

ANESTHESIOLOGY



Deborah J. Culley, M.D., Editor

**The proposal to lower P value thresholds to .005. JAMA 2018; 319:1429–30.**

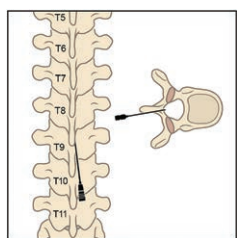
One of the major misconceptions in science is the issue of statistical significance. Many scientific conclusions and even policy decisions are based on whether a P value passes a specific, usually 0.05, threshold. In this editorial, the author reviews in comprehensive detail how P values are misinterpreted, over-trusted, and misused. By doing so, he puts the emphasis on the fact that “a P value, or statistical significance, does not measure the size of an effect or the importance of a result.” He then discusses a recent proposal made by a large coalition of 72 methodologists to lower the routine P value threshold for claiming statistical significance from 0.05 to 0.005. This measure would help to filter out “noise” while most valuable information will remain. Importantly, he argues that lowering statistical significance should be viewed as a temporizing measure before completely abandoning P value thresholds and replacing them with other inferential tools, such as Bayesian statistics. (Summary: Laszlo Vutskits. Image: J. P. Rathmell.)

Take home message: The importance of P values is highly questionable when interpreting scientific results. Adoption of a new statistical standard has been suggested. This can be achieved *via* incentives from major journals and funding agencies as well as through radical changes in training curriculum.

**Effect of loading dose of atorvastatin prior to planned percutaneous coronary intervention on major adverse cardiovascular events in acute coronary syndrome: The SECURE-PCI randomized clinical trial. JAMA 2018; 319:1331–40.**

Clinical studies suggest that early statin therapy may improve outcomes in patients with acute coronary syndrome. This study randomized 4,191 patients from 53 sites in Brazil with acute coronary syndrome who were not on long-term statin therapy to receive two loading doses of atorvastatin 80 mg or placebo before and 24 h after a planned percutaneous coronary intervention. The objective of the study was to determine whether statin loading decreased major adverse cardiovascular events. Sixty-five percent of the randomized patients underwent percutaneous coronary intervention with the remainder undergoing medical therapy (27%) or coronary artery bypass graft (8%). Major adverse cardiovascular events occurred in 6.2% of treated patients *versus* 7.1% who received placebo (absolute difference, 0.85%; 95% CI, –0.70 to 2.4%; $P = 0.27$). A prespecified subgroup analysis revealed a lower rate of major adverse cardiovascular events in the 65% of patients who underwent percutaneous coronary intervention and were randomized to the statin group when compared to the placebo group (hazard ratio, 0.72; 95% CI, 0.54 to 0.96; $P = 0.02$). (Summary: Martin J. London. Image: J. P. Rathmell.)

Take home message: Loading doses of atorvastatin in patients with acute coronary syndrome anticipated to undergo percutaneous coronary intervention did not reduce the rate of major adverse cardiovascular events at 30 days.

**Is it time to reconsider postoperative epidural analgesia in patients undergoing elective ventral hernia repair? An AHSQC analysis. Ann Surg 2018; 267:971–6.**

Epidural analgesia is commonly used for abdominal procedures. This study aimed to study whether epidural analgesia in patients undergoing ventral hernia repair was associated with improved outcomes. This study used the American Hernia Society Quality Collaborative database to address this question in 1,526 propensity-matched patients. The group that had epidural analgesia had an increased hospital length of stay (5.5 vs. 4.9 days, $P < 0.05$). In addition, patients receiving epidural analgesia had an increased rate of having any postoperative complications (36% vs. 24%, $P = 0.02$), but a lower incidence of renal failure (0% vs. 0.7%, $P < 0.05$). Most interesting was the finding that pain scores 30 days after surgery were higher in the epidural group ($P = 0.04$). These findings suggest that epidural analgesia may not improve outcomes in patients undergoing elective ventral hernia repair. (Summary: Deborah J. Culley. Image: With permission, from Rathmell JP: Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine, 2nd edition, Philadelphia, Lippincott, 2012.)

Take home message: Epidural analgesia may not decrease hospital length of stay and may increase pain scores 30 days after elective ventral hernia repair.



Medical education and health care delivery: A call to better align goals and purposes. *Acad Med* 2018; 93:384–90.

The healthcare delivery system continues to evolve with the triple aim of improving outcomes and patient experience while reducing costs. To best prepare providers to function in the complex, evolving delivery system, the authors describe how medical education needs to evolve in an aligned manner. The authors of this manuscript provide practical examples of how a unified approach, and alignment of goals and priorities, between healthcare delivery and medical education could lead to overall improvement. The authors suggest that this realignment is necessary for successful healthcare reform. While this article focuses on undergraduate medical education, the concepts are easily extrapolated to any level of education within health care, including residency, fellowship, and even faculty development in anesthesiology. (Summary: Cathleen Peterson-Layne. Image: ©ThinkStock.)

Take home message: Medical education in the future will likely require a unified approach to improve patient outcomes while reducing cost.



Rare $Na_v1.7$ variants associated with painful diabetic peripheral neuropathy. *Pain* 2018; 159:469–80.

Neuropathy is a common complication of diabetes mellitus. Unexpectedly, only one third of those with diabetic neuropathy experience pain with their condition. The authors of this study hypothesized that variants of the pain-associated $Na_v1.7$ sodium ion channel gene might mediate susceptibility to developing painful symptoms among those with diabetic neuropathy. After extensive examination, quantitative sensory testing and skin biopsy, the $Na_v1.7$ genes were sequenced in 111 patients. The investigators found 12 rare gene variants in 10 of the patients with painful neuropathy, and none in patients with neuropathy but no pain. Electrophysiology confirmed gain-of-function changes for two of the genes. Measures of the severity of the neuropathy correlated poorly with the painful symptoms. The results provide further evidence for genetic ion channel variants contributing to some, although perhaps not all, cases of painful diabetic neuropathy. Genetic studies in patients with painful neuropathies may eventually allow precision targeting of analgesic therapies based on genetic variation. (Summary: J. David Clark. Image: ©ThinkStock/J. P. Rathmell.)

Take home message: Genetics may play a role in the development of pain in diabetic patients with neuropathies.



Effect of boarding on mortality in ICUs. *Crit Care Med* 2018; 46:525–31.

Intensive care unit beds are highly utilized in most hospitals, and occasionally patients whose characteristics would predict the need for a particular type of intensive care unit are boarded in another intensive care unit due to bed unavailability. The authors describe a retrospective cohort study, controlled for unmeasured confounding, designed to evaluate whether being boarded in an alternative intensive care unit setting was associated with higher mortality. Among the 8,429 patients identified by the study, 1,871 were boarded in an alternative intensive care unit. The authors identified a relative risk of intensive care unit mortality of 1.2 (95% CI, 1.0 to 1.4) and a similar relative risk of in-hospital mortality (1.2; 95% CI, 1.0 to 1.49). Further prospective studies will be required to determine whether boarding in an intensive care unit is associated with an increased risk of in-hospital or 30-day mortality. (Summary: Deborah J. Culley. Image: ©ThinkStock.)

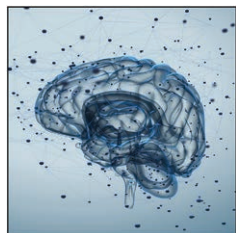
Take home message: Boarding in an intensive care unit may be associated with an increased risk of mortality.



Nociceptor sensory neurons suppress neutrophil and $\gamma\delta$ T cell responses in bacterial lung infections and lethal pneumonia. *Nat Med* 2018; 24:417–26.

The trachea, bronchi, and airways of the lung are innervated by peripheral sensory afferent neurons originating from vagal and spinal sensory neurons with cell bodies in the vagal and dorsal root ganglia. The subset of nociceptor neurons responding to noxious stimuli induce pain, coughing, and bronchoconstriction, which may protect the lung. There is evidence that these nociceptors cross-talk with immune cells in the respiratory tract in mouse models of asthma. The authors investigated the role of sensory neurons in pulmonary host defenses against bacterial infection and lethal pneumonia, studying the transient receptor potential vanilloid 1 (TRPV1) ion channel that responds to capsaicin, protons, and heat stimuli. Using a murine strain that expresses the human diphtheria-toxin receptor (under control of TRPV1 regulatory sequences), the authors found that TRPV1+ afferents in the vagal ganglia modulated innate immune responses against methicillin-resistant *Staphylococcus aureus* lethal pneumonia. Ablation of these neurons improved survival, neutrophil, and T-cell responses and bacterial clearance despite increased bacterial dissemination, suggesting that differences in lung clearance *versus* barrier function are mediated by distinct neuronal subsets. (Summary: Martin J. London. Image: J. P. Rathmell.)

Take home message: Nociceptors play a critical role in regulating lung immunity and outcomes of bacterial lung infection. Future therapies may incorporate targeting of neuroimmunologic communication to enhance host protection against pneumonia.



Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature* 2018; 555:377–81.

Continuous generation of new neurons in the adult mammalian hippocampus is generally considered an important form of adult neuronal plasticity underlying hippocampal-related learning and memory function. While most experimental data on this phenomenon derive from rodent experiments, it remains unclear whether and to what extent neurogenesis is present in humans. In this study, the authors investigated this question by examining 59 postmortem and postoperative samples of the human hippocampus between gestational week 14 and 35 yr of age. Using a combination of immunohistochemical analyses, they show that the extent of neurogenesis steeply declines during the first year of life and that no newly formed neurons can be detected in samples from the adult hippocampus. These results were corroborated with *in vivo* experiments performed in nonhuman primates, where hippocampal neurogenesis was

also sharply decreased during early postnatal life. (Summary: Laszlo Vutskits. Image: ©ThinkStock.)

Take home message: Hippocampal neurogenesis does not seem to persist into adulthood in humans. These results suggest that neurogenesis may not be a mechanism mediating learning and memory formation in adult humans.

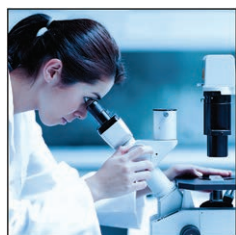


Pain as a risk factor for common mental disorders. Results from the Netherlands Mental Health Survey and Incidence Study-2: A longitudinal, population-based study. *Pain* 2018; 159:712–8.

Chronic pain and psychologic disorders often coexist. Less well characterized is the sequence in which the pain and psychologic disorders occur. In this study involving more than 5,300 patients from The Netherlands, the investigators followed patients using two waves of evaluations separated by three years. Both questionnaires and formal diagnostic interviews were used. They found that both moderate to severe pain and moderate to severe pain interference (pain-induced functional impairment) conferred odds ratios greater than 2 for the development of mood and anxiety disorders. There was no link between pain or pain interference and the development of a substance abuse disorder over the same

3-yr period. Moreover, the investigators failed to identify interaction effects between pain severity or interference due to pain and a previous history of mental disorders. The authors suggested that the detection and treatment of pain may be an effective way to prevent the development of psychologic disorders. (Summary: J. David Clark. Image: ©ThinkStock.)

Take home message: Moderate to severe pain may be associated with the development of mental health disorders.



Surgeon scientists are disproportionately affected by declining NIH funding rates. *J Am Coll Surg* 2018; 226:474–81.

Over the past decade the number of research grants funded by the National Institutes of Health have decreased while the number of applications has steadily increased. The authors of this study utilized the National Institutes of Health Research Portfolio Online Reporting Tools Expenditures to collect data between 2006 and 2016 on each grant from a surgery department, including the type of grant, award dates, funding amount, and number of publications associated with each grant. They found that while National Institutes of Health spending has increased by \$4 billion over this interval, the amount to surgeons has decreased from a peak of \$314 million in 2007 to \$292 million in 2016 ($P = 0.04$). Despite a stable number of applications, the authors also noted that the success rate for funded grants among surgeons (16%) is lower than the national norm (19%, $P = 0.01$) despite increased productivity in publishing

impactful articles. (Summary: Deborah J. Culley. Image: ©ThinkStock.)

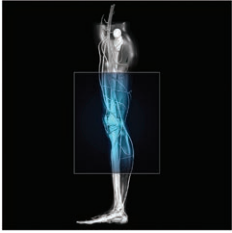
Take home message: National Institutes of Health funding to surgeons has decreased more than that of the national average over the course of the last 10 yr.



A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018; 378:1121–31.

High-flow oxygen administration *via* a nasal cannula is increasingly used to provide respiratory support in all age groups in the intensive care unit. However, the efficacy, safety, and feasibility of this therapeutic modality in other clinical settings remain to be determined. In this randomized multicenter trial, the authors tackled these questions by focusing on infants who had bronchiolitis with a need for supplemental oxygen therapy. A total of 1,472 patients from 17 centers were randomized to receive either standard oxygen therapy or high-flow oxygen therapy on the ward. The primary endpoint of the study was escalation of care due to treatment failure. While 12% of patients received escalation of care in the high-flow group, the need for further respiratory support reached 23% in the standard oxygen therapy group (risk difference –11%; 95% CI, –15 to –7%; $P < 0.001$). Importantly, 61% of patients in the standard therapy group with the need for additional treatment responded well to high-flow rescue therapy. Neither the duration of hospital stay nor the duration of oxygen therapy was different between the two groups. (Summary: Laszlo Vutskits. Image: ©ThinkStock.)

Take home message: Instauration of high-flow oxygen therapy outside of the intensive care unit is an appealing treatment option in infants with bronchiolitis. It results in significantly lower rates of therapeutic escalation due to treatment failure when compared with standard oxygen therapy in this patient population.

**Major adverse limb events and mortality in patients with peripheral artery disease: The COMPASS trial. J Am Coll Cardiol 2018; 71:2306–15.**

Patients with peripheral artery disease are at increased risk for major adverse limb events. Current antiplatelet agents and oral anticoagulants have not demonstrated efficacy in reducing the incidence of major adverse limb events. The authors used data from a larger randomized trial comparing low-dose rivaroxaban and aspirin to aspirin alone in patients with coronary artery or peripheral artery disease (COMPASS trial, N = 27,395). Among these, 6,391 patients had lower extremity peripheral artery disease in whom the authors investigated complication rates among patients with major adverse limb events relative to those without and the impact of low-dose rivaroxaban plus aspirin relative to aspirin alone on complication rates. One hundred and twenty-eight patients developed major adverse limb events.

Major adverse limb events increased the hazard ratio of subsequent hospitalization (hazard ratio, 7.2; 95% CI, 5.5 to 9.4; $P < 0.001$), vascular amputations (hazard ratio, 197.5; 95% CI, 97.3 to 400.8; $P < 0.001$), and death (hazard ratio, 3.2; 95% CI, 1.87 to 5.56; $P < 0.001$). Compared to aspirin alone, the combination of rivaroxaban and aspirin significantly reduced the incidence of major adverse limb events by 43% (hazard ratio, 0.57; 95% CI, 0.37 to 0.9; $P = 0.01$). (Summary: Martin J. London. Image: ©ThinkStock.)

Take home message: Major adverse limb events in patients with lower extremity peripheral artery disease are associated with poor prognosis. Rivaroxaban plus aspirin may lower the incidence of major adverse limb events and its associated complications.