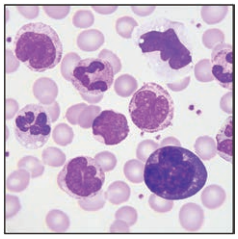
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists



DNA binding to TLR9 expressed by red blood cells promotes innate immune activation and anemia. Sci Transl Med 2021; 13:eabj1008. PMID: 34669439.

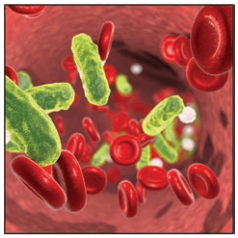
Erythrocytes are essential for oxygen delivery, but also have nongas exchanging immune functions. It was recently discovered that erythrocytes express toll-like receptor 9 (TLR9), which scavenges cell-free CpG-containing DNA (derived from bacteria or host mitochondria). However, how erythrocyte-dependent DNA binding contributes to inflammation during infections remains unclear. TLR9 expression was found to be increased on the surface of erythrocytes in murine models of sepsis and in critically ill patients with sepsis, and to facilitate sequestration of CpG-containing DNA. TLR9-mediated DNA binding altered the morphology of erythrocytes due to changes in the cytoskeletal proteins spectrin and actin. Subsequent loss of the antiphagocytotic epitope of the CD47 protein, also expressed on the surface of erythrocytes, leads to accelerated phagocytosis of erythrocytes in the spleen accompanied by activation of macrophages with increased production of the proinflammatory cytokines interferon-γ and interleukin-6. Using an erythrocyte-specific TLR9 knockout mouse model, it was possible to show that both phagocytosis of CpG-tagged erythrocytes as well as CpG-induced inflammation were directly dependent on TLR9 expression. Erythrocyte-bound DNA was found to be higher in critically ill sepsis patients with anemia (less than or equal to 7 g/dl) as well as severely diseased (Apache score III) anemic (less than or equal to 9.6 g/dl) COVID-19 patients. *(Article Selection: Michael Zaugg, M.D. Image: Getty Images.)*

Take home message: Erythrocytes function as immune sensors and alert the immune system to the presence of pathogens and tissue damage. This pathogen-sensing role comes at a cost, namely inflammation-induced anemia.

Association of tramadol vs codeine prescription dispensation with mortality and other adverse clinical outcomes. JAMA 2021; 326:1504–15. PMID: 34665205.

With the growing appreciation of the risks in using strong opioids for chronic noncancer pain, so-called "weak opioids" including tramadol, are becoming more popular. However, there is limited safety information for tramadol in this population. This retrospective propensity score–matched cohort study included nearly 370,000 patients newly prescribed either tramadol or codeine in Spain. The principal causes of chronic pain in this population were back pain, neck or shoulder pain, and osteoarthritis. Within the first year of use, tramadol was associated with a higher incidence of all-cause mortality (13.00 *vs.* 5.61 per 1,000 person-years; hazard ratio, 2.31; 95% CI, 2.08 to 2.56), cardiovascular events (10.03 *vs.* 8.67 per 1,000 person-years; hazard ratio, 1.15; 95% CI, 1.05 to 1.27), and fractures (12.26 *vs.* 8.13 per 1,000 person-years; hazard ratio, 1.50; 95% CI, 1.37 to 1.65) relative to codeine. The risk of falls, opioid abuse, sleep disorders, and other adverse events were similar. Subgroup analysis showed that all-cause mortality was highest among younger patients and cardiovascular risk higher in women. *(Article Selection: J. David Clark, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: These data suggest that tramadol use has an adverse event profile that should be considered when selecting a pharmacologic treatment for common chronic pain conditions.



Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med 2021; 49:e1063–143. PMID: 34605781.

The International Guidelines for the Management of Sepsis and Septic Shock are widely used since 2008 to guide sepsis treatment. The document updates its most recent iteration (2017). Clinical questions were structured in the Population, Intervention, Control, and Outcomes format and evaluated using the GRADE approach with the quality of evidence scored as high, moderate, low, or very low. Best practice statements are ungraded strong recommendations. A total of 93 recommendations are reported, addressing screening and initial resuscitation, infection, hemodynamics, ventilation, additional therapies, and goals of care and long-term outcomes. The majority of recommendations are based on weak evidence (58%). Selected highlights include downgrading the recommendation for 30 ml/kg IV crystalloid for initial resuscitation in patients with hypoperfusion or septic shock from a strong to a weak recommendation based on low quality of evidence. Also, recommending against use of quick sequential organ failure assessment as a sole screening tool. Antibiotic recommendations include delivering antimicrobials within 1 h of sepsis recognition with stratification of timing based on the likelihood of sepsis and presence of shock. For patients with possible sepsis without shock, rapid assessment of the likelihood of infection should be performed. Antimicrobials should be administered within 3 h from when sepsis was first recognized if suspicion persists. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: The Surviving Sepsis Campaign has updated its influential 2017 guidelines for sepsis management.

Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: An individual participant-level data meta-analysis. Lancet 2021; 18:1053–64. PMID: 34461040.

The effects of antihypertensive treatment on cardiovascular outcomes in individuals 70 yr old and older, remain debated. This meta-analysis used individual participant-level data from randomized controlled trials of antihypertensive therapy with at least 1,000 persons-years of follow-up in each treatment group (seven prespecified subgroups of increasing systolic blood pressure) using data from the Blood Pressure Lowering Treatment Trialists' Collaboration. Data from 358,707 participants included in 51 randomized trials were included. The hazard ratios for the risk of major cardiovascular events per 5 mmHg reduction in systolic blood pressure for each age group were 0.82 (95% CI, 0.76 to 0.88) in individuals younger than 55 yr old, 0.91 (95% CI, 0.88 to 0.95) in those ages 55 to 64 yr old, 0.91 (95% CI, 0.88 to 0.95) in those ages 65 to 74 yr old, 0.91 (95% CI, 0.87 to 0.96) in those ages 75 to 84 yr old, and 0.99 (95% CI, 0.87 to 1.12) in those 85 yr old and older. There was no evidence of a heterogeneous treatment effect by categories of systolic blood pressure on the risk of major cardiovascular events in any of the age groups (all adjusted *P* interaction greater than 0.07). Similar patterns of proportional risk reductions were observed for a 3 mmHg reduction in diastolic blood pressure. *(Article Selection: David Faraoni, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: Treating hypertension in the elderly appears to incur a similar treatment benefit regardless of starting systolic blood pressure or age strata.

Slowed canonical progress in large fields of science. Proc Natl Acad Sci USA 2021; 118:e2021636118. PMID: 34607941.

There is a relentless increase in the number of research papers published per year, and publication metrics drive research funding and science careers. It might be expected that increased numbers of publications in a scientific field would advance innovative knowledge more quickly. However, there is an argument that the cognitive overload induced by excessive numbers of new papers may obscure the recognition, integration, and development of new ideas. Also, the intense competition has the effect of narrowing the citations preferentially to only a few well-cited papers. The "rich get richer," but knowledge stagnates. Thus, new papers lose the ability to disrupt existing concepts and modes of thought and counterintuitively, scientific progress may slow. Analysis from the Web of Science dataset between 1960 and 2014 showed that the Gini coefficient of inequality increased (a Gini coefficient ~0.5 implies 17% of citations came from the top 1% papers); the citation decay rate decreased; and the disruptive impact decreased in proportion to the logarithm of the annual number of published papers. *(Article Selection: Jamie Sleigh, M.D. Image: Adobe Stock.)*

Take home message: To prevent "ossification" of scientific knowledge, structures are needed that actively recognize and promulgate new and disruptive ideas.

Incidence of infertility and pregnancy complications in US female surgeons. JAMA Surg 2021; 156:905–15. PMID: 34319353.

Surgeons and other physicians often delay childbearing to establish their careers. There are occupational hazards in a surgical career (*e.g.*, long work hours, prolonged standing), but the effect on fertility has not been described in detail. A self-administered survey was developed and electronically disseminated from November 2020 to February 2021 assessing the incidence of pregnancy loss, use of assisted reproductive technology, and pregnancy-related complications among female surgeons compared to nonsurgeon female partners of male surgeons in the United States. The survey was returned by 1,175 surgeons and 850 were analyzed (692 women, median age 40 yr). Almost half (42%) of female surgeons reported a pregnancy loss, more than twice the rate of the general population. Compared to controls, female surgeons were older at first birth (33 *vs.* 31 yr, $P < 0.001$), more likely to work more than 60 h a week (57% *vs.* 10%, $P < 0.001$), and more likely to have pregnancy complications (48% *vs.* 27%, $P < 0.001$), musculoskeletal disorders (37% *vs.* 18%, $P < 0.001$), nonelective cesarean delivery (26% *vs.* 15%, $P = 0.01$), and postpartum depression (11% *vs.* 6%, $P = 0.04$). *(Article Selection: Meghan Prin, M.D. Image: J. P. Rathmell.)*

Take home message: Female surgeons report a significantly higher risk of infertility and pregnancy-associated complications than nonsurgeon female partners of male surgeons. As the proportion of women in surgery increases, a change in surgical culture to support pregnancy will be paramount to reduce these risks.

 DOI: 10.1097/ALN.0000000000004125

Experiences of LGBTQ+ residents in US general surgery training programs. JAMA Surg 2021 Oct 20 [Epub ahead print]. PMID: 34668969.

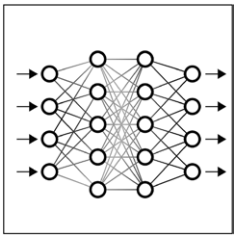
Lesbian, gay, bisexual, transgender, queer, and other gender minority (LGBTQ+) residents represent a high-risk group for mistreatment. This study investigated the experience of LGBTQ+ general surgery residents using a voluntary anonymous survey administered to all general surgery residents training following the 2019 American Board of Surgery In-Training Examination. Self-reported mistreatment, sources of mistreatment, perceptions of learning environment, career satisfaction, burnout, thoughts of attrition, and suicidality were queried. Associations were examined using multivariable regression models, accounting for interactions between gender and LGBTQ+ identity. A total of 6,956 residents completed the survey (86% response). Of those, 305 respondents (5%) identified as LGBTQ+ and 6,076 (95%) as non-LGBTQ+. Discrimination, sexual harassment, and bullying were significantly more common in LGBTQ+ respondents (59% *vs.* 42%, $P < 0.001$; 48% *vs.* 29%, $P < 0.001$; 75% *vs.* 67%, $P = 0.005$, respectively); attending surgeons were the most common source in both men and women. LGBTQ+ residents had more frequent considerations of leaving their program (odds ratio, 2.04; 95% CI, 1.52 to 2.74) and suicide (odds ratio, 1.95; 95% CI, 1.26 to 3.04). The latter perception was eliminated after adjusting for mistreatment (odds ratio, 1.47; 95% CI, 0.90 to 2.39). *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: Mistreatment most commonly due to attending surgeons is a common experience for LGBTQ+ surgery residents, leading to significant adverse personal ramifications.

Reducing surgical site infections in low-income and middle-income countries (FALCON): A pragmatic, multicentre, stratified, randomised controlled trial. Lancet 2021; 398:1687–99. PMID: 34710362.

Surgical site infection is the most common postoperative complication. Guidelines recommend costly alcoholic chlorhexidine skin preparation and fascial closure using triclosan-coated sutures. The study evaluated these interventions in low-income and middle-income countries (54 hospitals in seven countries) in a 2×2 factorial, randomized controlled trial stratified by infection risk (clean-contaminated *vs.* contaminated or dirty) for abdominal surgery (N = 5,788). Intervention groups were (1) chlorhexidine and noncoated suture, (2) chlorhexidine and triclosan-coated suture, (3) povidone-iodine and noncoated suture, or (4) povidone-iodine and triclosan-coated suture. The primary outcome was surgical site infection. The overall surgical site infection rate was 22% (clean-contaminated stratum 16%, contaminated or dirty stratum 30%). For both strata, there was no evidence of a difference in the risk of surgical site infection with chlorhexidine *versus* povidone-iodine (clean-contaminated stratum 15% *vs.* 16%, relative risk 0.97 [95% CI, 0.82 to 1.14]; contaminated or dirty stratum 28% *vs.* 32%, relative risk 0.91 [95% CI, 0.81 to 1.02]), or with triclosan-coated sutures *versus* noncoated sutures (clean-contaminated stratum 15% *vs.* 16%, relative risk 0.90 [95% CI, 0.77 to 1.06]; contaminated or dirty stratum 29% *vs.* 31%, relative risk 0.98 [95% CI, 0.87 to 1.10]). With both strata combined, there were no differences using chlorhexidine or triclosan-coated sutures. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

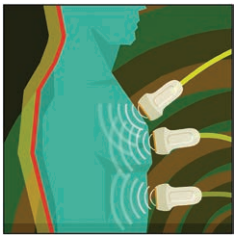
Take home message: Neither 2% alcoholic chlorhexidine skin preparation nor triclosan-coated sutures were superior to lower-cost povidone or noncoated suture in preventing surgical site infection in clean-contaminated or contaminated or dirty surgical wounds in low- or middle-income countries in patients undergoing abdominal surgery.



Performance metrics for the comparative analysis of clinical risk prediction models employing machine learning. Circ Cardiovasc Qual Outcomes 2021; 14:e007526. PMID: 34601947.

Machine learning is increasingly used for analysis of large datasets and development of risk predictions models, but commonly reported metrics may not be sufficient to capture the advantages of this approach. Two models predicting the risk of acute kidney injury after percutaneous coronary intervention were compared in this study. Model 1 used 13 variables and logistic regression with no interaction terms, whereas model 2 is a published model using the same 13 variables employing gradient descent boosting (a machine learning technique). The models were developed using data from the National Cardiovascular Data Registry CathPCI Registry, including percutaneous coronary intervention (PCIs) between 2011 and 2017. The major finding was that the C-statistic (AUC-ROC) and calibration slope, the most published metrics for discrimination and calibration, do not have sufficient sensitivity for capturing the advantage of machine learning models. Additional metrics, including the components of the Brier score (loss or mean-squared-error of the predictions) and visualization of the reclassification accuracy, need to be considered when comparing models. *(Article Selection: David Faraoni, M.D., Ph.D. Image: Adobe Stock.)*

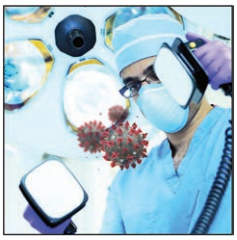
Take home message: Commonly reported metrics, such as C-statistics and calibration slope, may not have sufficient sensitivity to identify improvement of machine learning models. Additional metrics, summarized in this study, may be required.



Procalcitonin and lung ultrasonography point-of-care testing to determine antibiotic prescription in patients with lower respiratory tract infection in primary care: Pragmatic cluster randomised trial. BMJ 2021; 374:n2132. PMID: 34548312.

Lung ultrasound and procalcitonin testing are widely used in critical care medicine to assess need for antibiotic therapy in suspected pulmonary infection. Their effectiveness in ambulatory practice is unclear. Ambulatory patients with symptoms of lower respiratory infection consulting a general practitioner were included in a pragmatic cluster randomized trial to assess whether point-of-care procalcitonin and lung ultrasonography can safely reduce unnecessary antibiotic use. General practitioners from 60 Swiss practices screened 469 patients (median age 53 yr, 59% female) with symptoms. Practitioners were randomized to use point-of-care procalcitonin-guided antibiotic therapy (greater than or equal to 0.25 mcg/l; n = 195 patients, 6% with elevation), point-of-care procalcitonin guided with lung ultrasonography (n = 152 patients, 10% with elevation), or usual care (no testing/ultrasound; n = 122 patients). The primary outcome was the proportion of patients in each group prescribed an antibiotic by day 28. The procalcitonin group had a lower probability of antibiotic prescription by day 28 compared to the usual care group (odds ratio 0.40 *vs.* 0.70, cluster corrected difference –0.26 [95% CI, –0.41 to –0.10]). There was no significant difference between the ultrasound/procalcitonin and procalcitonin groups (0.41 *vs.* 0.40, –0.03 [–0.17 to 0.12]). *(Article Selection: BobbieJean Sweitzer, M.D. Image: A. Johnson, Vivo Visuals Studio.)*

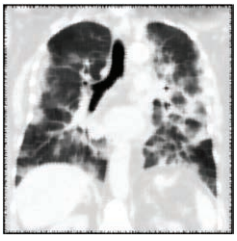
Take home message: Point-of-care procalcitonin testing led to a 26% lower probability of antibiotic prescriptions without affecting patients' safety compared to usual care. Additional use of lung ultrasound did not further lower antibiotic prescriptions.



2021 interim guidance to health care providers for basic and advanced cardiac life support in adults, children, and neonates with suspected or confirmed COVID-19. Circ Cardiovasc Qual Outcomes 2021; 14:e008396. PMID: 34641719.

In April 2020, the American Heart Association (AHA) published their first Interim Guidance for Basic and Advanced Cardiac Life Support in Adults, Children, and Neonates with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in response to the SARS-CoV-2 pandemic. In October 2020, new overall cardiopulmonary resuscitation (CPR) guidelines with the latest evidence-based algorithms and recommendations were published. This updated 2021 interim guidance aligns with these two guidelines and provides updated information on controversial topics regarding the need for appropriate PPE and aerosol control for suspected and confirmed COVID-19 patients in settings where vaccinations have been readily adopted. The emphasize that provision of timely chest compressions is of paramount importance and should not be delayed while personal protective equipment are donned given evidence suggesting that chest compressions are not aerosol generating. They update and reiterate recommendations for use of HEPA or high-efficiency viral filters on all airway and ventilation devices used and provide detailed instruction for use of ventilators. Also highlighted are use of mechanical compression devices, lack of utility of intubation boxes, and details of management for prone CPR. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell/Adobe Stock.)*

Take home message: Updated recommendations for the management of cardiopulmonary arrest in adults, children, and neonates with suspected or confirmed COVID-19 have been published by the AHA.



Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: Results from three observational cohorts. Lancet Respir Med 2021; 9:1377–86. PMID: 34653374.

Numerous publications speculate on subphenotypes of COVID-19-related acute respiratory distress syndrome (ARDS), but adequately power observational data are missing. This multicenter, prospective observational cohort study (PRoVENT-COVID) of 22 Dutch intensive care units included mechanically ventilated patients with COVID-19 admitted between March and May 2020 (derivation cohort, 1,007 patients). Two U.S. centers provided replication cohorts (288 and 326 patients). Two subphenotypes were identified in a longitudinal latent class analysis. Subphenotype 1 presented with lower mechanical power, minute ventilation, and ventilatory ratio within the first 4 days of invasive mechanical ventilation, while Pao_2/Fio_2, pH, and compliance of the respiratory system were similar. Mortality at day 28 was not different between the two subphenotypes (subphenotype 1: 185 [28%] of 671 patients; subphenotype 2: 109 [32%] of 336 patients, $P = 0.10$), while subphenotype 1 had higher ventilator-free days at day 28 (median 5, interquartile range 0 to 17 *vs.* 0, 0 to 15, $P = 0.016$). Ventilatory ratio or mechanical power over the first 4 days of invasive mechanical ventilation were coded as stable (trajectory A) or upwards (trajectory B). Upward trajectories were prognostic factors for 28-day mortality (ventilatory ratio: odds ratio 1.64; 95% CI, 1.17 to 2.29; mechanical power: odds ratio 1.82; 95% CI, 1.24 to 2.66). Results of upward ventilatory ratio trajectories were confirmed in the replication cohorts. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

Take home message: From a relatively homogeneous presentation, diverging trajectories of ventilatory ratio and mechanical power provide the optimal prognostic ability for determination of duration of ventilation and mortality in patients with COVID-19 ARDS.

DOI: 10.1097/ALN.0000000000004125