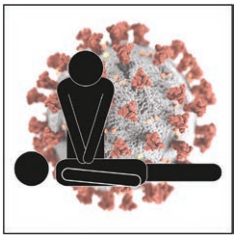
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Interim guidance for basic and advanced life support in adults, children, and neonates with suspected or confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With the Guidelines®-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in collaboration with the American Academy of Pediatrics, American Association for Respiratory Care, American College of Emergency Physicians, The Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists: Supporting organizations: American Association of Critical Care Nurses and National EMS Physicians. Circulation 2020; 141:e933–43. PMID: 32270695.

In response to the coronavirus disease 2019 (COVID-19) outbreak, the American Heart Association, in coordination with other influential organizations, published guidelines for basic and advanced life support for adult, children, and neonate patients with suspected or known COVID-19. The guidelines aim to facilitate optimal care for such patients sustaining cardiac arrest while ensuring the safety of rescuers. The first recommendation is to reduce provider exposure by donning personal protective equipment before entering the scene, limiting personnel on scene, considering mechanical cardiopulmonary resuscitation devices for adults and children meeting height and weight criteria as available, and communicating COVID-19 status to providers new to the scene. The second recommendation proposes prioritizing oxygenation and ventilation strategies with lower aerosolization risks. This is achieved by employing a closed-circuit system by intubating with a cuffed endotracheal tube and connecting to a ventilator with a high-efficiency viral filter in the path of exhaled gas and using an in-line suction catheter. Finally, providers should consider when resuscitation is appropriate by addressing the goals of care and taking patient risk factors into account when adopting policies to guide resuscitation decisions. Additional recommendations include considerations for specific settings and situations such as out-of-hospital cardiac arrest for lay rescuers and emergency medical service providers, in-hospital cardiac arrest, maternal cardiac arrest, and neonatal resuscitation. *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock/Centers for Disease Control and Prevention; image illustration, M. Lane-Fall.)*

Take home message: A multiorganization effort has published guidelines on the resuscitation of patients with confirmed or suspected COVID-19 that aim to help rescuers provide optimal care to patients in cardiac arrest while protecting rescuers.

Marked sexual dimorphism in neuroendocrine mechanisms for the exacerbation of paclitaxel-induced painful peripheral neuropathy by stress. Pain 2020; 161:865–74. PMID: 31917777.

Stress has been identified as a risk factor for chemotherapy-induced neuropathic pain. However, the underlying mechanisms remain uncertain. This study assessed the impact of stress and neurohormonal stress mediators on chemotherapy-induced peripheral neuropathy caused by paclitaxel in adult male and female rats. Over a 4-day course of administration, paclitaxel (total 4 mg/kg) caused mechanical hyperalgesia in both male and female rats peaking at day 7 but also present at day 28. The hyperalgesia was greater in rats exposed to unpredictable sound stress (a known contributor to inflammatory pain) before paclitaxel administration compared to those exposed subsequently. Paclitaxel did not produce hyperalgesia in adrenalectomized rats. Intrathecal antisense oligodeoxynucleotides were administered to reduce expression of glucocorticoid and ß-adrenergic receptors to evaluate the role of epinephrine and corticosterone on nociception. ß2-adrenergic receptor treatment resulted in a greater reduction in hyperalgesia in female rats relative to male rats while decreased glucocorticoid receptor expression reduced hyperalgesia in male rats only. With concurrent administration, hyperalgesia was attenuated in both female and male rats. Stress resiliency (based on a neonatal handling protocol) resulted in significantly reduced hyperalgesia, while stress sensitivity (based on a neonatal limited bedding protocol) had no effect. *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: Neuroendocrine stress may have a sexually dimorphic effect on paclitaxel-induced painful peripheral neuropathy. Antagonism of ß-adrenergic and glucocorticoid receptors on nociceptors may have prophylactic potential.

Assessment of the contribution of the work relative value unit scale to differences in physician compensation across medical and surgical specialties. JAMA Surg 2020 Apr 15 [online ahead of print]. PMID: 32293659.

Pay differences across medical and surgical specialties have been blamed on disparately high compensation rates assigned to procedures. This cross-sectional study assessed the degree to which physician compensation across specialties is dependent on compensation rates built into Medicare Part B work relative value units (amount of physician time on a service multiplied by compensation rate = work relative value units [wRVUs]). The final analysis included 42 medical and surgical specialties and 6,587 current procedural terminology codes. For medical specialties, compensation rates ranged from 0.029 to 0.057 wRVUs per minute (pathology and emergency medicine, respectively). The range in surgical specialties was from 0.035 to 0.051 wRVUs per minute (hand surgery and neurosurgery, respectively). Thirty-four of 42 specialties (81%) were within a narrow range (0.035 to 0.045 wRVUs per minute). Overall, compensation rates for surgical specialties were 7.2% higher than those for medical specialties, a nonsignificant difference (P = 0.07). The narrow range likely reflects that most specialties spend more than 60% of time on preservice activities such as preparation and evaluation of patients and postservice activities such as patient transfer or communicating with other caregivers rather than face-to-face patient time. *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: The compensation rates assumed in Medicare work relative value unit valuations contribute only a small degree to differences in physician compensation.

Structure of M^{pro} from SARS-CoV-2 and discovery of its inhibitors. Nature 2020; 582:289–93. PMID: 32272481.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease enzyme M^{pro} plays an important role in mediating replication and transcription of the virus, making it a promising drug target. This study utilized structure-assisted drug design, virtual drug screening, and high-throughput screening to identify drug leads to target M^{pro}. The computer-aided drug design identified the mechanism-based inhibitor, N3. Then, the crystal structure of M^{pro} in complex with N3 was determined. More than 10,000 compounds (approved drugs, clinical trial drug candidates, and other pharmacologically active compounds) were assayed through structure-based virtual and high-throughput screening. Six compounds were found to have promising inhibitory activity with M^{pro}. The compounds included the FDA-approved drugs disulfiram and carmofur and clinical or preclinical trial drugs ebselen, shikonin, tideglusib, and PX-12. Ebselen exhibited the strongest M^{pro} inhibitory activity (IC_{50} of 0.67 μM). *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: A strategy employing structure-based virtual and high-throughput screening has identified several potential candidate compounds targeting a critical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease enzyme that may assist in vaccine development. This approach may be useful for other novel infectious diseases that currently lack treatments.

Timing of endoscopy for acute upper gastrointestinal bleeding. N Engl J Med 2020; 382:1299–308. PMID: 32242355.

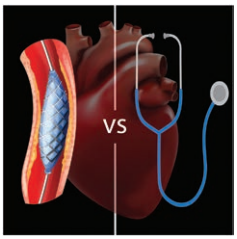
Acute upper gastrointestinal bleeding is a common medical emergency with an in-hospital mortality of 10%. Endoscopy within 24 h of presentation helps identify sources of bleeding allowing for hemostatic treatment of actively bleeding lesions, thereby reducing risk of further bleeding and possible surgery. This randomized trial investigated if timing of endoscopy influences mortality from any cause at 30 days after randomization. A total of 516 patients with acute upper gastrointestinal bleeding and a Glasgow-Blatchford score of 12 or higher (0 to 23 scale, increasing mortality) were randomly assigned to either urgent endoscopy within 6 h of consultation (258 patients) or early endoscopy from 6 to 24 h after consultation (258 patients). Endoscopic hemostatic treatment was used in 155 patients (60.1%) in the urgent endoscopy group *versus* 125 (48.4%) of the early endoscopy group. Mortality at day 30 was 8.9% in the urgent endoscopy group and 6.6% in the early endoscopy group (hazard ratio 1.35 [95% CI, 0.72 to 2.54]; P= 0.34); difference in mortality rates 2.3 percentage points (95% CI, –2.3 to 6.9). Within 30 days, further bleeding occurred in 10.9% of urgent endoscopy patients and 7.8% in the early endoscopy group (difference 3.1 percentage points [95% CI, –1.9 to 8.1]). *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: Endoscopy within 6 h of consultation for acute upper gastrointestinal bleeding in high-risk patients was not associated with lower 30-day all-cause mortality than endoscopy administered at 6 to 24 h.

Ten-year trends in surgical mortality, complications, and failure to rescue in Medicare beneficiaries. Ann Surg 2020; 271:855–61. PMID: 31306158.

Although 30-day surgical mortality continues to decline, the underlying mechanisms remain controversial. This retrospective study evaluated the potential impact of two suspected factors: an absolute reduction in complications leading to mortality or an improvement in the ability to treat postoperative complications (an improved "failure to rescue" rate). Medicare claims data from 702,268 patients at 3,404 hospitals from 2005 to 2014 undergoing one of four high-risk surgical procedures (abdominal aortic aneurysm repair, pulmonary resection, colectomy, or pancreatectomy) were evaluated. Hospitals were stratified into quintiles based on change in mortality over time. Endpoints were risk-adjusted 30-day mortality, serious complications, and failure to rescue rates. The top 20% of hospitals decreased mortality by 37% (95% CI, 9 to 5.7%; $P < 0.001$), serious complications by 11% (95% CI, 15.2 to 13.5%; $P < 0.001$), and failure to rescue by 25% (95% CI, 25.2 to 18.9%; $P < 0.001$). In contrast, the bottom 20% of hospitals had increases in all three endpoints (mortality: 12% [95% CI, 6.9 to 7.7%; $P < 0.001$]; serious complications: 5% [95% CI, 14.6 to 15.4%; $P < 0.001$]; and failure to rescue: 4% [95% CI, 21.5 to 22.3%; $P < 0.001$]). Decreasing failure to rescue rates accounted for 64% of improvement in mortality over time, whereas an absolute improvement in serious complication rates accounted for only 5%. *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

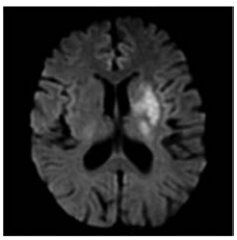
Take home message: Ongoing improvements in in-hospital mortality rates appear to be largely due to improving rescue of patients after postoperative complications rather than an absolute reduction in such complications.



Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020; 382:1395–407. PMID: 32227755.

Reducing the risk of death and ischemic events are primary goals of treating patients with stable coronary artery disease. In this international randomized trial, 5,179 patients with stable coronary artery disease and moderate or severe ischemia on prerandomization imaging or stress testing (excluding a number of exceptions) were assigned to either an invasive or conservative strategy and followed for a median 3.2 yr. The invasive strategy included angiography and revascularization when feasible in addition to medical therapy. Conservative therapy included medication alone. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. At 6 months, the cumulative rate for the primary outcome was 5.3% in the invasive therapy group and 3.4% in the conservative therapy group (difference 1.9 percentage points [95% CI, 0.8 to 3]) and at 5 yr, 16.4% and 18.2%, respectively (difference –1.8 percentage points [95% CI, –4.7 to 1]). *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: In patients with stable coronary artery disease and moderate to severe ischemia on imaging or stress testing, a conservative therapy of medication alone *versus* an invasive therapy (medication plus angiography and revascularization when feasible) did not reduce the risk of ischemic events or all-cause mortality over a median of 3.2 yr.



Cerebrospinal fluid influx drives acute ischemic tissue swelling. Science 2020; 367:eaax7171. PMID: 32001524.

Cerebrospinal fluid protects the brain from mechanical injury and provides it with a continuous source of ions and fluids *via* a glial cell-mediated lymphatic (termed "glymphatic") function. After acute ischemic stroke, the brain swells due to a net gain of cations and draws fluid from surrounding sources. This study evaluated whether glymphatic flow plays a role in edema formation as the brain is already encased in cerebrospinal fluid. After occluding the middle cerebral artery in mice, *in vivo* diffusion-weighted magnetic resonance and multimodal optical imaging was used to examine cerebrospinal fluid dynamics. Histologic mouse and human autopsy tissue samples were used to assess edema that formed in adjacent to cerebrospinal fluid inflow routes. Cerebrospinal fluid was found to be the earliest source of fluid and ions in brain swelling. The inciting event appears to be the spread of depolarizations in ischemic tissue. Inflow was dependent on the aquaporin-4 water channel, which is expressed by glial cells. Increased fluid accumulation was seen in tissue surrounding perivascular spaces and cerebral ventricles as compared to deep brain regions far from cerebrospinal fluid reservoirs. *(Article Selection: J. David Clark, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: Cerebrospinal fluid may be a source of ischemic edema, and glymphatic inflow of the fluid might be the initial event causing tissue swelling.

 DOI: 10.1097/ALN.0000000000003463

Occurrence and risk factors of chronic pain after critical illness. Crit Care Med 2020; 48:680–7. PMID: 32039992.

Outcomes research after intensive care unit (ICU) admission is increasingly focusing on patient-centered impacts on health-related quality of life, including chronic pain. This Dutch retrospective cohort study examined the prevalence, risk factors, and impact on daily life for chronic pain after critical illness using three cohorts of ICU patients (greater than or equal to 48-h ICU admission): (1) Any ICU survivors (n = 1,842) from which the prevalence and a prediction model were derived; (2) 1-yr survivors with newly acquired chronic pain (n = 160) from which clinical features and impact on daily life were evaluated; and (3) 1-yr survivors with pain who lived within 50 miles of the study hospital (n = 42) to assess neuropathic features. An estimated 18% (95% CI, 16 to 20%) developed chronic pain, reporting a median intensity of 4 on a 0 to 10 numeric rating scale (interquartile range, 2 to 6) in the week before responding to the survey. Neuropathic pain characteristics were present in 50% of patients. The impact of chronic pain was most evident on daily living, social activities, and mobility. In a multivariable analysis, female sex and number of days with c-reactive protein greater than 100 mg/l were associated with pain. *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: Chronic pain appears to be a common consequence of critical illness, with significant impact on the daily lives of patients.

Association between preoperative metformin exposure and postoperative outcomes in adults with type 2 diabetes. JAMA Surg 2020 Apr 8 [online ahead of print]. PMID: 32267474.

Metformin, the most common noninsulin drug prescribed to type 2 diabetics, is known to have anti-inflammatory properties and has been associated with a reduction in cardiovascular disease in diabetics. This retrospective cohort study evaluated 5,460 type 2 diabetics (mean age 68 yr) undergoing major surgery (six surgical categories) requiring general anesthesia and postoperative hospital admission with or without preoperatively prescribed metformin in a propensity-matched cohort at 15 hospitals within one U.S. healthcare system. Medication exposure was defined as one or more metformin prescriptions in the 180-day period before surgery. The primary outcome was 90-day all-cause mortality; secondary outcomes were 30-day mortality, hospital readmission, and the preoperative neutrophil to leukocyte ratio. Preoperative metformin prescriptions were associated with a lower risk of 90-day mortality (adjusted hazard ratio 0.72 [95% CI, 0.55 to 0.95]; absolute risk ratio 1.28% [95% CI, 0.26 to 2.31]). The risk of readmission was also lower (considering mortality as a competing risk) at 30 days (absolute risk ratio 2.09% [95% CI, 0.35 to 3.82]; subdistribution hazard ratio 0.84 [95% CI, 0.72 to 0.98]) and at 90 days (absolute risk ratio 2.78% [95% CI, 0.62 to 4.95]; subdistribution hazard ratio 0.86 [95% CI, 0.77 to 0.97]). The preoperative neutrophil to leukocyte ratio was also lower in metformin users (mean neutrophil to leukocyte ratio 4.5 [95% CI, 4.3 to 4.6] *vs.* 5.0 [95% CI, 4.8 to 5.3]; $P < 0.001$). *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: Preoperative metformin use in type 2 diabetics presenting for major surgery was associated with lesser 90-day postoperative mortality.

Simple versus complex preoperative carbohydrate drink to preserve perioperative insulin sensitivity in laparoscopic colectomy: A randomized controlled trial. Ann Surg 2020; 271:819–26. PMID: 31356274.

Surgically induced insulin resistance is known to disrupt postoperative glucose/protein metabolic hemostasis and is associated with hyperglycemia, infection, and longer hospital stays. Early recovery pathway guidelines recommend preoperative oral administration of a complex carbohydrate drink (maltodextrin based) to reduce postoperative insulin resistance. However, many centers utilize cheaper, more readily available simple carbohydrate drinks (fructose and glucose based). This randomized controlled trial compared a simple carbohydrate drink with a complex one to determine any difference in reduction of insulin resistance after laparoscopic colon resection. Thirty nondiabetic adult patients were randomized to receive either a complex carbohydrate drink (400 ml containing 40 g maltodextrin and 10 g of fructose) or a simple carbohydrate drink (400 ml containing 50 g of fructose) 2 h before surgery. Intraoperative insulin sensitivity was assessed using a hyperinsulinemic euglycemic clamp technique (*M* value, glucose uptake in skeletal muscle and adipose tissue measured as the mean glucose infusion rate required to maintain normoglycemia). Intraoperative insulin sensitivity was maintained in both groups (mean *M* value 8.3 *vs.* 8.8 $mg \cdot kg^{-1} \cdot min^{-1}$; $P = 0.7$). Postoperative insulin sensitivity, assessed with a homeostatic computerized model and fasting glucose values, was also preserved in both groups. No differences in complications or length of stay were observed. *(Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)*

Take home message: In nondiabetic patients undergoing laparoscopic colon resection, use of a simple carbohydrate drink has a similar impact on perioperative insulin sensitivity relative to a complex carbohydrate solution.