the oral antibiotic group;  $P = 0.58$ ). (Article Selection: Laszlo Vutskits. Image: J. P. Rathmell.)

**Take home message:** Oral antibiotic therapy for postoperative orthopedic infections was noninferior to intravenous antibiotic therapy when administered for 6 weeks.



### Artificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests. *Eur Respir J* 2019; 53:1801660.

Artificial intelligence is now being evaluated in health care. This study explored the accuracy and variability of pulmonologists in interpreting pulmonary function tests and compared them to an artificial intelligence–based software program that was developed and validated on more than 1,500 patient cases. The study included data from 120 pulmonologists in 16 European hospitals and evaluated 50 pulmonary function tests per pulmonologist, resulting in 6,000 independent interpretations. Artificial intelligence software was used to examine the pulmonary function tests. American Thoracic Society/European Respiratory Society guidelines were used as the standard for pulmonary function test pattern interpretation.

Diagnoses were based on clinical history and test results. Pattern recognition of pulmonary function tests by pulmonologists matched the guidelines in 75% of the cases (range, 56 to 88%). However, the interrater variability was only 0.67 (kappa). Interestingly, pulmonologists made a correct diagnosis in only 45% of the cases (range, 24 to 62%) and there was large interrater variability (kappa = 0.35). The artificial intelligence–based software matched the pulmonary function test pattern interpretations (100%) and assigned a correct diagnosis in 82% of all cases ( $P < 0.0001$  for both measures). (Article Selection: Beatrice Beck-Schimmer. Image: ©gettyimages.)

**Take home message:** Interpretation of pulmonary function tests by pulmonologists is associated with marked variability and errors. The use of artificial intelligence–based software may serve as a powerful decision support tool to improve interpretation of pulmonary function tests.



### Association of left ventricular ejection fraction and symptoms with mortality after elective noncardiac surgery among patients with heart failure. *JAMA* 2019; 321:572–9.

It is unclear whether left ventricular ejection fraction and symptoms of heart failure are associated with adverse postoperative outcomes. This retrospective cohort study evaluated the risk of postoperative mortality among patients with heart failure in the setting of varying levels of left ventricular systolic dysfunction and symptom severity compared to patients without heart failure. The Veterans Affairs Surgical Quality Improvement Project database was analyzed for heart failure, left ventricular ejection fraction, and presence of heart failure symptoms within 30 days postoperatively. The primary outcome

was 90-day postoperative mortality. Patients with heart failure had a higher risk of 90-day postoperative mortality than those patients that did not have heart failure (adjusted odds ratio (OR), 1.67 [95% CI, 1.57 to 1.76]). Symptomatic patients with heart failure were more likely to die than those without heart failure (adjusted OR, 2.37 [95% CI, 2.14 to 2.63]), as were asymptomatic patients with heart failure (adjusted OR, 1.53 [95% CI, 1.44 to 1.63]). (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** Patients with a history of heart failure are at an increased risk of 90-day postoperative mortality regardless of whether their heart failure is symptomatic.



### Bag-mask ventilation during tracheal intubation of critically ill adults. *N Engl J Med* 2019; 380:811–21.

Oxygen desaturation is common during tracheal intubation of critically ill patients. This study examined whether positive-pressure ventilation using a bag-mask device during tracheal intubation can prevent hypoxemia without increasing the risk of aspiration in critically ill patients. Adults undergoing tracheal intubation were randomized to receive either ventilation between induction and laryngoscopy with a bag-mask device or no ventilation. The primary outcome was the lowest oxygen saturation observed during the interval between induction and 2 min after tracheal intubation. The median lowest oxygen saturation among 401 enrolled patients was 96% (interquartile range, 87 to 99) in the bag-mask ventilation group and 93% (interquartile range, 81 to 99) in the no-ventilation group ( $P = 0.01$ ). A total of 21 patients (11%) in the bag-mask ventilation group had severe hypoxemia, as compared to 45 patients (23%) in the no-ventilation group (relative risk, 0.48; 95% CI, 0.30 to 0.77). Aspiration was reported in 3% of intubations in the bag-mask ventilation group and 4% in the no-ventilation group ( $P = 0.41$ ). The incidence of new opacity on chest radiography in the 48 h after tracheal intubation was 16% and 15%, in the bag-mask ventilation and no-ventilation groups, respectively ( $P = 0.73$ ). (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** Bag-mask ventilation between induction and tracheal intubation in critically ill adults may reduce hypoxia and may not be associated with a higher risk of aspiration pneumonia.