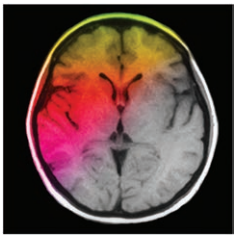
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Determination of brain death/death by neurologic criteria: The World Brain Death Project. JAMA 2020 Aug 3 [Epub ahead of print]. PMID: 32761206.

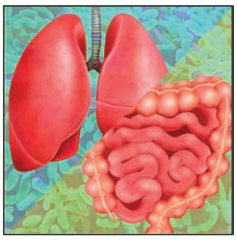
Given a wide variation in diagnosing brain death between and within countries, a group of international professional societies convened a panel of experts to review more than 700 papers, achieve consensus, and formulate recommendations. Before evaluation, the patient should have a neurologic diagnosis consistent with complete and irreversible loss of brain function with an absence of conditions that could confound the clinical examination. The diagnosis of brain death requires clinical demonstration of coma, brainstem areflexia, and apnea. Clinical features include: (1) no arousal to strong external stimuli for any sensory modality; (2) fixed unreactive pupils; (3) absent corneal, oculocephalic, and oculovestibular reflexes; (4) absent facial movement to painful stimuli; (5) absent gag reflex; (6) absent cough reflex to tracheal stimulation; (7) no brain-mediated motor response to noxious limb stimulation; (8) no respiratory effort in the presence of pH less than 7.30 or $Paco_2$ greater than 60 mmHg. If there are impediments to adequate clinical testing, ancillary blood flow studies or electrophysiological testing may be needed. Special considerations including pediatrics, patients on mechanical support, and societal, religious, and other considerations are addressed in detail. *(Article Selection: Jamie W. Sleigh, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: An international group of professional societies has developed comprehensive minimum requirements for determination of brain death by neurologic criteria in adults and children.

Medical marijuana, recreational cannabis, and cardiovascular health: A scientific statement from the American Heart Association. Circulation 2020; 142:e131–52. PMID: 32752884.

Cannabis, or marijuana, a traditionally recreational drug classified in the United States as a Schedule 1 controlled substance (defined as no accepted medical use, high potential for abuse, and an unacceptable safety profile), has potential therapeutic indications. "Medicinal" properties are related to multiple compounds, particularly Δ-9-tetrahydrocannabinol and cannabidiol. Cannabis use has markedly increased, but there are little data on its safety or clinical benefit. Formulations on the U.S. and Canadian markets can be consumed orally, sublingually, or rectally; or vaporized or smoked. They are not subject to U.S. Food and Drug Administration approval. Acute effects include euphoria, tachycardia, premature ventricular contractions, atrial fibrillation, ventricular arrhythmias, bronchitis, blurred vision, altered judgment, dysphoria, anxiety, paranoia, psychosis, and impaired motor coordination. Although medical benefits are supported by limited clinical study in several noncardiovascular conditions (pain, cachexia, nausea and vomiting, multiple sclerosis spasticity, and several forms of epilepsy), there are no well-documented cardiovascular benefits of cannabis. It increases myocardial oxygen demand and decreases myocardial oxygen supply. Smoked or vaporized cannabis may be particularly harmful. Heavy users who suddenly stop cannabis are at risk of a cannabis withdrawal syndrome. *(Article Selection: BobbieJean Sweitzer, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: This scientific statement provides a comprehensive literature review of the history, pharmacology, physiologic effects, safety, and evidence for or against medical uses of cannabis focusing on cardiovascular health.



Lung and gut microbiota are altered by hyperoxia and contribute to oxygen-induced lung injury in mice. Sci Transl Med 2020; 12:eaau9959. PMID: 32801143.

Hyperoxia has detrimental effects on lung physiology; its effects on the lung and gut microbiome and their influences on lung injury are unknown. In a cohort of intensive care unit patients, a significant association was noted between early oxygen exposure and cultured respiratory bacteria. Rates of isolation of *Staphylococcus aureus* were not affected, whereas rates of *Pseudomonas aeruginosa* decreased among patients receiving high inspired oxygen concentrations after controlling for clinical variables. Neonatal mice subjected to hyperoxia (FIO_2 75%) for 2 weeks had decreased bacterial community richness driven by the elimination of the *Erysipelotrichaceae* taxon, the most abundant anaerobe in the lungs of normoxia-exposed mice, determined by RNA gene sequencing. Adult mice subjected to acute hyperoxia (FIO_2 95%) had a significant decrease in anaerobic taxa with an increase in the oxygen-tolerant *Staphylococcus* family at 72 h. Disruption of the lung microbiome occurred in mice by 24 h, which preceded hyperoxia-induced lung injury (assessed by alveolar protein concentrations) that was not apparent until 72 h. In contrast, germ-free mice were protected from lung injury. Enteric antibiotics for 3 weeks before hyperoxia did not affect lung injury but increased alveolar neutrophilia. Systemic vancomycin did not affect lung injury; however, ceftriaxone, with broad gram-negative coverage, increased it. *(Article Selection: Charles W. Emala, Sr., M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

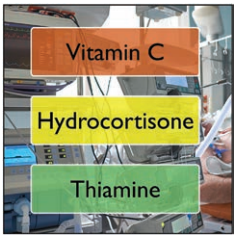
Take home message: Hyperoxia alters the lung microbiome in humans and mice. Detrimental changes in the lung bacterial microbiome influence hyperoxia-induced lung injury in mice.

 DOI: 10.1097/ALN.0000000000003613

Effects of liberal vs restrictive transfusion thresholds on survival and neurocognitive outcomes in extremely low-birth-weight infants: The ETTNO randomized clinical trial. JAMA 2020; 324:560–70. PMID: 32780138.

Transfusion thresholds for extremely low-birth-weight infants remain controversial. Previous studies suggest higher rates of cognitive impairment with restrictive transfusion thresholds. This randomized controlled trial conducted in 36 level III/IV neonatal intensive care units in Europe among infants with birth weights of 400 to 999 g at less than 72 h after birth, compared the therapeutic effect and safety of liberal *versus* restrictive red blood cell transfusion strategies, stratified for postnatal age and the presence of critical health state, on death or disability. Infants were randomly assigned to liberal (28 to 41%, n = 492) or restrictive (21 to 34%, n = 521) red blood cell transfusion thresholds. The incidence of any transfusion was 400 of 492 (81.3%) in the liberal and 315 of 521 (60.5%) in restrictive transfusion thresholds groups. Median volume transfused was 40 ml (interquartile range, 16 to 73 ml) *versus* 19 ml (interquartile range, 0 to 46 ml), respectively. The mean weekly hematocrit was 3 percentage points higher in the liberal threshold group. The primary outcome of death or disability at 24 months of corrected age was not significantly different between groups, nor were the secondary outcomes of cognitive deficit or cerebral palsy. Per-protocol analyses were consistent with the primary analysis. *(Article Selection: David Faraoni, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Among infants with birth weights of less than 1000 g, a restrictive transfusion strategy did not increase the likelihood of death or disability at 24 months of corrected age.



Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: The ACTS randomized clinical trial. JAMA 2020; 324:642–50. PMID: 32809003.

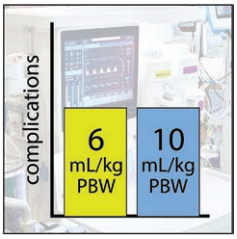
Previous study has suggested that the combination of ascorbic acid, corticosteroids, and thiamine may have a synergistic positive therapeutic effect in patients with septic shock. In this multicenter, blinded, randomized controlled trial, the authors randomized 205 adult patients at 14 centers in the United States on vasopressors for septic shock to receive 1500 mg intravenous ascorbic acid, 50 mg hydrocortisone, and 100 mg thiamine every 6 h for 4 days (n = 103) *versus* placebo (n = 102). There was no significant difference between groups in the primary outcome (change in Sequential Organ Failure Assessment score in the 72 h after enrollment), adjusted mean difference –0.8 (95% CI, –1.7 to 0.2; $P = 0.12$). There was also no significant difference in the incidence of renal failure (31.7% *vs.* 27.3%, adjusted risk difference 0.03 [95% CI, –0.1 to 0.2], $P = 0.58$), or 30-day mortality (34.7% *vs.* 29.3%, hazard ratio 1.3 [95% CI, 0.8 to 2.2], $P = 0.26$). The median number of shock-free days was higher in the intervention group (5 [interquartile range, 3 to 5] *vs.* 4 [interquartile range, 1 to 5] days; median difference 1.0 days; $P < 0.02$). The incidence of adverse events, most commonly hyperglycemia, hypernatremia, and new hospital acquired infection, were similar between groups. *(Article Selection: Marilyn D. Michelow, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: The combination of ascorbic acid, corticosteroids, and thiamine, compared with placebo, did not improve outcomes for adult patients with septic shock.

Opioids after surgery in the United States versus the rest of the world: The International Patterns of Opioid Prescribing (iPOP) multicenter study. Ann Surg 2020 July 9 [Epub ahead of print]. PMID: 32657939.

The United States is at the center of the global opioid epidemic, possibly due in part to overprescribing of opioids postoperatively. In this global multicenter prospective cohort study, the authors compared the total number of postoperative opioids dispensed and oral morphine equivalent doses prescribed on discharge to patients after general surgery procedures in the United States *versus* seven other countries (Lebanon, Colombia, Mexico, China, Thailand, The Netherlands, and Brazil) enrolling 4,690 adult patients at 14 hospitals (14% from the United States). Ninety-one percent of patients from the United States were prescribed postoperative opioids on hospital discharge compared with 5% of patients outside the United States; the median number of pills prescribed was 20 (range, 0 to 135), and the median oral morphine equivalent dose was 150 mg (0 to 1,680 mg) *versus* 0 (0 to 50 mg) and 0 (0 to 600 mg), respectively, outside the United States. Differences in prescribing patterns in the United States were statistically significant ($P < 0.001$) *versus* other countries for both median and mean values. Excluding China, where no postoperative opioids were prescribed, the differences were statistically significant. The opioid refill rate in the United States was 4.7% *versus* 1.0% outside of the United States ($P < 0.001$). There was a statistically significant difference in reported pain values at discharge in U.S. patients *versus* non-U.S. patients (median 4 *vs.* 1, $P < 0.001$), though only 43% of patients were asked to rate their pain at discharge (45% U.S. *vs.* 43% non-U.S.). *(Article Selection: Marilyn D. Michelow, M.D. Image: M. Lane-Fall/Adobe Stock.)*

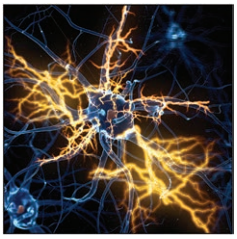
Take home message: Physicians in seven non-U.S. countries prescribe less opioids after common surgical procedures compared with their counterparts in the United States, with U.S. patients reporting higher postoperative pain values at discharge.



Effect of intraoperative low tidal volume vs conventional tidal volume on postoperative pulmonary complications in patients undergoing major surgery: A randomized clinical trial. JAMA 2020; 324:848–58. PMID: 32870298.

The ideal tidal volume for intraoperative ventilation and its relation to postoperative pulmonary complications is controversial. This single-center, outcome-blinded, randomized clinical trial of 1,236 adult patients undergoing major noncardiac surgery under general anesthesia allocated patients to receive a tidal volume of 6 ml/kg predicted body weight (n = 614; low tidal volume group) or 10 ml/kg predicted body weight (n = 592; conventional group) with positive end-expiratory pressure at 5 cm H_2O. The primary outcome was a composite of postoperative pulmonary complications within the first 7 postoperative days, including pneumonia, bronchospasm, atelectasis, pulmonary congestion, respiratory failure, pleural effusion, pneumothorax, or unplanned postoperative ventilation. A total of 1,206 (98.9%) patients completed the trial (mean age 63.5 yr; 494 [40.9%] women; 681 [56.4%] undergoing abdominal surgery). The primary outcome occurred in 231 of 608 patients (38%) in the low tidal volume group compared with 232 of 590 patients (39%) in the conventional tidal volume group (difference –1.3% [95% CI, –6.8% to 4.2%]; risk ratio 0.97 [95% CI, 0.84 to 1.11], $P = 0.64$). There were no significant differences in any of the secondary outcomes. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Intraoperative ventilation with low tidal volume compared with conventional tidal volume with positive end-expiratory pressure did not significantly reduce pulmonary complications within the first 7 postoperative days.



Importin α3 regulates chronic pain pathways in peripheral sensory neurons. Science 2020; 369:842–6. PMID: 32792398.

The mechanisms supporting persistent neuropathic pain after nerve injury such as might occur during surgery are poorly understood. The authors addressed the hypothesis that nucleocytoplasmic proteins regulate these persistent changes using mouse models. They found that importin α3 transport protein knockout mice showed lesser responses to noxious heat whereas overexpression of importin α3 in the knockout mice restored normal behavior. Critically, the importin α3 knockout mice developed transient allodynia and gait changes after nerve injury, whereas wild-type mice demonstrated changes lasting more than 90 days. Analysis of the transcriptomes of the injured nerves suggested that transcription factors including c-Fos were affected in the importin α3 knockout mice. The transcription factor c-Fos has long been associated with chronic pain. Experiments knocking down c-Fos expression in sensory neurons produced mice with behavioral phenotypes after nerve injury similar to the α3 knockout mice. Additional experiments showed that c-Fos was a substrate for importin α3-dependent nuclear transport. Using an *in silico* screen to identify drugs targeting the importin α3–c-Fos pathway, two medications were identified (sulmazole and sulfamethizole) that reduced pain-like behaviors in the nerve injury model. *(Article Selection: J. David Clark, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: A novel nucleocytoplasmic pathway has been identified that might provide novel therapeutic approaches for persistent neuropathic pain.

Effect of multilevel upper airway surgery vs medical management on the apnea-hypopnea index and patient-reported daytime sleepiness among patients with moderate or severe obstructive sleep apnea: The SAMS randomized clinical trial. JAMA 2020; 324:1168–79. PMID: 32886102.

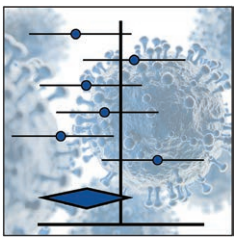
The authors evaluated whether combined palatal and tongue surgery is an effective treatment for patients with obstructive sleep apnea (OSA) when routine treatment has failed. They conducted a parallel-group, open-label, randomized trial of upper airway surgery (uvulopalatopharyngoplasty and tongue reduction; n = 51) *versus* medical management (n = 51) at six hospitals in 102 adults (age, 44.6 ± 12.8 yr; 18 [18%] women) with symptomatic moderate or severe OSA. The primary outcome measures were the apnea-hypopnea index (events/h; 15 to 30 indicates moderate, greater than 30 indicates severe OSA) and the Epworth Sleepiness Scale (range 0 to 24; greater than 10 indicates pathological sleepiness) at 6 months. The mean apnea-hypopnea index was 48 at baseline and 21 at 6 months for the surgery group and 45 at baseline and 34 at 6 months for medical management (mean baseline-adjusted between-group difference at 6 months, –17.6 events/h [95% CI, –26.8 to –8.4], $P < 0.001$). The mean Epworth Sleepiness Scale was 12 at baseline and 5 at 6 months in the surgery group and 11 at baseline and 10 at 6 months in the medical management group (mean baseline-adjusted between-group difference at 6 months, –6.7 [95% CI, –8.2 to –5.2]; $P < 0.001$). Two participants had serious adverse events. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Combined palatal and tongue surgery significantly reduced the number of apnea and hypopnea events and patient-reported sleepiness at 6 months compared to medical management.

Colchicine in patients with chronic coronary disease. N Engl J Med 2020 Aug 31 [Epub ahead of print]. PMID: 32865380.

The anti-inflammatory effects of colchicine used to treat pericarditis likely explain a reduction in risk of cardiovascular events in patients with recent myocardial infarction. This randomized, controlled, double-blind trial evaluated the effect of 0.5 mg of colchicine once daily *versus* placebo in 5,522 patients (2,762 colchicine, 2,760 placebo) with chronic coronary artery disease for a median duration of 28.6 months at 43 centers in Australia and The Netherlands. The primary endpoint was a composite of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. A primary endpoint event occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group (incidence 2.5 *vs.* 3.6 events per 100 person-years; hazard ratio 0.69 [95% CI, 0.57 to 0.83]; $P < 0.001$). The effect was consistent across all components of the primary and secondary composite endpoints. Death from noncardiovascular causes was nonsignificantly higher in the colchicine group (incidence 0.7 *vs.* 0.5 events per 100 person-years; hazard ratio 1.51 [95% CI, 0.99 to 2.31]). Gastrointestinal upset was the most common reason for discontinuation in the run-in phase but thereafter 10.5% in either group discontinued the study drug prematurely. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Daily administration of 0.5 mg colchicine reduced the relative risk of cardiovascular events in patients with chronic coronary artery disease by 31% compared to placebo.



Drug treatments for COVID-19: Living systematic review and network meta-analysis. BMJ 2020; 370:m2980. PMID: 32732190.

The coronavirus pandemic has infected more than 25 million people with more than 830,000 deaths worldwide, but evidence for effective interventions remains limited. This living systematic review and network analysis considered 23 randomized controlled trials that compared treatment drugs to each other, placebo, or standard care. Data were collected from the Centers for Disease Control and Prevention COVID-19 Research Articles Database. Bayesian random effects network meta-analysis was used to evaluate outcomes chosen by expert consensus: mortality, frequency and duration of mechanical ventilation, adverse events, hospital length of stay, intensive care unit length of stay, time to viral clearance, and time to symptom resolution. All but two of the included trials had a high risk of bias, and the certainty of evidence for most interventions was low. There was no reduction in mortality compared to standard care in a network analysis with either glucocorticoids, hydroxychloroquine, lopinavir-ritonavir, remdesivir, or umifenovir (risk ratio 0.84 [95% CI, 0.52 to 1.36]). By direct pairwise comparison, a mortality benefit (risk ratio 0.88 [95% CI, 0.80 to 0.97]) and a reduction in use of mechanical ventilation (risk ratio 0.74 [95% CI, 0.59 to 0.93]) was noted with glucocorticoids. *(Article Selection: Meghan E. Prin, M.D., M.S. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In an ongoing "living" systematic review, currently glucocorticoids were the only drugs that may reduce the risk of mortality and need for mechanical ventilation in COVID-19 infection.

Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: A retrospective, multicentre, international cohort study. Lancet 2020; 396:545–52. PMID: 32828186.

Septic shock is known to adversely affect cardiac function leading to cardiomyopathy with cardiogenic shock in up to 10% of patients. The use of venoarterial extracorporeal membrane oxygenation (ECMO) in this setting is controversial. The authors conducted a propensity weighted retrospective analysis using data from five university hospital ECMO centers in the United States and France comparing outcomes of patients who received venoarterial ECMO within 4 days of meeting predefined criteria (n = 82) with a control group of those who did not (n = 130). The venoarterial ECMO group were more severely ill as measured by: worse cardiac function (mean cardiac index 1.5 $l \cdot min^{-1} \cdot m^{-2}$ *vs.* 2.2 $l \cdot min^{-1} \cdot m^{-2}$), higher inotrope requirements (279 μg/kg per min *vs.* 145 μg/kg per min), higher serum lactate concentrations (8.9 mmol/l *vs.* 6.5 mmol/l) and more severe organ failure (17 *vs.* 13 Sequential Organ Failure scores), with a higher burden of lung infection (78% *vs.* 38%, $P < 0.001$). Despite this, the venoarterial ECMO group had significantly better raw and propensity adjusted 90-day survival (raw 60% *vs.* 25%, $P < 0.0001$; adjusted 51% *vs.* 14%, $P = 0.0029$). In a subset of 32 venoarterial ECMO patients assessed at 1 yr, long-term quality of life was judged satisfactory. *(Article Selection: Jamie Sleigh, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Despite the potential for unmeasured confounders and referral bias to influence the results, this analysis suggests that early application of venoarterial ECMO in this setting can be beneficial.