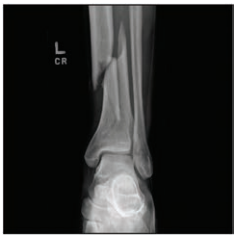
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Deborah J. Culley, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Effect of incisional negative pressure wound therapy vs standard wound dressing on deep surgical site infection after surgery for lower limb fractures associated with major trauma: The WHIST randomized clinical trial. JAMA 2020; 323:519–26.

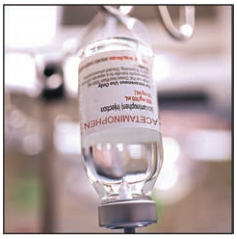
Serious limb injuries occur in 85% of patients with major trauma. Most common among these injuries are bone fractures. A systematic inflammatory response to major trauma coupled with damage to soft tissue adjacent to a fracture can lead to deep wound infection. This study compared the effectiveness of incisional negative pressure wound therapy *versus* standard wound dressing in reducing deep surgical site infection rates in wounds associated with surgery for major trauma–related lower limb fracture. Of the 1,548 randomized patients (mean age 50 yr) the primary outcome data was available for 1,519 (98%) patients. No significant differences were found in rate of deep surgical site infection at 30 days postsurgery. In the negative pressure wound therapy group, the rate of infection at 30 days was 5.84% (45 of 770) and 6.68% (50 of 749) in the standard dressing group (odds ratio 0.87 [95% CI, 0.57 to 1.33]; absolute risk difference –0.77% [95% CI, –3.19 to 1.66%]; $P = 0.52$). A per-protocol analysis of the dressing type that was actually applied yielded similar results: rate of infection in the negative pressure wound therapy group was 6.14% *versus* 6.57% in the standard dressing group (odds ratio 0.93 [95% CI, 0.6 to 1.44]; absolute risk difference 0.33% [95% CI, –2.93 to 2.15%]; $P = 0.76$). There were also no differences between the groups at 90 days after surgery. *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: This study suggests that there is no significant difference in deep surgical site infection between incisional negative pressure wound therapy compared to standard wound dressings in patients who have undergone surgery for lower limb fractures related to major trauma.

β-Blockade in rectal cancer surgery: A simple measure of improving outcomes. Ann Surg 2020; 271:140–6.

Preoperative β-blocker therapy has been shown to protect against postoperative mortality and complications in patients who have had noncardiac surgery. In this Swedish population-based cohort study, 11,966 adult patients who had elective abdominal resection for rectal cancer over a 10-yr period were analyzed. Of these, 3,513 (29.4%) had received preoperative prescriptions for β-blockers within 12 months of their surgical procedure. The primary outcome measures were 30-day cause-specific mortality, 1-yr all-cause mortality, and 30-day complications. Compared to the β-blocker negative group, the β-blocker positive group had a significantly lower 30-day postsurgery mortality rate (incidence rate ratio 0.06 [95% CI, 0.03 to 0.13]; $P = 0.001$). Significantly lower 30-day mortality rates due to respiratory-related deaths and multiorgan failure were also seen in the β-blocker group (incidence rate ratio 0.10 [95% CI, 0.02 to 0.40], $P = 0.001$; and incidence rate ratio 0.07 [95% CI, 0.02 to 0.29], $P < 0.001$, respectively). One-year overall survival was significantly better among those with preoperative β-blocker prescriptions with a 57% risk reduction in mortality (hazard ratio 0.43 [95% CI, 0.37 to 0.52], $P < 0.001$). *(Article Selection: Martin J. London. Image: Adobe Stock.)*

Take home message: A retrospective registry analysis found an association between a prescription for β-blockers within the 12 months before abdominal resection for rectal cancer and a lower incidence of 30-day and 1-yr all-cause mortality rates and the number of postoperative complications.



Randomized clinical trial of intravenous (IV) acetaminophen as an adjunct to IV hydromorphone for acute severe pain in emergency department patients. Acad Emerg Med 2020 Feb 20 [Epub ahead of print].

Due to the deleterious side effects of opioid analgesics (including misuse and overdose), there is interest in reducing their demand in the emergency room setting. This double-blind randomized trial aimed to determine whether analgesia was better in patients receiving a combination of hydromorphone and acetaminophen when compared to hydromorphone alone. All patients received hydromorphone 1 mg intravenously and were randomized to receive either 1 g of intravenous acetaminophen or 100 ml of normal saline (control). Of the 162 patients under the age of 65 who were enrolled, primary outcome data were available for 159. There was no difference in pain reduction 60 min after administration between the two groups. Those patients who received acetaminophen had a numeric rating scale score of 6.2 (baseline score minus 60-min score) whereas the normal saline group had a numeric rating score of 5.4 (difference between groups 0.8 units [95% CI, –0.01 to 1.8], $P = 0.08$). *(Article Selection: J. David Clark. Image: J. P. Rathmell.)*

Take home message: The addition of intravenous acetaminophen to intravenous hydromorphone in an emergency room setting was not associated with clinically relevant differences in pain.

DOI: 10.1097/ALN.0000000000003356

Cocoa to improve walking performance in older people with peripheral artery disease: The COCOA-PAD pilot randomized clinical trial. Circ Res 2020; 126:589–99.

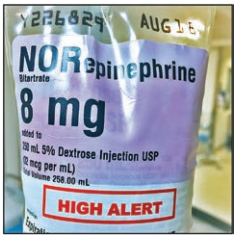
People with lower extremity peripheral artery disease often have declines in walking performance over time. The COCOA-PAD study is a randomized clinical trial that enrolled 44 participants 60 yr of age and older to receive a cocoa beverage (3 packets daily totaling 15 g of cocoa and 75 mg epicatechin) or placebo beverage. At 6-month follow-up, participants were tested for changes in 6-min walking distance at 2.5 h after consuming the final study beverage and again at 24 h after final study beverage. Among the 40 participants (91%) who completed the trial, the cocoa group improved their 6-min walking distance by 43 meters (90% CI, 22 to ∞; $P = 0.005$) compared to the placebo group. At 24 h, the improvement was 18 meters compared to placebo, but this difference was not significant (90% CI, –1.7 to ∞; $P = 0.12$). The cocoa group also had improved calf muscle perfusion ($P = 0.098$), mitochondrial cytochrome *c* oxidase activity ($P = 0.013$), increased capillary density ($P = 0.014$), and reduced central nuclei ($P = 0.024$). *(Article Selection: Martin J. London. Image: Adobe Stock.)*

Take home message: The results of this small pilot study suggest that flavanol-rich cocoa may improve walking performance, limb perfusion, and skeletal muscle measures in people with peripheral artery disease.

Out-of-network bills for privately insured patients undergoing elective surgery with in-network primary surgeons and facilities. JAMA 2020; 323:538–47.

Unexpected out-of-network billing can be a financially disruptive result of hospital procedures. This "balance bill," the remainder of an out-of-network bill after reimbursement by the insurance company, can be quite expensive to patients. The present study aimed to identify factors associated with such billing using claims data from a large commercial insurer that involved out-of-network billing for elective procedures. Among 347,356 procedures over a 5-yr period with in-network primary surgeons and facilities, 20.5% (95% CI, 19.4 to 21.7%) had an out-of-network bill. The mean potential balance bill per procedure was $2,011 (95% CI, $1,866 to $2,157). Anesthesiologists and surgical assistants were each responsible for 37% of balance bills (mean potential balance bills were $1,219 and $3,633, respectively). Additional out-of-network bills came from pathologists, medical consultants, radiologists, and other clinicians. Other factors associated with higher risk of out-of-network bills were membership in health insurance exchange plans and surgical complications. Presence of out-of-network bills was also associated with significantly higher total charges, standardized payments, and out-of-pocket cost-sharing. *(Article Selection: Martin J. London. Image: Adobe Stock.)*

Take home message: A considerable percent of elective surgeries with in-network primary surgeons and facilities may result in costly out-of-network bills for commercially insured patients.



Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: A randomized clinical trial. JAMA 2020 Feb 12 [Epub ahead of print].

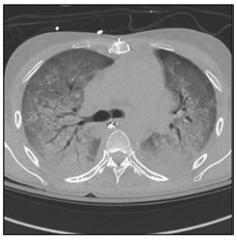
Vasopressors are often used to treat hypotension in intensive care units but have also been associated with cardiac, metabolic, immune, and microbiome effects that may be dangerous for older patients. This prospective clinical trial was designed to determine whether permissive hypotension and decreased vasopressor use was associated with reduced 90-day mortality rates. Patients 65 yr and older who were admitted to an intensive care unit with vasodilatory hypotension (n = 2,600) were randomized 1:1 to vasopressors management guided by mean arterial pressure target of 60 to 65 mmHg (permissive hypotension) or by usual care. Although the permissive hypotension group had lower exposure to vasopressors in both median duration and total dose compared to the usual care group, there was no significant difference in all-cause mortality at 90 days, with 500 (41%) deaths among 1,221 permissive hypotension patients and 544 (44%) deaths out of 1,242 usual care patients (absolute risk difference –2.85% [95% CI, –6.75 to 1.05]; $P = 0.15$). *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: Decreased vasopressor support and permissive hypotension may not reduce 90-day all-cause mortality rates when compared to usual care in older patients admitted to an intensive care unit with vasodilatory hypotension.

A responsible educational handover: Improving communication to improve learning. Acad Med 2020; 95:194–9.

The American Medical Association's Accelerating Change in Medical Education consortium has resulted in five recommendations to improve the transition between undergraduate and graduate medical education programs through better communication. These transitions are often hindered by disincentives to provide complete student performance information, lack of information on students' final year of study, and limited resources to review large numbers of applications. Based on the competency-based medical education principle that the continuum of education, training, and practice should be seamless, the consortium recommendations call for an "educational handover." This concept would include information on the final school year, incentivize individualized curriculum, and foster student self-directed learning. The first recommendation states that the purpose of the handover would be to provide "continued improvement in learner ability and performance." The remaining recommendations detail that the handover be in a standardized format based on a cyclic process that begins early in students' academic career; that it be focused on individualized learning plans produced by learner and advisor; and that medical schools and residency programs provide sufficient infrastructure to support learner improvement. *(Article Selection: Cathleen Peterson-Layne. Image: J. P. Rathmell.)*

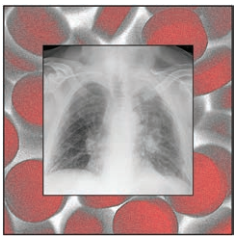
Take home message: A recent American Medical Association consortium proposed recommendations to develop an educational handover between undergraduate and graduate education that would foster individual student learning trajectories and ultimately create a more seamless, collaborative continuum of physician training.



Effect of intravenous interferon β-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: A randomized clinical trial. JAMA 2020 Feb 17 [Epub ahead of print].

Acute respiratory distress syndrome (ARDS) has a hospital mortality rate of 40% yet there are currently no approved drugs to treat it other than supportive care. An uncontrolled inflammatory response is thought to result in pulmonary vascular leakage. Because interferon β-1a has been shown to prevent vascular leakage, this clinical trial was conducted to determine if its administration improved outcomes in patients with ARDS. Patients (n = 301) with moderate to severe ARDS were randomized to receive either 10 mg intravenous recombinant human interferon β-1a or placebo once daily for 6 days. The primary outcome was a composite score of death and number of ventilator-free days at day 28 (range –1 for death to 27 if patients were off ventilator the first day). The median composite score of death and ventilator-free days in the interferon group was 10 days and 8.5 days in the placebo group ($P = 0.82$). Adverse events related to treatment occurred in 41 (28.5%) patients in the interferon group and in 33 (21.7%) patients in the placebo group. *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: When compared to placebo, a course of interferon β-1a for 6 days did not result in improved outcomes in patients with moderate to severe ARDS.



Dose-dependent association of gabapentinoids with pulmonary complications after total hip and knee arthroplasties. J Bone Joint Surg Am 2020; 102:221–9.

To reduce postoperative pain and reliance on opioids, gabapentinoids have been used as perioperative analgesics, though the optimal dose to reduce opioid consumption while minimizing risks of pulmonary complications has not been established. This study evaluated dose-dependent effects of gabapentinoids (gabapentin and pregabalin) on postoperative pulmonary complications and opioid consumption in patients who had total hip or knee arthroplasty. The retrospective population-based cohort consisted of 858,306 patients who had either of these elective procedures. Compared to placebo, patients who received either gabapentinoid at any dose had greater odds of pulmonary complications, and the odds were greater with higher doses of each drug (gabapentin: 1 to 350 mg, adjusted odds ratio 1.25 [95% CI, 1.18 to 1.33]; 351 to 700 mg, adjusted odds ratio 1.31 [95% CI, 1.23 to 1.39]; 701 to 1,050 mg, adjusted odds ratio 1.36 [95% CI, 1.23 to 1.51]; greater than 1,050 mg, adjusted odds ratio 1.51 [95% CI, 1.4 to 1.63]; and pregabalin: 1 to 110 mg, adjusted odds ratio 1.24 [95% CI, 1.17 to 1.32]; 111 to 250 mg, adjusted odds ratio 1.16 [95% CI, 1.08 to 1.24]; greater than 250 mg, adjusted odds ratio 1.81 [95% CI, 1.57 to 2.09]. Neither drug at any dose reduced opioid consumption to a clinically meaningful degree. *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: Although gabapentinoids are used in perioperative analgesia protocols, this study showed that they had an association with postoperative pulmonary complications that were greater at higher doses. Gabapentinoids at any dose did not result in a clinically meaningful reduction in opioid use.

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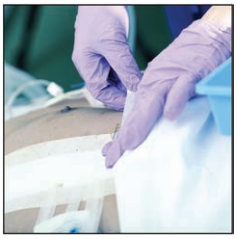
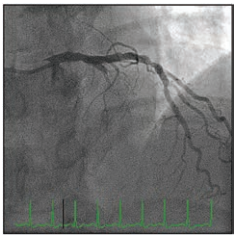


Preoperative, single, high-dose glucocorticoid administration in abdominal wall reconstruction: A randomized, double-blinded clinical trial. Surgery 2020; 167:757–64.

Glucocorticoid administration before surgery reduces postoperative pain, nausea, and vomiting, and attenuates the inflammatory response without severe side effects. This trial was designed to determine if similar benefits occur in patients undergoing abdominal wall reconstruction for large ventral hernias. Forty patients were randomized to either intravenous methylprednisolone 125 mg or placebo at the induction of anesthesia. On the first postoperative day, there was no difference between groups in mean pain level while at rest in supine position (1.7 methylprednisolone group *vs.* 2.2 placebo group, $P = 0.92$). However, the methylprednisolone group experienced less pain than the placebo group during activity (3 *vs.* 5, $P = 0.011$) and while coughing (3.4 *vs.* 5.9, $P = 0.01$). During the first 5 postoperative days, the methylprednisolone group experienced less pain at rest in supine position ($P = 0.004$), when moving from supine to sitting ($P = 0.015$), and when coughing ($P = 0.036$). Plasma C-reactive protein concentrations were also reduced in the methylprednisolone group ($P = 0.039$). *(Article Selection: J. David Clark. Image: Adobe Stock.)*

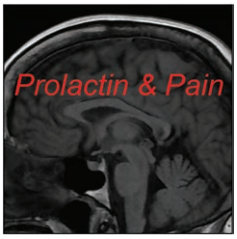
Take home message: A single treatment with high-dose methylprednisolone may reduce postoperative pain and mitigate the inflammatory response in patients undergoing abdominal wall reconstruction for large ventral hernias.



Long-term outcomes associated with total arterial revascularization vs non-total arterial revascularization. JAMA Cardiol 2020 Feb 19 [Epub ahead of print].

Graft selection may influence coronary artery bypass graft (CABG) outcomes. This population-based retrospective cohort study compared long-term clinical outcomes of total arterial revascularization with nontotal arterial revascularization (CABG with at least one arterial and one saphenous vein graft) in 49,404 patients with primary isolated CABG. Participants were propensity score matched and followed for a mean of 4.6 and maximum of 9 yr. Although number of bypasses was similar in both groups, the total arterial revascularization group had more arterial grafts (mean 2.4 *vs.* 1.2, $P < 0.01$). In-hospital deaths were similar in both groups (15 in the total arterial revascularization group *vs.* 12 in the nontotal arterial revascularization group, $P = 0.32$). Over 8 yr, the total arterial revascularization group was less likely to have major adverse cerebrovascular and cardiac events than the nontotal arterial revascularization group (hazard ratio 0.78 [95% CI, 0.68 to 0.89]). The total arterial revascularization group also had less death (hazard ratio 0.80 [95% CI, 0.66 to 0.97]) and myocardial infarction (hazard ratio 0.69 [95% CI, 0.51 to 0.92]). There was no significant difference between groups in stroke and repeated revascularization. *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: Total arterial revascularization may result in less adverse cerebrovascular and cardiac events, death, and myocardial infarction in patients undergoing CABG.



The prolactin receptor long isoform regulates nociceptor sensitization and opioid-induced hyperalgesia selectively in females. Sci Transl Med 2020; 12(529).

Accumulating evidence demonstrates that pain mechanisms are often sex dependent, potentially explaining differences in pain prevalence and treatment responsiveness in men and women. This study demonstrates that female mice have an active prolactin signaling mechanism supporting opioid-induced hyperalgesia not present in male mice. Both prolactin and prolactin receptor expression were higher in female when compared to male mice. By decreasing the expression of the nociception fighting long form of the prolactin receptor with opioid exposure or CRISPR editing, hyperalgesia resulted. This was presumably due to unopposed signaling through the nociception enhancing short form of the prolactin receptor. Likewise, overexpression of the prolactin receptor long form or elimination of prolactin signaling altogether using genetic and pharmacologic approaches prevented opioid-induced hyperalgesia, but only in female mice. Importantly, the prolactin effects were not observed in pain models involving nerve injury. These observations suggest therapeutic approaches to reducing opioid hyperalgesia directed at prolactin signaling may be effective and sex specific. *(Article Selection: J. David Clark. Image: J. P. Rathmell.)*

Take home message: Drug therapies that limit prolactin/short-receptor prolactin signaling or gene therapies that target prolactin may reduce pain selectively in females.