

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



### Antenatal dexamethasone for early preterm birth in low-resource countries. *N Engl J Med* 2020 Oct 23 [Epub ahead of print]. PMID: 33095526.

Antenatal glucocorticoids have been shown to reduce preterm infant mortality and morbidity in women in developed countries, but their use in low-resource countries is controversial. The authors conducted a placebo-controlled randomized trial of intramuscular dexamethasone (6 mg every 12 h to a maximum of 4 doses) in pregnant women between 26 and 33 weeks gestation at risk for preterm birth in 29 South Asian and African hospitals. The primary outcomes were neonatal death alone, stillbirth or neonatal death, and possible maternal bacterial infection. A total of 2,852 women (with 3,070 fetuses) underwent randomization. The trial was stopped for benefit at the second interim analysis. Comparing the dexamethasone group *versus* placebo, neonatal death occurred in 20% *versus* 24% of infants (relative risk 0.84 [95% CI, 0.72 to 0.97],  $P = 0.03$ ), stillbirth or neonatal death occurred in 26% *versus* 29% of infants or fetuses (relative risk 0.88 [95% CI, 0.78 to 0.99],  $P = 0.04$ ), and the incidence of possible maternal bacterial infection was 5% *versus* 6% (relative risk 0.76 [95% CI, 0.56 to 1.03]) with no significant between-group difference in the incidence of adverse events. (Article Selection: Laszlo Vutskits, M.D. Image: Adobe Stock.)

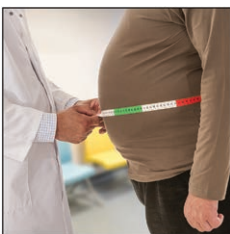
**Take home message:** Antenatal dexamethasone significantly reduces risks of neonatal death alone and stillbirth or neonatal death, without a greater incidence in possible maternal bacterial infection, compared to placebo among women in low-resource countries at risk for preterm birth.



### Association of lumbar puncture with spinal hematoma in patients with and without coagulopathy. *JAMA* 2020; 324:1419–28. PMID: 33048155.

Coagulopathy is considered a risk factor for spinal hematoma in lumbar puncture. The authors report a nationwide (Denmark), population-based cohort study (2008 to 2018) using medical registries to detect subjects undergoing lumbar puncture (83,711 lumbar punctures among 64,730 patients) with cerebrospinal fluid analysis stratifying subjects with coagulopathy (platelets lower than  $150 \times 10^9/l$ , international normalized ratio (INR) greater than 1.4, or activated partial thromboplastin time longer than 39 s). The primary outcome was 30-day risk of spinal hematoma. A secondary outcome was risk of traumatic lumbar puncture (greater than  $300 \times 10^6$  erythrocytes/l). Thrombocytopenia was present in 9% of patients, elevated INR in 2%, and prolonged activated partial thromboplastin time in 3%. Comparing patients without coagulopathy *versus* patients with coagulopathy, spinal hematoma occurred within 30 days for 0.20% (95% CI, 0.16 to 0.24%) *versus* 0.23% (95% CI, 0.15 to 0.34%). Independent risk factors included male sex (adjusted hazard ratio 1.72 [95% CI, 1.15 to 2.56]), age 41 through 60 yr (adjusted hazard ratio 1.96 [95% CI, 1.01 to 3.81]) and age 61 through 80 yr (adjusted hazard ratio 2.20 [95% CI, 1.12 to 4.33]). Risk did not increase significantly with the severity of coagulopathy, by pediatric specialty or medical indication, nor by the cumulative number of procedures. Traumatic lumbar punctures occurred more frequently among patients with elevated INR levels or elevated activated partial thromboplastin time. (Article Selection: Martin J. London, M.D. Image: Adobe Stock.)

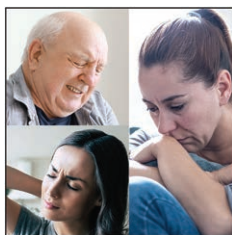
**Take home message:** In a retrospective nationwide cohort study the risk of spinal hematoma after lumbar puncture was low and not different between those with and without coagulopathy, although the observed rates may be confounded by preferential selection of lower-risk patients.



### Life expectancy after bariatric surgery in the Swedish Obese Subjects study. *N Engl J Med* 2020; 383:1535–43. PMID: 33053284.

Obesity lowers life expectancy, and bariatric surgery may improve life expectancy in obese subjects. This long-term follow-up analysis from the prospective intervention Swedish Obese Subjects study examined mortality after bariatric surgery in a cohort of 2,007 patients receiving bariatric surgery between 1987 and 2001, compared with a control group of 2,040 patients receiving usual obesity care and 1,135 patients without obesity. At 20 to 24 yr follow-up, 23% in the bariatric surgery group, 26% in the usual obesity care group, and 11% in the reference cohort had died. The hazard ratio for death in the bariatric surgery group compared with the usual care group was 0.77 (95% CI, 0.68 to 0.87;  $P < 0.001$ ), and the hazard ratio for death between the reference cohort and the usual obesity care group was 0.44 (95% CI, 0.31 to 0.48;  $P < 0.001$ ). Life expectancy in the usual obesity care group was 3 yr shorter than in the surgery group (95% CI, 1.8 to 4.2;  $P < 0.001$ ), and 9 yr shorter in the usual obesity care group than the reference cohort (95% CI, 6.4 to 10.5;  $P < 0.001$ ). In subgroup analysis, the mortality benefit of bariatric surgery was similar in high- and low-risk patients. (Article Selection: Marilyn D. Michelow, M.D. Image: Adobe Stock.)

**Take home message:** Bariatric surgery improved long-term life expectancy in patients with obesity compared to usual obesity care, but mortality remained higher relative to the general population.

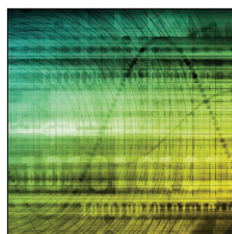


### Decoding the mystery of American pain reveals a warning for the future. *Proc Natl Acad Sci USA* 2020; 117:24785–9. PMID: 32958666.

With an accumulating burden of disease and degenerative changes with aging, the prevalence of self-reported (Gallup polls, U.S. and European governmental polls) pain has been hypothesized to increase with advancing age, a trend observed in most developed countries. However, pain prevalence in the United States assessed using large cross-sectional surveys appears to peak in middle age followed by a decline. The authors analyzed statistically a group of such surveys over different time periods to demonstrate that successive birth cohorts (covering 1930 to 1990) have been reporting more pain throughout their lives than preceding cohorts. They demonstrate that it is not that pain declines among the elderly, but

rather that later birth cohorts are more likely to report more pain. This pattern of increased pain is mostly attributable to subjects without college educations, although changes in occupation (from more physical to more sedentary) or ranges of obesity were not significant risk factors. (*Article Selection: J. David Clark, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.*)

**Take home message:** The increasing prevalence of self-reported pain over successive birth cohorts appears to be primarily related to deterioration in social and economic conditions experienced by less well-educated Americans born after 1950. These observations are likely to have significant implications for healthcare utilization in the future.



### Developing and validating subjective and objective risk-assessment measures for predicting mortality after major surgery: An international prospective cohort study. *PLoS Med* 2020; 17:e1003253. PMID: 33057333.

With increasing availability of large datasets, preoperative risk stratification has become an important tool to guide clinical decisions and resource allocation. In this prospective cohort study, the authors compared the accuracy of available objective surgical risk tools with subjective clinical judgment (*e.g.*, American Society of Anesthesiologists Physical Status) in predicting 30-day mortality after major surgery. For 1 week in 2017, prospective risk, surgical, and outcome data were collected in 22,631 adult patients who underwent surgery requiring at least one overnight stay in 274 hospitals in the

United Kingdom, Australia, and New Zealand. The authors compared subjective assessment with three objective tools for predicting 30-day mortality: the Portsmouth-Physiology and Operative Severity Score for the Enumeration of Mortality, the Surgical Risk Scale, and the Surgical Outcome Risk Tool. Logistic regression models combining subjective assessment and the best objective tool were evaluated. The Surgical Outcome Risk Tool demonstrated the best discrimination of the objective tools (area under receiver operating characteristic curve [AUC] = 0.90 [95% CI, 0.88 to 0.92]), but subjective assessment demonstrated equally good discrimination (AUC = 0.89 [95% CI, 0.86 to 0.91]) compared to the Surgical Outcome Risk Tool ( $P = 0.309$ ). Combining subjective assessment and the Surgical Outcome Risk Tool improved discrimination (AUC = 0.92 [95% CI, 0.90 to 0.94]). (*Article Selection: David Faraoni, M.D., Ph.D. Image: Adobe Stock.*)

**Take home message:** A combination of subjective clinical judgment with objective risk models improved perioperative risk prediction relative to either method alone.



### Gabapentin for chronic pelvic pain in women (GaPP2): A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2020; 396:909–17. PMID: 32979978.

Chronic pelvic pain is a condition affecting 20% or more of females causing both suffering and disability. Effective treatment options remain limited. Off-label use of gabapentin has been suggested, but data from clinical trials are lacking. To address this gap, the gabapentin for chronic pelvic pain (GaPP2) collaborative conducted a 39-center randomized double-blind trial in the United Kingdom. Entry criteria included: female sex 18 to 50 yr of age, chronic pelvic pain of at least 3 months duration, and no obvious pelvic pathology at laparoscopy. A total of 306 participants were randomized to gabapentin, titrated up

to 2,700 mg/day or matched placebo, for 16 weeks. The study's two primary outcome measures were worst and average pain scores (assessed using a 0 to 10 numeric rating scale) at weeks 13 to 16 of therapy. Gabapentin had no significant effect on pain scores; the mean change in the worst pain score from baseline was mean  $\pm$  SD,  $-1.4 \pm 2.3$  in the gabapentin group and  $-1.2 \pm 2.1$  in the placebo group (adjusted mean difference  $-0.20$  [97.5% CI,  $-0.81$  to  $0.42$ ],  $P = 0.47$ ). Gabapentin was associated with a higher incidence of self-reported adverse effects (dizziness, drowsiness, and visual disturbances) compared to placebo (7% vs. 2%,  $P = 0.04$ ). (*Article Selection: J. David Clark, M.D., Ph.D. Image: Adobe Stock.*)

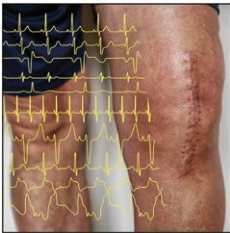
**Take home message:** Off-label use of gabapentin for females with chronic pelvic pain and no evidence of pelvic pathology was ineffective in reducing average or worst pain scores and was associated with a higher incidence of adverse effects.



### Delivering transformative action in paediatric pain: A Lancet Child & Adolescent Health Commission. *Lancet Child Adolesc Health* 2021; 5:47–87. PMID: 33064998.

Appropriate management of pediatric pain remains a challenge. The Lancet Child and Adolescent Health Commission puts into perspective four transformative goals which, if implemented, will improve the lives of children and adolescents with pain and their families over the next decade. First, the Commission outlines a strategy to make children's pain matter to others. They advocate for the importance of understanding the social science of pain and discuss how the absence of voice can lead to an assumption that there is an absence of need. Second, they argue that development of safe and effective treatments will only emerge if they are informed by an in-depth understanding of the developmental aspects of nociception and pain systems. Third, they recommend that pain can and should be assessed, no matter the age or clinical status of the child. Finally, they emphasize that every child should have access to evidence-based pain assessment and subsequent treatment using the most effective methods and means available. A detailed list of priorities for research, clinical practice, and political actions are articulated around these four transformative goals. The ensemble of these goals should be conducted in parallel to achieve a meaningful change in pediatric pain management. (Article Selection: Laszlo Vutskits, M.D. Image: Adobe Stock.)

**Take home message:** A multidisciplinary Commission of Pediatric Pain experts has published in review article format a multipronged approach to improving detection and treatment of pain in infants, children, and adolescents.

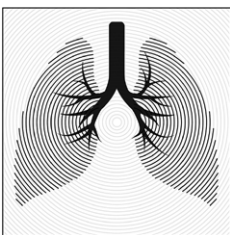


### Frequency and outcomes of preoperative stress testing in total hip and knee arthroplasty from 2004 to 2017. *JAMA Cardiol* 2020 Sep 30 [Epub ahead of print]. PMID: 32997100.

While the American College of Cardiology and the American Heart Association advocate for evidence-based preoperative cardiac assessments based on patient functional status, risk factors, and the urgency and nature of surgery, temporal trends and outcomes of preoperative testing in specific noncardiac surgery populations have not been rigorously described. This retrospective, cross-sectional study included 801,396 elective total hip (27.9%) and total knee arthroplasty (72.1%) patient records (2003 to 2017), from the IBM MarketScan Commercial and Medicare Supplemental Databases (median age

62 yr, 58.1% female). The study aimed to describe temporal trends in preoperative cardiac stress testing within 60 days before surgery, characteristics associated with testing, and cardiac events during the total joint arthroplasty hospitalization. Over the study period, the rate of preoperative cardiac stress testing was 10%, with a decline in testing from 2006 through 2017 at an annual rate ranging from  $-0.71\%$  to  $-0.40\%$ . Patient factors associated with preoperative cardiac stress testing included age, male sex, and at least one Revised Cardiac Risk Index condition. The overall rate of myocardial infarction or cardiac arrest was 0.24%, which was not associated with patient risk factors or preoperative testing. (Article Selection: Meghan Prin, M.D., M.S. Image: M. Lane-Fall/Adobe Stock.)

**Take home message:** In a retrospective cohort analysis using national administrative databases, preoperative stress testing decreased from 2006 to 2017 while the rate of coded cardiac complications was unchanged between those tested or not.



### Lung ultrasound and pulmonary congestion during stress echocardiography. *JACC Cardiovasc Imaging* 2020; 13:2085–95. PMID: 32682714.

The "B-profile" detected by lung ultrasound is considered a sign of pulmonary congestion. To assess the significance of this pattern during stress echocardiography, the authors prospectively performed transthoracic echocardiography and lung ultrasound (before, at, or immediately after peak stress) in 2,145 patients undergoing this procedure at 11 centers. B-lines were scored 0 to 10 in each of four locations. New regional wall motion abnormalities, reduced left ventricular contractile reserve, abnormal coronary flow velocity reserve, and abnormal heart rate reserve were also assessed. Subjects were grouped by absence of stress B-lines (score: 0 to 1, 64.7%), mild B-lines (score: 2 to 4, 20%), moderate B-lines (score: 5

to 9, 9.7%) and severe B-lines (score: great than 10, 5.4%). During a median follow-up of 15.2 months, 38 deaths and 28 nonfatal myocardial infarctions occurred in 64 patients. Independent predictors of death and nonfatal myocardial infarction included severe B-lines (hazard ratio 3.54 [95% CI, 1.47 to 8.69],  $P = 0.006$ ), abnormal heart rate reserve (hazard ratio 2.28 [95% CI, 1.22 to 4.26],  $P = 0.010$ ), abnormal coronary flow velocity reserve (hazard ratio 2.18 [95% CI, 1.06 to 4.48],  $P = 0.034$ ), and age (hazard ratio 1.03 [95% CI, 1.00 to 1.06],  $P = 0.037$ ). (Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)

**Take home message:** Severe B-lines on lung ultrasound during peak stress predict death and nonfatal myocardial infarction and may assist in risk stratification.



### Multiplexed plasma immune mediator signatures can differentiate sepsis from noninfective SIRS: American Surgical Association 2020 annual meeting paper. *Ann Surg* 2020; 272:604–10. PMID: 32932316.

The systemic inflammatory response syndrome (SIRS) is commonly triggered by sepsis, but it can also be triggered in the absence of sepsis leading to inappropriate antibiotic usage. Cytokine inflammatory responses can be initiated by microbial “pathogen-associated molecular patterns,” and/or from injured tissue displaying “damage-associated molecular patterns.” The authors used a multiplexed assay of 31 different cytokines from plasma of patients with: sepsis of varying severity ( $n = 29$ ); trauma-induced SIRS ( $n = 11$ ); and healthy controls ( $n = 11$ ) incorporating decision trees and machine learning

statistical techniques to identify significant intergroup differences. Septic patients had high concentrations of interleukin-6, interleukin-1 $\alpha$ , and triggering receptor expressed on myeloid cells-1 (TREM-1). In contrast, sterile injury was associated with widespread mediator suppression. Application of a two-group multivariate random-forest model (evaluating combinations of cytokines) correctly classified 11 of 11 injury patients and 28 of 29 infection patients. (Article Selection: Jamie Sleigh, M.D. Image: M. Lane-Fall/Adobe Stock.)

**Take home message:** Machine learning based on multiplexed plasma cytokine assays may eventually allow distinction between sepsis-related and injury-related SIRS with the potential to reduce inappropriate antibiotic usage.

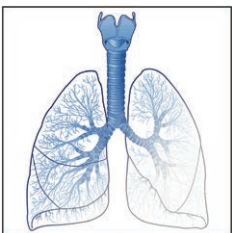


### Part 1: Executive summary: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2020; 142:S337–S357. PMID: 33081530.

The American Heart Association has updated the 2015 recommendations for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care. A series of publications presents reports from writing groups evaluating literature on basic and advanced life support for adults, pediatric patients, and neonates as well as resuscitation education science and systems of care. New clinical recommendations, updated algorithms, and areas of focus for adult resuscitation include CPR during transport, CPR before calling for help, feedback for CPR quality, analysis of rhythm during chest compressions,

vasopressor use during cardiac arrest, modes of defibrillation, point of care echocardiography during CPR, targeted temperature management, and resuscitation for opioid-associated emergencies. Pediatric care topics include initial and interval doses of epinephrine for cardiac arrest, ventilation rate during CPR, and traumatic shock management. Neonatal topics include epinephrine for resuscitation, oxygen concentration for preterm infants at birth, and tracheal intubation and suction of nonvigorous newborns with meconium staining. Recommendations for first aid include control of life-threatening external bleeding, stroke recognition, cooling for heatstroke and dental avulsion. In total, the 2020 American Heart Association Guidelines include 491 recommendations of which 51% are based on limited evidence and 17% on expert opinion and thus persistent knowledge gaps that require additional research are also emphasized. (Article Selection: BobbieJean Sweitzer, M.D., F.A.C.P. Image: M. Lane-Fall/Adobe Stock.)

**Take home message:** New and updated recommendations for resuscitation and cardiovascular care based on recommendations of individual American Heart Association writing groups have been published as summarized in this executive summary.



### Small airway loss in the physiologically ageing lung: A cross-sectional study in unused donor lungs. *Lancet Respir Med* 2020 Oct 5 [Epub ahead of print]. PMID: 33031747.

The decline in lung function due to aging has been attributed to mechanisms including loss of alveolar tissue, increased chest wall rigidity, reduced elastic lung recoil, and lower dynamic lung volumes. However, data regarding the effect of aging on airways of small diameter (less than 2.0 mm) remain scarce. In this cross-sectional study, lungs retrieved from donors were analyzed using *ex vivo* computed tomography and whole-lung high-resolution computed tomography (micro-computed tomography). The aim was to determine total airway numbers stratified by airway diameter. Micro-computed tomog-

raphy in particular allowed for the measurement of number, length, and diameter of terminal bronchioles. Lungs from 32 nonsmoking donors (aged 16 to 83 yr) were included in the study. Between 30 and 80 yr, an age-dependent reduction in number of small airways with a diameter of 2 to 2.5 mm and with a diameter of less than 2 mm was found, with a  $\beta$  coefficient per decade of  $-0.119$  (95% CI,  $-0.193$  to  $-0.045$ ;  $R^2 = 0.29$ ) and of  $-0.158$  ( $-0.233$  to  $-0.084$ ;  $R^2 = 0.47$ ), respectively. No age-dependent reduction in number of airways greater than 2.5 mm in diameter was shown. The micro-computed tomography analysis demonstrated that after 30 yr of age, the number of terminal bronchioles steadily decreased ( $\beta$  coefficient per decade  $-2035$ ; 95% CI,  $-2818$  to  $-1252$ ;  $R^2 = 0.55$ ). (Article Selection: Beatrice Beck-Schimmer, M.D. Image: M. Lane-Fall/Adobe Stock.)

**Take home message:** This study reveals an important component of physiological lung aging by showing an age-dependent reduction in number of small airways and terminal bronchioles.