SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists

A molecular single-cell lung atlas of lethal COVID-19. Nature 2021; 595:114–9. PMID: 33915568.

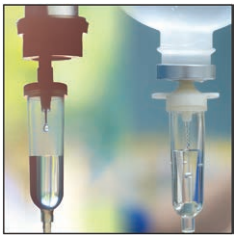
Single-nucleus RNA sequencing was performed in more than 116,000 cellular nuclei isolated during rapid autopsies from the lungs of 19 fatal cases of COVID-19 and 7 control lungs after surgical resection, to develop a lung atlas comparing alterations in cellular composition, transcriptional cell states, and cell-to-cell interactions. The goal of this cellular and signaling atlas is to inform an understanding of long-term pulmonary complications of COVID-19 and identify novel therapeutic targets. The primary findings included abnormally activated, IL-1ß-producing monocytes/macrophages, impairment of alveolar epithelial regeneration, and expansion of a pathological form of fibroblasts that facilitate fibrosis. Monoctye-derived macrophages showed genetic changes associated with impaired T-cell immunity. Impaired alveolar epithelial regeneration was indicated by the failure of alveolar type II cells to transition to alveolar type I cells. COVID-19 lungs had greater subsets of pathological fibroblasts, known drivers of lung fibrosis in idiopathic pulmonary fibrosis and scleroderma. Inferred protein activity from single-nucleus transcriptomes predicted enhanced MMP14 and STAT3 signaling as druggable targets to attenuate fibrosis. Additionally, despite an apparent adequate humoral immune response indicated by the generation of neutralizing antibodies against the receptor-binding domain of the SARS-CoV-2 spike protein, there were inadequate T-cell responses in the lungs of COVID-19 patients. *(Article Selection: Charles Emala, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: This is an atlas of the lung cells and signaling pathways associated with COVID-19 fatalities based on RNA sequencing from more than 116,000 lung cellular nuclei from 19 patients. This may inform an understanding of the long-term outcomes of lung injury in surviving COVID-19 patients and identify novel therapeutic targets.

Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: The BaSICS randomized clinical trial. JAMA 2021 Aug 10 [Epub ahead of print]. PMID: 34375394.

The differential effects of a balanced (Plasma-Lyte 148) *versus* 0.9% sodium chloride solution on 90-day survival and acute kidney injury in critically ill patients remain controversial. This double-blind, factorial (fluid type, infusion speed), randomized clinical trial from 75 intensive care units (ICUs) in Brazil included patients with at least one risk factor for adverse outcomes requiring at least one episode of fluid expansion with an anticipated ICU admission of more than 24 h. Patients were randomized to either fluid throughout their ICU admission between May 2017 and March 2020. The primary outcome was 90-day survival. A total of 11,052 patients were randomized and 10,520 (95%) were analyzed (mean age, 61 ± 17 yr; 44% women). There was no significant interaction between the two interventions (fluid type and infusion speed; $P = 0.98$). Planned surgical admissions accounted for 48% of all patients; 61% had hypotension or vasopressor use and 44% were receiving mechanical ventilation at enrollment. Patients received a median of 1.5 l of fluid the first day after enrollment. By day 90, mortality occurred in 26% of the balanced solution group *versus* 27% in the saline group (adjusted hazard ratio, 0.97; 95% CI, 0.90 to 1.05; $P = 0.47$). There were no treatment-related severe adverse events in either group. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

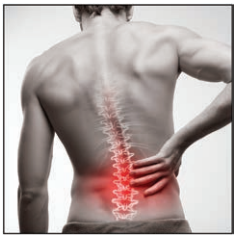
Take home message: In a large multicenter trial comparing a balanced solution to 0.9% saline, there was no difference in 90-day post-ICU admission survival in critically ill patients requiring fluid challenges.



Effect of slower vs faster intravenous fluid bolus rates on mortality in critically ill patients: The BaSICS randomized clinical trial. JAMA 2021; 326:830–8. PMID: 34547081.

The effects of rapidity of infusion during fluid challenges in critically ill patients is uncertain. This double-blind, factorial (fluid type, infusion speed), randomized clinical trial from 75 intensive care units (ICUs) in Brazil included patients with at least one risk factor for adverse outcomes requiring at least one episode of fluid expansion with an anticipated ICU admission of more than 24 h were randomized to either a slower rate (333 ml/h) or control group (999 ml/h) during ICU admission between May 2017 and March 2020. The primary outcome was 90-day survival. A total of 11,052 patients were randomized and 10,520 (95%) were analyzed (mean age, 61 ± 17 yr; 44% women). Patients assigned to the slower rate received a mean of 1,162 ml on the first day *versus* 1,252 ml for the control group. By day 90, mortality was 26.6% in the slower rate group *versus* 27.0% in the control group (adjusted hazard ratio, 1.03; 95% CI, 0.96 to 1.11; $P = 0.46$). *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In a large, randomized trial of critically ill patients requiring fluid challenges, infusing either saline or a balanced salt solution at a slower *versus* faster rate did not reduce 90-day mortality.



Decompression with or without fusion in degenerative lumbar spondylolisthesis. N Engl J Med 2021; 385:526–38. PMID: 34347953.

In patients with lumbar spinal stenosis and degenerative spondylolisthesis, the need for decompression with instrumented fusion *versus* decompression surgery alone is uncertain. This open-label, multicenter, noninferiority trial randomized patients with symptomatic lumbar stenosis with single-level spondylolisthesis of 3 mm or more to either decompression alone or decompression with instrumented fusion. The primary outcome was a reduction of at least 30% in the score on the Oswestry Disability Index (range, 0 to 100; higher scores indicating more impairment) over the 2 yr after surgery. A noninferiority margin of −15 percentage points was used. A total of 267 patients were randomized. The mean change from baseline to 2 yr in the Oswestry Disability Index score was −21 in the decompression-alone group and −21 in the fusion group (mean difference, 0.7; 95% CI, −2.8 to 4.3). In an intent-to-treat analysis, 71% in the decompression-alone group and 73% in the fusion group had a reduction of at least 30% in the Oswestry Disability Index score (difference, −1.4 percentage points; 95% CI, −12.2 to 9.4), establishing noninferiority of decompression alone. Similar noninferior results were noted in a per-protocol analysis. Reoperation occurred in 12% in the decompression-alone group *versus* 9% in the fusion group (difference, 3.4 percentage points; 95% CI, −4.6 to 11.5). *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: In subjects with degenerative lumbar spondylolisthesis, decompression alone was noninferior to decompression with instrumented fusion over a period of 2 yr.

Gender disparity in citations in high-impact journal articles. JAMA Netw Open 2021; 4:e2114509. PMID: 34213560.

The impact of author sex on subsequent literature citations of research or commentary articles published in high-impact medical journals has not been systematically evaluated. This cross-sectional study included all original research and commentary articles from five high-impact medical journals (*Annals of Internal Medicine*, *British Medical Journal*, *JAMA*, *JAMA Internal Medicine*, and *The New England Journal of Medicine*) from 2015 to 2018 recording the sex of the primary and senior authors of each article and the number of literature citations using the Web of Science. The latter, stratified by primary and senior author sex, were compared. Of the 5,554 articles analyzed, 36% had women primary authors and 26% senior authors. A statistically significantly lower median (interquartile range) number of citations was noted by sex (primary author women 36 [17 to 82] citations *vs.* men 54 [22 to 141] citations; senior author women 37 [17 to 93] citations *vs.* men 51 [20 to 128] citations; $P < 0.001$). In addition, citations were lower for articles with both women primary and senior authors *versus* men (33 [15 to 68] citations *vs.* 59 [23 to 149] citations; $P < .001$). Differences did not change over time and were less pronounced among commentary articles. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Original research articles in the highest-impact medical journals written by women were cited significantly less frequently than those written by men, particularly when both primary and senior authors were women.

Milrinone as compared with dobutamine in the treatment of cardiogenic shock. N Engl J Med 2021; 385:516–25. PMID: 34347952.

The optimal drug for inotropic support in cardiogenic shock remains controversial. This pragmatic randomized double-blind trial compared milrinone to dobutamine in 192 subjects admitted to a cardiac intensive care unit at a quaternary Canadian center diagnosed with cardiogenic shock (Society for Cardiovascular Angiography and Interventions definition: stages B to E). A standardized dosing protocol (five steps) was used; adjustment was left to clinical judgement of the treating physician. The primary composite outcome included in-hospital all-cause mortality, cardiac arrest, cardiac transplant; or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack, or stroke; or renal replacement therapy. Secondary outcomes included the primary individual components. Treatment groups were well matched (ages 69 *vs.* 72; female 38% *vs.* 35%; ischemic cardiomyopathy 69% *vs.* 65%, milrinone *vs.* dobutamine, respectively). A total of 192 participants (96 in each group) were analyzed. Pulmonary artery catheters were used in only 23 subjects. Comparing milrinone to dobutamine, no significant difference was noted in the primary outcome: 49% *versus* 54% (relative risk, 0.90; 95% CI, 0.69 to 1.19; $P = 0.47$). No heterogeneity of treatment effect between prespecified subgroups was noted. No significant differences were noted for secondary outcomes. In-hospital mortality was similar (37% *vs.* 43%; relative risk, 0.85; 95% CI, 0.60 to 1.21). *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In a single-center pragmatic randomized study of patients with cardiogenic shock admitted to the cardiac intensive care unit, no significant differences between milrinone and dobutamine were noted in a primary composite outcome or individual component secondary outcomes.

Effect of a sedation and ventilator liberation protocol vs usual care on duration of invasive mechanical ventilation in pediatric intensive care units: A randomized clinical trial. JAMA 2021; 326:401–10. PMID: 34342620.

The optimal strategy for weaning infants and children from mechanical ventilation is uncertain. This pragmatic multicenter, stepped-wedge, cluster randomized clinical trial of 18 pediatric intensive care units in the United Kingdom (February 2018 to October 2019) sequentially randomized critically ill infants and children requiring mechanical ventilation to a protocol intervention (n = 4,688) *versus* usual care (n = 4,155). The intervention involved assessment of sedation level, daily screening for readiness to undertake a spontaneous breathing trial, a spontaneous breathing trial to test ventilator liberation potential, and daily rounds to review sedation and readiness screening and set patient-relevant targets. The primary outcome was the duration of invasive mechanical ventilation (initiation until successful extubation). The treatment effect was a hazard ratio adjusted for calendar time and hospital site. A total of 8,843 subjects (median age, 8 months [interquartile range, 1 to 46 months]; 42% female) completed the trial. Protocol intervention resulted in a significantly shorter median time to successful extubation (64.8 *vs.* 66.2 h, respectively; adjusted median difference, −6.1 h [interquartile range, −8.2 to −5.3 h]; adjusted hazard ratio, 1.11 [95% CI, 1.02 to 1.20]; $P = 0.02$). The incidence of serious adverse events was similar between groups. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In infants and children requiring prolonged mechanical ventilation, use of a standardized sedation and ventilator liberation protocol was associated with a statistically significant but marginally clinically important reduction in time to first successful extubation.

Frequency of preoperative advance care planning for older adults undergoing high-risk surgery: A secondary analysis of a randomized clinical trial. JAMA Surg 2021; 156:e211521. PMID: 33978693.

Preoperative advance care planning for patients undergoing major surgery is increasingly emphasized. However, the extent to which it occurs is unknown. This secondary analysis from a multisite randomized trial evaluated a question prompt list (11 questions) on preoperative communication for adults 60 yr or older with at least one comorbidity and an oncologic or vascular diagnosis at five U.S. academic medical centers. From an audio-recorded preoperative consultation, any statement regarding advance care planning from the surgeon, patient, or family member was noted. The medical record was examined for the presence of a preoperative written directive. Interviews with patients experiencing postoperative complications were conducted. In 213 patients (57% male; mean age, 72 yr), only 13 conversations of advance care planning were noted; 66% did not have a preoperative advance directive. No associations were noted between the presence of a directive and patient age, the number of comorbidities, or type of procedure (oncologic [32%] *vs.* vascular [42%]; $P = 0.22$). There was no difference in preoperative communication or documentation between patients mailed a question prompt list 35% *versus* usual care 33% ($P = 0.77$). In general, patients with complications did not think it was important to discuss their preferences with their surgeon preoperatively. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: In a clinical trial, preferences for postoperative life-sustaining treatments in high-risk older adults undergoing major surgery were infrequently explored, addressed, or documented preoperatively.

In anticipation of pain: Expectancy modulates corticospinal excitability, autonomic response, and pain perception. PAIN 2021; 162:2287–96. PMID: 34256382.

Pain is a complex phenomenon involving perceptual (intensity), autonomic, and motor components. The expectation of pain can amplify pain perception, although the impact of expectancy on autonomic and motor components is not well understood. The authors used a psychophysical testing paradigm in which high- or low-intensity painful thermal stimuli were paired with a simple visual cue to impart expectancy in 32 healthy subjects. Autonomic responses (skin conductance) and distal motor responses (electromyography) to transcranial magnetic stimulation of the cortex were recorded. The expectation of receiving a high-intensity stimulus led to higher ratings of pain intensity than when a high-intensity stimulus was not expected ($F [1, 31] = 16.88$; $P < 0.001$). Additional analysis showed that motor responses were suppressed, and autonomic responses enhanced by pain expectancy. Modeling the subject's responses revealed that pain perception mediated the effects of noxious stimulation on autonomic responses. Expecting a high level of pain alters the experienced pain intensity, autonomic changes, and motor responses that may include protective reflexes. *(Article Selection: J. David Clark, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Pain expectations should be addressed during therapy, particularly when patients' expectations cause them to avoid movement such as is critical to recovery from injuries and surgery.

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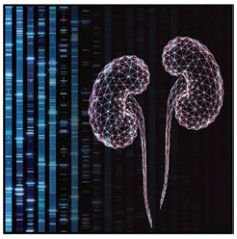
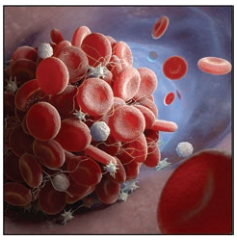


Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. Nature Commun 2021; 12:4350. PMID: 34272381.

Genome-wide association studies have suggested that estimated creatinine-based glomerular filtration rate, the most common measure of renal function, has a strong heritable component, although residual uncertainty is attributed to low-frequency variants. However, serum creatinine is a metabolite from muscle metabolism confounding its association with renal function. It is a challenge in genome-wide association studies to dissect mechanisms of biomarker metabolism from modulators of kidney function. Little data are available on alternative biomarkers (blood urea nitrogen, serum cystatin C). Fine-mapping of genome-wide association studies signals is used to narrow down to the few variants driving signals and will benefit most from increased sample size. Using databases of 1,201,909 patients (CKDGen Consortium and UK Biobank; 84% European ancestry), meta-analyses were done looking for gene loci that could be associated with variations in biomarkers and blood urea nitrogen. For the creatinine measure, 424 loci (201 novel) were identified ($P < 5\times10^{-8}$), which explained 9.8% of the glomerular filtration rate variance. Of these, 82% were validated by the other biomarkers. The median size of credible sets of variants (99% posterior probability of association) was 23 genes. *(Article Selection: Jamie Sleigh, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Using a greatly enhanced sample size relative to previous studies, 23 genes have been identified in a genome-wide association study that provide strong evidence for mechanistic insights and provide a starting point for biologic investigation.



Abelacimab for prevention of venous thromboembolism. N Engl J Med 2021; 385:609–17. PMID: 34297496.

Abelacimab is a human monoclonal antibody that binds to the catalytic domain of factor XI and locks it in its inactive conformation, preventing the activation of factor XII or thrombin. Abelacimab immediately lowers the concentration of functional factor XI in a dose-dependent manner. This phase 2 prospective randomized study compared the antithrombotic effect of three regimens of abelacimab (30, 75, and 150 mg) with a standard prophylactic dose of enoxaparin (40 mg) in patients undergoing unilateral total knee arthroplasty. The primary clinical endpoint was the incidence of deep vein thrombosis between 8 and 12 postoperative days. The principal safety endpoint was the incidence of clinically relevant bleeding from randomization through day 30. Venous thromboembolism occurred in 13 of 102 patients (13%) in the 30-mg abelacimab group, 5 of 99 patients (5%) in the 75-mg abelacimab group, and 4 of 98 patients (4%) in the 150-mg abelacimab group compared with 22 of 101 patients (22%) in the enoxaparin group. The 75-mg and 150-mg abelacimab regimens were superior to enoxaparin ($P < 0.001$). Bleeding occurred in 2%, 2%, and none of the patients in the 30-mg, 75-mg, and 150-mg abelacimab groups, respectively, *versus* none of the patients in the enoxaparin group. *(Article Selection: David Faraoni, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: Factor XI inhibition using abelacimab is an effective strategy to prevent postoperative venous thrombosis and is associated with a low risk of bleeding.

Does this adult patient have hypertension? The rational clinical examination systematic review. JAMA 2021; 326:339–47. PMID: 34313682.

This systematic review was conducted to summarize the literature on the accuracy of blood pressure measurement methods (office or home) compared with 24-h ambulatory measurement for diagnosing hypertension. The latter is the reference standard given substantial evidence demonstrating strong association with future cardiovascular events. A total of 12 cross-sectional studies (n = 6,877) comparing conventional office measurement to ambulatory measurement and six studies (n = 2,049) comparing home to ambulatory were included; two of these studies (n = 3,040) used consecutive samples. Random effects summary sensitivity, specificity, and likelihood ratios were calculated for blood pressure measurement methods for the diagnosis of hypertension. Conventional office oscillometric measurement (1 to 5 measurements in a single visit with blood pressure 140/90 mmHg) had a sensitivity of 51% (95% CI, 36 to 67%), specificity of 88% (95% CI, 80 to 96%), positive likelihood ratio of 4.2 (95% CI, 2.5 to 6.0), and negative likelihood ratio of 0.56 (95% CI, 0.42 to 0.69). Mean home blood pressure (with blood pressure 135/85 mmHg) had a sensitivity of 75% (95% CI, 65 to 86%), specificity of 76% (95% CI, 65 to 86%), positive likelihood ratio of 3.1 (95% CI, 2.2 to 4.0), and negative likelihood ratio of 0.33 (95% CI, 0.20 to 0.47). *(Article Selection: BobbieJean Sweitzer, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Conventional office blood pressure measurement is not reliable for diagnosing hypertension. Home measurement may be helpful, but when office and home are divergent, 24-h ambulatory measurement should be considered to establish the diagnosis.