SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
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Key Papers from the Most Recent Literature Relevant to Anesthesiologists

## Generalizability of cardiovascular disease clinical prediction models: 158 independent external validations of 104 unique models. Circ Cardiovasc Qual Outcomes 2022; 15:e008487. PMID: 35354282.

The use of clinical prediction models is increasingly common to guide patient care, although their performance when applied to new patient cohorts is not well delineated. One hundred fifty-eight external validations of 104 models in three domains of cardiology (primary prevention, acute coronary syndrome, and heart failure) using publicly available clinical trial cohorts were performed. Performance was assessed using discrimination, calibration, and net benefit. To better understand poor model performance, model-clinical trial cohort pairs were stratified on relatedness (a domain-specific set of characteristics to qualitatively grade the similarity of derivation and validation patient populations). The model-based C-statistic was also assessed for changes in discrimination related to differences in case-mix between the derivation and validation samples as well as the impact of model updating on model performance. Discrimination lessened significantly between model derivation (0.76 [interquartile range, 0.73–0.78]) and validation (0.64 [interquartile range, 0.60–0.67], $P < 0.001$); approximately half of this loss was because of narrower case-mix in the validation samples. Models had more discrimination when tested in related compared with distantly related trial cohorts. Ninety-one percent of models had a risk of harm at some possible decision threshold; this risk could be lessened by updating model intercept, calibration slope, or complete re-estimation. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

***Take home message:*** Significant declines in cardiovascular clinical prediction model performance are likely when applying them to new patient populations, resulting in substantial risk of harm.

## Prophylactic oral dextrose gel and neurosensory impairment at 2-year follow-up of participants in the hPOD randomized trial. JAMA 2022; 327:1149–57. PMID: 35315885.

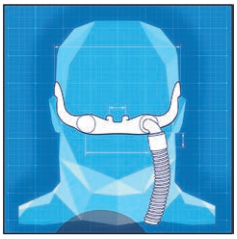
Prophylactic oral dextrose gel can reduce neonatal hypoglycemia although later effects are uncertain. Long-term follow-up data were reported from a multicenter placebo-controlled trial (18 Australian and New Zealand centers) of late preterm or term at-risk infants randomized to prophylactic 40% dextrose (n = 681) or placebo (n = 678) gel, 0.5 ml/kg, administered *via* buccal mucosa 1 h after birth. The primary outcome was neurosensory impairment at 2 yr corrected age and 44 secondary outcomes (cognitive, language, and motor composite Bayley III scores [higher scores indicate better performance]). There was no difference in the primary outcome (21% dextrose *vs.* 19% placebo; unadjusted risk difference, 2% [95% CI, –2% to 7%]; adjusted risk ratio, 1.13 [95% CI, 0.90 to 1.41]). Although the risk of cognitive and language delay was not significantly different between the dextrose and placebo groups, the dextrose gel group had a significantly higher risk of motor delay (2.5% *vs.* 0.7%; risk difference, 2% [95% CI, 0.40% to 3%]; adjusted risk ratio, 3.79 [95% CI, 1.27 to 11.32]) and lower composite scores for cognitive (adjusted mean difference, –1.30 [95% CI, –2.55 to –0.05]), language (adjusted mean difference, –2.16 [95% CI, –3.86 to –0.46]), and motor (adjusted mean difference, –1.40 [95% CI, –2.60 to –0.20]) performance. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

***Take home message:*** Among late preterm and term infants at risk of neonatal hypoglycemia, prophylactic oral 40% dextrose gel at 1 h of age, compared with placebo, resulted in no significant difference in the risk of neurosensory impairment at 2 yr corrected age.

## Sex-related outcomes of medical, percutaneous, and surgical interventions for coronary artery disease: JACC Focus Seminar 3/7. J Am Coll Cardiol 2022; 79:1407–25. PMID: 35393023.

While ischemic heart disease is the leading global cause of death for men and women, women generally have worse outcomes. This is attributable to differences in biology and culture, but also to the near absence of women in research before the 1993 NIH Revitalization Act. Sex-specific research is imperative to remedy these differences. Research to date has yielded a few important lessons. Women respond better to lipid-lowering medications but are less likely to achieve target cholesterol concentrations due to prescribing disparities. Women have higher baseline platelet reactivity in response to aspirin and P2Y12 inhibitors, which may explain worse outcomes after percutaneous coronary intervention. Women account for the majority of patients with ischemia and no coronary obstruction. While trial results for this condition are forthcoming, there are currently no treatment guidelines. Women have greater adjusted mortality after coronary bypass surgery due in part to later referrals, anatomy, and underrepresentation in trial data. The interaction of age with sex should also be considered. For example, hormone therapy reduces cardiovascular events in perimenopausal women under age 60 but may be harmful in older women. The development of sex-specific guidelines based on further research may improve outcomes in women. *(Article Selection: Meghan Prin, M.D., M.S. Image: Adobe Stock.)*

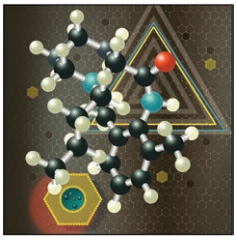
***Take home message:*** There are important sex-related differences in the etiology and outcomes of cardiovascular disease, and sex-specific research and treatment guidelines are needed.



## Effect of high-flow nasal cannula therapy vs continuous positive airway pressure following extubation on liberation from respiratory support in critically ill children: A randomized clinical trial. JAMA 2022; 327:1555–65. PMID: 35390113.

Although continuous positive airway pressure (CPAP) has long been used to provide postextubation respiratory support in children, high-flow nasal cannula therapy is increasingly preferred as an alternative. The FIRST-ABC stepdown randomized controlled trial was a pragmatic, unblinded, multicenter, parallel-group, noninferiority trial to evaluate the noninferiority of high-flow nasal cannula therapy in children as the first-line mode of noninvasive respiratory support after extubation compared to CPAP. The primary outcome was the time from randomization to liberation from respiratory support (start of a 48-h period free from invasive or noninvasive respiratory support). Six secondary outcomes were also assessed (including mortality at day 180 and reintubation within 48 h). Of the 600 randomized children, 553 children (high-flow nasal cannula therapy, 281; CPAP, 272) were included in the primary analysis. High-flow nasal cannula therapy failed to meet noninferiority, with a median time to liberation of 51 h (95% CI, 43 to 68) *versus* 43 h (95% CI, 30 to 48) for CPAP (adjusted hazard ratio, 0.83; one-sided 98% CI, 0.70 to ∞). Of the six prespecified secondary outcomes, five showed no statistically significant difference, including the rate of reintubation within 48 h (13% *vs.* 12%). Mortality at day 180 was significantly greater for high-flow nasal cannula therapy (6% *vs.* 2%; adjusted odds ratio, 3.07 [95% CI, 1.1 to 8.8]). *(Article Selection: David Faraoni, M.D., Ph.D. Image: A. Johnson, Vivo Visuals Studio.)*

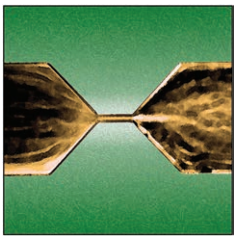
***Take home message:*** High-flow nasal cannula therapy postextubation in critically ill children failed to meet the criterion for noninferiority compared to routine use of continuous positive airway pressure.



## Efficacy of liposomal bupivacaine and bupivacaine hydrochloride vs bupivacaine hydrochloride alone as a periarticular anesthetic for patients undergoing knee replacement: A randomized clinical trial. JAMA Surg 2022; 157:481–9. PMID: 35385072.

The impact of liposomal bupivacaine on perioperative outcomes is controversial. This multicenter study (11 sites, United Kingdom) randomized 533 patients undergoing unilateral knee replacement for osteoarthritis to 266 mg liposomal bupivacaine mixed with 100 mg bupivacaine *versus* 100 mg bupivacaine alone by periarticular injection during surgery. The primary outcomes were the Quality of Recovery 40 (QoR-40) score at 72 h and the pain visual analog scale (VAS) area under the curve (AUC) from 6 to 72 h postsurgery. Secondary outcomes included the QoR-40 and mean pain VAS on the evening of surgery and at postoperative days 1, 2, and 3; cumulative opioid consumption at 72 h; and functional outcomes and quality of life at 6 weeks, 6 months, and 1 yr, and cost effectiveness for 1 yr. There was no difference between the groups in QoR-40 scores at 72 h or the pain VAS score AUC at 6 to 72 h. Only one statistically different data point was identified within the secondary outcomes: liposomal bupivacaine recipients had lower pain scores on the evening of surgery (adjusted difference, –0.54 [97.5% CI, –1.07 to –0.02]; $P = 0.02$). There were no differences in opioid consumption or functional outcomes between the groups. Liposomal bupivacaine was found not to be cost effective. No difference in adverse events was found between the groups. *(Article Selection: Charles Emala, M.D. Image: A. Johnson, Vivo Visuals Studio.)*

***Take home message:*** In patients undergoing unilateral knee replacement surgery, periarticular injection of liposomal bupivacaine plus bupivacaine was not superior to bupivacaine alone in measures of Quality of Recovery 40 scores or in the area under the curve of visual analog pain scores over the 6 to 72 h after surgery.



## A microfluidic device for real-time on-demand intravenous oxygen delivery. Proc Natl Acad Sci U S A 2022; 119:e2115276119. PMID: 35312360.

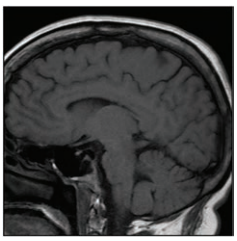
Direct provision of oxygen *via* the intravenous route could help stabilize hypoxic patients. Previous research focused on delivering intravenous oxygen by generating oxygen-filled microparticles as injectable oxygen carriers, but poor shelf stability, macrobubble formation, and toxicity were major problems. In this study, a microfluidic device with controllable gas fractions and volumetric flow rates was created enabling on-demand and real-time production of lipidic oxygen microbubbles. The device geometry consisted of three in-line nozzles with progressively smaller openings, where under steady state conditions bubbles with narrow size distributions (95% of all bubbles less than 10 μm) were generated by shear forces ("nanospraying"). The carrier fluid consisted of distearoyl phosphatidylcholine (10 mg/ml) and PEG40S (2.8 mg/ml) with a maximum flow rate of 12 ml/h, while the gas flow rate was less than 0.7 ml/min at 4 atm. It was tested *in vitro* using deoxygenated human blood, raising $Spo_2$ from 15% to 95% within minutes. In a rat model, administration of 0.4 ml intravenous oxygen/min (approximately 10% of the baseline oxygen consumption of a rat) for 30 min increased mixed venous oxygen saturation by 34%, equating to an increase in arterial oxygen saturation by 50%, without microbubble coalescence or vascular obstruction. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adapted from original article.)*

***Take home message:*** These studies suggest that direct intravenous provision of oxygen using microfluidic technology appears feasible in an *in vitro* and animal model.

## Association of acute respiratory failure in early childhood with long-term neurocognitive outcomes. JAMA 2022; 327:836–45. PMID: 35230393.

Long-term effects of mechanical ventilation for acute respiratory failure in children are unknown. This prospective sibling-matched cohort study from 31 U.S. pediatric intensive care unit (ICU) centers included patients up to 8 yr (normal prior or only moderate neurocognitive dysfunction after pediatric ICU discharge) matched to biological siblings (4 to 16 yr) with normal cognitive function. The primary outcome was the intelligence quotient determined by the age-appropriate Vocabulary and Block Design subtest of the Wechsler Intelligence Scale. Secondary outcomes included measures of global cognitive function. One hundred twenty-one patients (55 [45%] female) with a median (interquartile range) age of 1.0 (0.2 to 3.2) yr with a median invasive mechanical ventilation time of 5.5 (3.1 to 7.7) days matched with siblings (72 [60%] female) with a median age of 8.4 (7.0 to 10.2) yr at testing were included. Intelligence quotient was lower in patients compared to matched siblings (102 *vs.* 104; mean difference, –2.8 [95% CI, –5.4 to –0.2], $P = 0.03$). Significant differences between patients and matched siblings were also found for processing speed (mean difference, 4.4 [95% CI, 0.2 to 8.5]), nonverbal memory (mean difference, –0.9 [95% CI, –1.6 to –0.3], $P = 0.007$), visuospatial skills (mean difference, –0.9 [95% CI, –1.8 to –0.1], $P = 0.03$), and fine motor control (mean difference, –3.1 [95% CI, –4.9 to –1.4], $P < 0.001$). *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

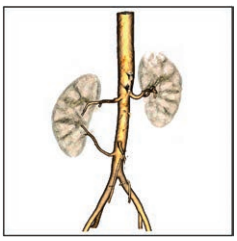
***Take home message:*** Intelligence quotient score and other cognitive test results in children after hospitalization and ventilation for respiratory failure were significantly lower compared with matched siblings. The importance of these small differences remains uncertain.



## Increased global integration in the brain after psilocybin therapy for depression. Nat Med 2022; 28:844–51. PMID: 35411074.

Hallucinogenic drugs appear to have significant antidepressant effects, but their mechanisms of action are not well understood. In an open-label trial, 16 subjects with severe depression assessed with the Beck's Depression Inventory (mean ± SD, 35 ± 7) were given low (10 mg) and high (25 mg) doses of psilocybin 7 days apart, and functional magnetic resonance imaging scans were performed before and after treatment. In a second double-blind study, 43 patients with major depression were randomized to receive either two doses of 25 mg psilocybin and 6 weeks of daily placebo (psilocybin arm), or two doses of 1 mg psilocybin and 6 weeks of daily escitalopram (escitalopram arm). In both trials, subjects had rapid and sustained improvement in depression. In the open-label study, Beck's Depression Inventory decreased a mean of –21 points (95% CI, –27 to –15, $P < 0.001$); in the randomized study, symptom improvement favored the psilocybin arm (mean difference, –9 [95% CI, –14 to –4], $P = 0.002$). Clinical improvements correlated with decreased brain modularity (open-label trial, $r = 0.64$, $P = 0.023$; randomized trial, mean difference, –0.39 [95% CI, –0.75 to –0.02], $P = 0.039$), and increased, more flexible functional connectivity between the default mode network and other higher-order cognitive networks, as assessed by functional magnetic resonance imaging. These changes were not seen with escitalopram. *(Article Selection: Jamie Sleigh, M.D. Image: J. P. Rathmell.)*

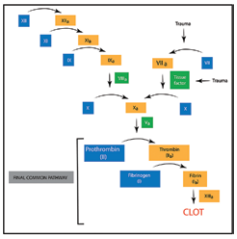
***Take home message:*** Psilocybin results in greater brain network integration, which is associated with a reduction in depression.



## Predictive accuracy of a perioperative laboratory test–based prediction model for moderate to severe acute kidney injury after cardiac surgery. JAMA 2022; 327:956–64. PMID: 35258532.

Early prediction of acute kidney injury (AKI) after cardiac surgery may assist in optimizing subsequent therapy and outcomes. This study reports data for prediction models based on routinely obtained basic metabolic panel laboratory values from a retrospective observational cohort of adults undergoing cardiac surgery at the Cleveland Clinic (n = 58,526) validated at three community hospitals (n = 4,734). Areas under the receiver operating characteristic curve (AUC) for moderate to severe AKI per Kidney Disease: Improving Global Outcomes (KDIGO) criteria, as well as AKI requiring dialysis, were assessed within 72 h and 14 days after surgery. In the derivation cohort (median age, 66 yr; 67% male; 91% White), rates of moderate to severe AKI and AKI requiring dialysis were 4.6% and 1.48% within 72 h and 5.4% and 1.74% within 14 days. The models had high predictive discrimination for AKI within 72 h (AUC, 0.876 [95% CI, 0.869 to 0.883]) and 14 days (AUC, 0.854 [95% CI, 0.850 to 0.861]) and for dialysis within 72 h (AUC, 0.916 [95% CI, 0.907 to 0.926]) and 14 days (AUC, 0.900 [95% CI, 0.889 to 0.909]). In the validation cohort of 4,734 patients, similar results were obtained for AKI within 72 h (AUC, 0.860 [95% CI, 0.838 to 0.882]) and 14 days (AUC, 0.842 [95% CI, 0.820 to 0.865]); dialysis within 72 h (AUC, 0.879 [95% CI, 0.840 to 0.918]) and within 14 days (AUC, 0.873 [95% CI, 0.836 to 0.910]). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

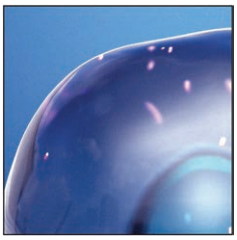
***Take home message:*** In a large retrospective cohort study, a prediction model based on using perioperative basic metabolic panel laboratory values demonstrated clinically acceptable predictive accuracy for moderate to severe acute kidney injury and need for dialysis within 72 h and 14 days after cardiac surgery, although validation prospectively is needed.




## Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet 2022; 399:1383–90. PMID: 35385695.

Asundexian is a novel, oral small molecule, activated coagulation factor XIa (FXIa) inhibitor with postulated minimal effects on hemostasis. This multicenter (93 sites in 14 countries), randomized, double-blind, phase 2 dose-finding study of asundexian 20 mg or 50 mg once daily *versus* apixaban 5 mg twice daily included patients 45 yr or older with atrial fibrillation, a $CHA_2DS_2$-VASc score of at least 2 to 3, and increased bleeding risk to determine optimal dosing and safety of asundexian in patients with atrial fibrillation. The primary endpoint was a composite of major or clinically relevant nonmajor bleeding according to International Society on Thrombosis and Haemostasis criteria. A total of 755 patients were randomized (249 asundexian 20 mg, 254 asundexian 50 mg, 250 apixaban) and 753 analyzed (mean age, 74 yr, 41% female, mean $CHA_2DS_2$-VASc score 3.9). Treatment inhibited FXIa activity for asundexian 20 mg was 81% trough *versus* 90% peak concentrations, and for 50 mg was 92% trough *versus* 94% peak concentrations. The primary outcome was significantly lessened by treatment, ratios of incidence proportions 0.50 (90% CI, 0.14 to 1.68) for asundexian 20 mg (three events), 0.16 (0.01 to 0.99) for asundexian 50 mg (one event), and 0.33 (0.09 to 0.97) for pooled asundexian (four events) *versus* apixaban (six events). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

***Take home message:*** In patients with atrial fibrillation, the novel FXIa inhibitor asundexian once daily resulted in near-complete *in vivo* FXIa inhibition and lower rates of bleeding *versus* standard dosing of apixaban.



## Beneficial effects of citrulline enteral administration on sepsis-induced T cell mitochondrial dysfunction. Proc Natl Acad Sci U S A 2022; 119:e2115139119. PMID: 35173051.

Sepsis induces severe immune cell dysfunction ("immune paralysis") with lymphopenia, elevated number of immunosuppressive regulatory T cells, and the emergence of myeloid-derived suppressor cells, all of which is associated with secondary infections, multiorgan failure, and high mortality. Suppressor cell–induced T-cell dysfunction is thought to be due to arginine deprivation caused by the sepsis-induced catabolic state with elevated arginase activity. This animal study tested whether enhancing arginine availability during sepsis would reduce immunosuppression using a "two-hit" mouse model of sepsis with cecal ligation and puncture followed by the antibiotic meropenem 6 h after cecal ligation and puncture for 5 days (first hit) plus secondary pneumonia (second hit) triggered on day 5 after cecal ligation and puncture by intratracheal instillation of a methicillin-resistant *Staphylococcus aureus*. Oral administration of citrulline (150 mg · $kg^{-1}$ · $day^{-1}$) increased plasma arginine concentrations, restored mitochondrial ATP production and proliferation of T cells, and reduced T-cell apoptosis, sepsis-related regulatory T cells, and myeloid-derived suppressor cells. Citrulline also reduced the severity of the secondary pulmonary infection and total bacterial load, but cecal ligation and puncture survival rate was not significantly greater. Administration of citrulline, which is converted to arginine, was found to be more efficient than arginine in increasing systemic arginine availability because citrulline, as opposed to arginine, is not metabolized in the liver. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

***Take home message:*** This study provides evidence from a mouse model that enteral administration of citrulline can restore T-cell function and reduce sepsis-induced lung injury, but not increase survival.

## Treatment for mild chronic hypertension during pregnancy. N Engl J Med 2022; 386:1781–92. PMID: 35363951.

This open-label, multicenter (70 U.S. sites) trial randomized pregnant women (singleton fetuses, gestational age less than 23 weeks) with new or known mild chronic hypertension (systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg on two occasions at least 4 h apart before 20 weeks' gestation in those without prior history or treatment for chronic hypertension) to receive antihypertensive treatment starting at blood pressure higher than 140/90 mm Hg *versus* development of severe hypertension (systolic blood pressure greater than or equal to 160 mm Hg or diastolic blood pressure greater than or equal to 105 mm Hg; control group). The composite primary outcome included preeclampsia with severe features, medically indicated birth at less than 35 weeks, placental abruption, or fetal or neonatal death. Secondary outcomes were serious neonatal or maternal complications, preeclampsia, and preterm birth. The safety outcome was birth weight below the 10th percentile for age. A total of 29,772 women were screened and 2,408 were ultimately randomized (mean age, 32 y; 48% Black; approximately 55% on Medicaid). The primary outcome was lower in the treatment compared to the control group (30% *vs.* 37%; adjusted risk ratio, 0.82 [95% CI, 0.74 to 0.92]; $P < 0.001$). No significant differences were noted in any of the secondary or safety outcomes. *(Article Selection: BobbieJean Sweitzer, M.D. Image: Adobe Stock.)*

***Take home message:*** In pregnant women with chronic mild hypertension, active treatment targeting blood pressure less than or equal to 140/90 mm Hg *versus* waiting for development of severe hypertension results in better pregnancy outcomes.