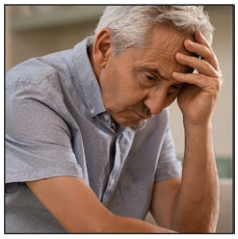
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
ANESTHESIOLOGY®
Martin J. London, M.D., Editor
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Intrinsic connectivity of the human brain provides scaffold of tau aggregation in clinical variants of Alzheimer's disease. Sci Transl Med 2022; 14:eabc8693. PMID: 36001678.

The deposition of tau neurofibrillary tangles and amyloid-β plaques are classic histopathologic findings in Alzheimer's disease, but a correlation between brain tau topography and clinical phenotypes of Alzheimer's is unknown. Preclinical studies suggest that tau pathology has cell-to-cell propagation properties, thus the present study questioned whether tau aggregation is differentially concentrated in distinct brain network hubs in different Alzheimer's phenotypes. Positron emission tomography (PET) and structural, diffusion-weighted, and functional magnetic resonance imaging analyses were conducted in control and Alzheimer's patients with amnestic, posterior cortical atrophy, behavioral/dysexecutive or progressive aphasia phenotypes of Alzheimer's. The tau-PET tracer MK6240 in each clinical variant of Alzheimer's matched to a different functional network. Each Alzheimer's phenotype correlated to a known canonical network: amnestic to the default mode, the posterior cortical atrophy to visuospatial network, the behavioral/dysexecutive to salience network, and the progressive aphasia to the language network. Subsequently, white matter tracts were also shown to be differentially associated with different Alzheimer's phenotypes, suggesting a possible propagation pathway for tau pathology. The results are consistent with a concept that tau pathology aggregates along intrinsic connectivity pathways *via* cell-to-cell propagation, highlighting the therapeutic potential of therapies that block the uptake or transmission of tau. *(Article Selection: Charles Emala, M.D. Image: Adobe Stock.)*

Take home message: The functional and structural networks of the human brain provide the framework for tau aggregation propagation which are distinct among clinical phenotypes of Alzheimer's disease.

Artificial intelligence-enabled detection and assessment of Parkinson's disease using nocturnal breathing signals. Nat Med 2022; 28:2207–15. PMID: 35995955.

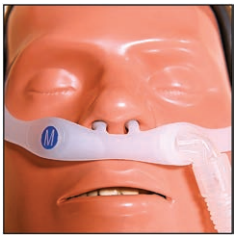
Parkinson's disease is the fastest growing neurologic disorder worldwide. Treatment relies on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which is subjective. Parkinson's affects respiratory drive and muscle function, which can be detected in nocturnal sleep patterns. Using sleep data from several large U.S. tertiary care and research databases (11,964 nights, more than 120,000 h of nocturnal breathing signals from 757 Parkinson's disease subjects [mean ± SD age 69 ± 10 yr] and 6,914 control subjects [66 ± 18 yr]) obtained from either a wearable belt or an in-room radio signal (reflected off the patient's body while they sleep at home), an artificial intelligence model was developed that processes breathing data using a neural network to infer the presence of Parkinson's disease and assesses severity according to the MDS-UPDRS standard. The artificial intelligence models for diagnosis demonstrated an area under the curve of 0.889 (wearable belt) and 0.906 (wireless radio signal). The artificial intelligence model estimated severity and progression in accordance with the Movement Disorder Society's Rating Scale (R = 0.94). *(Article Selection: Meghan Prin, M.D., M.S. Image: Adobe Stock.)*

Take home message: An artificial intelligence model using at-home minimally invasive or noninvasive sleep-derived data may facilitate objective early diagnosis and progression of Parkinson's disease.

Pediatric battery-related emergency department visits in the United States: 2010–2019. Pediatrics 2022; 150:e2022056709. PMID: 36032018.

Button batteries are now ubiquitous in consumer electronic devices. Data from the National Electronic Injury Surveillance System report an estimated 70,322 battery-related emergency department visits in children younger than 18 y from 2010 to 2019, yielding an annual average of 9.5 visits/100,000 children. This rate was highest in children 5 y and younger, and 12% of these patients were hospitalized with button battery ingestions (85% of cases). These estimates were 2.1 times higher compared with an earlier study period (1990 to 2009). Previous reports have noted an almost sevenfold increase in major complications and deaths after button battery ingestions in children since introduction of the 20 mm CR2032 lithium batteries in 2006. Updated ingestion guidelines from the National Capital Poison Center now include the administration of honey to neutralize the strong alkali reaction before taking the child to the hospital. Sucralfate may also be administered in the emergency department. *(Article Selection: Alan Jay Schwartz, M.D., M.S.Ed., and Debnath Chatterjee, M.D. Image: Adobe Stock.)*

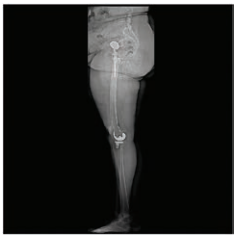
Take home message: Button battery ingestion is on the rise and accounts for most battery-related hospitalizations. Dissemination of preventative options and early treatment recommendations may help in curbing this public health problem.



Effect of high-flow nasal cannula therapy vs continuous positive airway pressure therapy on liberation from respiratory support in acutely ill children admitted to pediatric critical care units: A randomized clinical trial. JAMA 2022; 328:162–72. PMID: 35707984.

High-flow nasal cannula and continuous positive airway pressure are popular modes of noninvasive support in the pediatric critical care setting. This was a pragmatic, multicenter, randomized noninferiority clinical trial in 24 U.K. pediatric critical care units of children (0 to 15 yr; median age, 9 months; 39% female) requiring noninvasive respiratory support. Patients were randomly assigned 1:1 to either high-flow nasal cannula at a flow rate based on body weight (n = 301) or continuous positive airway pressure (7 to 8 cm H_2O; n = 299). The primary outcome was the time from randomization to liberation from respiratory support (the start of a 48-h period free from all forms of respiratory support). Seven secondary outcomes were assessed, including mortality at critical care unit discharge, intubation within 48 h, and use of sedation. The median time to liberation in the high-flow nasal cannula group was 53 h (95% CI, 46 to 61 h) *versus* 48 h (95% CI, 41 to 56 h) in the continuous positive airway pressure group (absolute difference, 5 h [95% CI, –10 to 17 h]). This met the criterion for noninferiority. Of the seven prespecified secondary outcomes, use of sedation, mean duration of critical care stay, and mean duration of acute hospital stay were lower in the high-flow nasal cannula group. The most common adverse event was nasal trauma (high-flow nasal cannula: 6 of 295 [2%]; continuous positive airway pressure: 18 of 278 [7%]). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

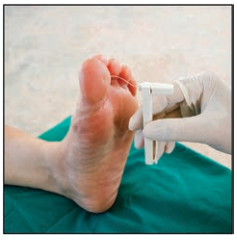
Take home message: In this randomized trial of critically ill children requiring noninvasive respiratory support, high-flow nasal cannula was found to be noninferior to continuous positive airway pressure.



Effect of aspirin vs enoxaparin on symptomatic venous thromboembolism in patients undergoing hip or knee arthroplasty: The CRISTAL randomized trial. JAMA 2022; 328:719–27. PMID: 35997730.

Although the use aspirin-based thromboprophylaxis has increased over the past decade, limited evidence exists regarding the safety and efficacy of aspirin when used as a sole prophylactic agent. The CRISTAL trial was a cluster-randomized, crossover trial across 31 hospitals (performing greater than 250 knee or hip arthroplasty procedures per year) in Australia. Adult patients undergoing hip or knee arthroplasty procedures were enrolled at each hospital. Hospitals were randomized to administer aspirin (100 mg/d) or enoxaparin (40 mg/d) for 35 days after total hip and for 14 days after total knee arthroplasty. Crossover occurred after the patient enrollment target had been met for the first group. The primary outcome was symptomatic venous thromboembolism within 90 days, including pulmonary embolism and deep venous thrombosis. Enrollment was stopped after an interim analysis (9,711 patients out of 15,562 planned). Within 90 days of surgery, symptomatic venous thromboembolism occurred in 256 patients (79 pulmonary embolism and 18 above-knee and 174 below-knee deep venous thrombosis). The symptomatic venous thromboembolism rate in the aspirin group was 3.45% *versus* 1.82% in the enoxaparin group (estimated difference, 1.97%; 95% CI, 0.54 to 3.41%). This failed to meet the criterion for noninferiority for aspirin and was significantly superior for enoxaparin ($P = 0.007$). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

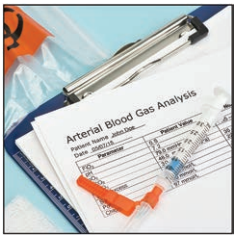
Take home message: Enoxaparin resulted in a significantly lower 90-day rate of symptomatic venous thromboembolism when compared with aspirin in patients undergoing hip or knee arthroplasty.



Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): A multicentre, double-blind, randomised crossover trial. Lancet 2022; 400:680–90. PMID: 36007534.

First-line oral treatments provide only modest benefit in diabetic neuropathic pain. Although patients often receive multiple adjuvants, there are few data on comparative-effectiveness of combination therapy. This double-blind, non–placebo-controlled crossover study randomly assigned 140 patients at 13 U.K. centers with diabetic neuropathy to amitriptyline supplemented by pregabalin, pregabalin supplemented by amitriptyline, and duloxetine supplemented by pregabalin (84 completed at least two pathways). Participants were titrated up to 75 mg amitriptyline, 600 mg pregabalin, and 120 mg duloxetine. At 6 weeks, those reporting pain scores less than 3 out of 10 continued on monotherapy while those with higher scores received supplemental pharmacotherapy. At the 16-week endpoint, the 7-day pain score average (primary outcome) decreased from (mean ± SD) 6.6 ± 1.5 to 3.3 ± 1.8 in all pathways, with the largest difference being –0.1 (98% CI, –0.5 to 0.3) for duloxetine-pregabalin *versus* amitriptyline-pregabalin and for pregabalin-amitriptyline *versus* amitriptyline-pregabalin. At 6 weeks, 61% of participants experienced at least 30% pain reduction with no significant differences between groups; at 16 weeks, 66% reported at least 30% pain reduction. Mean pain score reduction in patients on combination therapy was 1.0 ± 1.3 [1.3] *versus* 0.2 ± 1.5 in those remaining on monotherapy; $P = 0.085$). Most discontinuations from side effects occurred during monotherapy, with fewer occurring with pregabalin-amitriptyline (5%) than with other combinations ($P = 0.031$). *(Article Selection: Steven Cohen, M.D. Image: Adobe Stock.)*

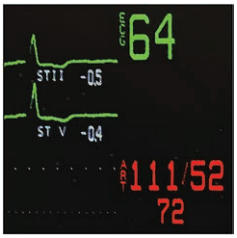
Take home message: Combination oral treatment for diabetic neuropathic pain was well tolerated and may provide benefit over monotherapy, with all three combination pathways having similar analgesic effectiveness.



Oxygen targets in comatose survivors of cardiac arrest. N Engl J Med 2022; 387:1467–76. PMID: 36027567.

The appropriate oxygenation target for mechanical ventilation in comatose survivors of out-of-hospital cardiac arrest is not known. This randomized trial with a two-by-two factorial design randomly assigned 789 intubated and mechanically ventilated comatose adults with out-of-hospital cardiac arrest (1:1 ratio) in Denmark of either a restrictive (partial pressure of oxygen [Pao_2] 68 to 75 mmHg) or a liberal oxygen target (Pao_2 98 to 105 mmHg). Patients were assigned to one of two blood-pressure targets that were reported separately. The primary outcome was a composite of death from any cause or hospital discharge with severe disability or coma (Cerebral Performance Category 3 or 4; range 1 to 5, higher values indicating more severe disability) within 90 days after randomization. Secondary outcomes were neuron-specific enolase levels at 48 h, death from any cause, the score on the Montreal Cognitive Assessment (range 0 to 30, higher scores indicating better cognitive ability), the score on the modified Rankin scale (range 0 to 6, higher scores indicating greater disability), and the Cerebral Performance Category at 90 days. There were no significant differences between groups in the primary outcome (32% *vs.* 34%, respectively; (hazard ratio, 0.95; 95% CI, 0.75 to 1.21; $P = 0.69$) nor in any of the secondary outcomes (death 28% *vs.* 31%), all scores and enolase levels were nonsignificant. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

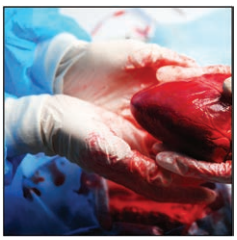
Take home message: Targeting a higher or lower partial pressure of oxygen during mechanical ventilation of survivors of out of hospital cardiac arrest had no influence on survival or disability.



Blood-pressure targets in comatose survivors of cardiac arrest. N Engl J Med 2022; 387:1456–66. PMID: 36027564.

The appropriate mean blood pressure targets in comatose survivors of out-of-hospital cardiac arrest are not known. The authors report a two-by-two factorial design randomized trial of 789 intubated and mechanically ventilated, comatose adults with out-of-hospital cardiac arrest (1:1 ratio) in Denmark of a higher (77 mmHg) or lower target (63 mmHg) (oxygen targets discussed in preceding summary above). Blood pressure targets were assessed during the period of invasive arterial monitoring; the high-target protocol standardized volume resuscitation, norepinephrine, or supplemental dopamine infusion use. The primary and secondary outcomes are presented in the oxygen target summary above. A total of 789 patients were analyzed (393 high-target, 396 low-target groups). There were no differences in either the primary or secondary outcomes between groups (primary outcome composite 34% high *vs.* 32% low, hazard ratio, 1.08; 95% CI, 0.84 to 1.37; $P = 0.56$; mortality 31% *vs.* 29% hazard ratio, 1.13; 95% CI, 0.88 to 1.46); median Cerebral Performance Category 1 (interquartile range, 1 to 5) in both groups; corresponding median modified Rankin scale scores were 1 (interquartile range, 0 to 6) in both groups, median Montreal Cognitive Assessment scores 27 (interquartile range, 24 to 29) high *versus* 26 (interquartile range, 24 to 29) low. Median neuron-specific enolase levels were also similar between groups. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: In this randomized trial of survivors of out-of-hospital cardiac arrest requiring mechanical ventilation, there were no significant differences in major physiologic or disability related outcomes in targeting a higher mean arterial blood pressure of 77 mmHg or lower mean pressure of 63 mmHg.



Donor macrophages modulate rejection after heart transplantation. Circulation 2022; 146:623–38. PMID: 35880523.

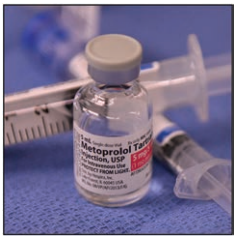
Forty percent of heart transplant recipients will suffer from a rejection within the first year after surgery. The strong systemic immunosuppression currently needed after transplantation is responsible for the increased incidence of infections and malignancies. Hence, an alternative approach to achieve allograft immunotolerance is required. This murine heart transplantation model study aimed to investigate how the donor heart's intrinsic immunity influences allograft acceptance. This study deciphers the specific immunologic roles of tissue resident macrophages and of monocyte-derived macrophages that originate from the donor and recipient, respectively. Using single-cell RNA sequencing, the transcriptional signatures of monocytes, macrophages, and dendritic cells demonstrated that donor and recipient macrophage expression profiles were nonoverlapping. Donor macrophages distinguished themselves based on the expression of the C-C chemokine receptor 2 (CCR2+ or CCR2–) and persisted after heart transplantation (from days 1 to 3), but both populations disappeared due to ongoing rejection (after day 7). Using CCR2-linked diphtheria toxin receptor transgenic mice, selective depletion of donor CCR2+ macrophages resulted in extended allograft survival, while selective depletion of donor CCR2– fostered rapid rejection. CCR2+ macrophages signaled *via* myeloid differentiation primary response protein 88 (MyD88) and the conditional deletion of MyD88 was sufficient to prevent CCR2+ macrophage activation and extend allograft survival. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: These results from a murine transplant model suggest that donor CCR2+ macrophages are promising targets to prevent heart transplant rejection.

2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J 2022; 43:3826–924. PMID: 36017553.

The 2022 European Society of Cardiology guidelines recommend a stepwise evaluation of patients integrating clinical risk factors and test results with the estimated stress of the planned surgical procedure and the risks of discontinuing medications such as anticoagulants. Medical therapies, coronary interventions, timing of surgery, and specific surgical and anesthetic techniques, or withholding treatment are recommended to optimize patients' perioperative outcomes. The recommendations are intended to prevent perioperative cardiovascular morbidity and mortality, specifically perioperative myocardial infarction and injury, stent thrombosis, acute heart failure, arrhythmias, pulmonary embolism, bleeding complications, stroke, and death. Patients younger than 65 yr of age without signs, symptoms, or history of cardiovascular disease or cardiovascular risk factors are considered low risk and can proceed with low- and intermediate-risk surgeries without additional preoperative risk assessment. For patients 65 yr and older, the presence of cardiovascular disease, risk factors for cardiovascular disease, frailty, and functional capacity along with the risk of surgery guide preoperative risk assessment, testing, interventions, and optimization. Clinical examination, patient-reported functional capacity, and noninvasive tests are fundamental for preoperative cardiac assessment. The guidelines acknowledge that evidence is lacking on the value of cardiac biomarkers, stress testing, or routine myocardial revascularization to reduce perioperative cardiovascular complications. *(Article Selection: BobbieJean Sweitzer, M.D. Image: European Society of Cardiology.)*

Take home message: The European Society of Cardiology has extensively updated their 2014 guidelines for the cardiac evaluation of patients planning noncardiac surgery.



Perioperative beta-blocker supply and survival in women with epithelial ovarian cancer and a history of cardiovascular conditions. J Clin Oncol [Epub ahead of print 2022 August 24]. PMID: 36001852.

Animal and *in vitro* evidence suggests that stress-inflammatory responses may stimulate tumor growth, increasing metastatic potential. Conversely, inhibition of the catecholamine-induced responses *via* β-adrenergic receptor blockade may improve survival. Small observational studies have reported mixed results. This is a population-based observational cohort study (two provinces in Australia accounting for 65% of the total population) of 3,844 females age 50 yr or older with a history of cardiovascular conditions undergoing surgery for epithelial ovarian cancer (2002 to 2014) evaluating treatment effects of selective β-blocker or nonselective β-blocker supply perioperatively on survival (through 2016) using covariate-balanced inverse probability of treatment weights with flexible parametric survival models allowing for time-varying survival effects. Of 10,590 with ovarian cancer, 3,844 were eligible for analysis. Administrative databases were used to determine timing of surgery, covariates, and medication prescriptions. Perioperatively, 560 (14.5%) women had active prescriptions for a selective β-blocker and 67 (1.7%) were a nonselective agent (91% propranolol). At 2 yr after surgery, a survival advantage was noted for nonselective use (80%, 95% CI, 68 to 88) *versus* 69% (67 to 70) for no use and this extended for on average 8 yr after surgery, while no association was noted for those with selective β-blocker prescriptions. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: This population-based cohort analysis of β-blocker prescription availability around the time of surgery for epithelial ovarian cancer suggests a survival benefit associated with the use of nonselective β-blockers.

The past, present, and future of antibiotics. Sci Transl Med 2022; 14:eabo7793. PMID: 35947678.

Before the advent of antibiotics, more than half of all deaths were from infections. However, we are at present in the middle of an antibiotic crisis caused by the spread of multidrug-resistant organisms and stagnation in the development of new antibiotics. Many large pharmaceutical companies have abandoned antibiotic innovation because of the high cost of bringing a drug to market and the relatively poor return on investment. There is a need to change investment policies to prioritize societal value over commercial profit. A successful antibiotic needs to be very nontoxic, be able to penetrate and kill senescent-phase organisms (biofilms), and have minimal impact on the patient's microbiome. Fortunately, there are several emerging drug developments that meet these requirements and have shown some promise. These include narrow-spectrum small molecules, bacteriophages, monoclonal antibodies, and vaccines. The effective use of these narrow-spectrum compounds is also predicated on the simultaneous development of fast, accurate point-of-care molecular diagnostic methods to identify the pathogenic organism, and its virulence and sensitivity. *(Article Selection: Jamie Sleigh, M.D. Image: J. P. Rathmell.)*

Take home message: With suitable structural coordination of the antibiotic development pipeline, clinicians should be able to look forward to having a diverse battery of tools to treat and prevent bacterial infection.