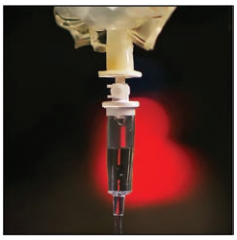
ANESTHESIOLOGY

Deborah J. Culley, M.D., Editor



Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med 2018; 378:2263–74.

Restricting fluids is a key component of enhanced recovery after surgery pathways. The purpose of this study was to determine whether fluid restriction lowers the rate of complications and increases disability-free survival when compared to liberal fluid administration as measured by the World Health Organization Disability Assessment Schedule score. The patients (N = 3,000) were randomly assigned to liberal (n = 1,490) or restricted (n = 1,493) fluid administration groups. Twenty-four hours after surgery, patients in the restricted group had received less fluid when compared to those in the liberal group ($P < 0.001$). There were no differences in death or disability (hazard ratio 1.05; 95% CI, 0.88 to 1.24; $P = 0.61$) between the two groups. Interestingly, patients randomized to restricted fluid administration had a higher incidence of acute kidney injury (hazard ratio 1.71; 95% CI, 1.29 to 2.27; $P < 0.001$) and surgical site infections (hazard ratio 1.22; 95% CI, 1.03 to 1.45; $P = 0.02$). *(Summary: Deborah J. Culley. Image: J. P. Rathmell.)*

Take home message: Fluid restriction may not decrease death and disability but may increase the risk of acute kidney injury and surgical site infections.

Multicentre randomized clinical trial of the effect of chewing gum after abdominal surgery. Br J Surg 2018; 105:820–8.

Enhanced recovery after surgery is a well-defined multimodal perioperative care pathway aimed at fast recovery after abdominal surgery. While early postoperative feeding is a main target within enhanced recovery after surgery, many patients develop intolerance of oral intake and postoperative nausea and vomiting. The present study tests the hypothesis that "sham feeding" with chewing gum enhances bowel recovery and reduces hospital length of stay in an enhanced recovery after surgery setting in a prospective randomized trial that included 2,000 patients from 12 hospitals. The control group (n = 1,000) received standard enhanced recovery after surgery care and the treatment group (n = 1,000) received the same care plus a chewing gum intervention, consisting of chewing gum for 30 min three times a day. Hospital length of stay was defined as primary endpoint. For both groups, median hospital length of stay was 7 days (range, 5 to 10 days; $P = 0.364$). There were also no differences in the secondary outcomes: time to first flatus ($P = 0.873$), time to first defecation ($P = 0.562$), or complication rates between the two groups ($P = 0.113$). *(Summary: Beatrice Beck-Schimmer. Image: ©ThinkStock.)*

Take home message: The addition of a postoperative chewing gum protocol as a part of an enhanced recovery after surgery protocol may not shorten hospital length of stay, have an impact on bowel recovery, or decrease complication rates. Of note, this article reflects the value of publishing properly designed studies in the setting of negative results.

Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018; 378:1965–75.

The effectiveness of venovenous extracorporeal membrane oxygenation in patients with severe adult respiratory distress syndrome (ARDS) is controversial. The authors performed an international, randomized trial at 64 centers randomly assigning patients with severe ARDS (Pao_2:fraction of inspired oxygen [Fio_2] less than 50 mmHg for more than 3 h, Pao_2:Fio_2 less than 80 mmHg for more than 6 h, arterial pH less than 7.25 with $Paco_2$ at least 60 mmHg for more than 6 h) to receive immediate extracorporeal membrane oxygenation or conventional treatment. Crossover to extracorporeal membrane oxygenation was allowed in patients with refractory hypoxemia. The primary endpoint was 60-day mortality. A sample size of 331 patients was projected. The trial was stopped at 240 patients after the fourth planned sequential interim analysis for futility. The primary outcome occurred in 35% of extracorporeal membrane oxygenation patients and 46% of the control group (relative risk 0.76; 95% CI, 0.55 to 1.04; $P = 0.09$). Crossover occurred in 28% of the control group at a mean of 6.5 days after randomization and 57% of these patients died. There were more bleeding events leading to transfusion (46% *vs.* 28%), cases of severe thrombocytopenia (27% *vs.* 16%), and fewer cases of ischemic stroke (0% *vs.* 5%) in the extracorporeal membrane oxygenation group. *(Summary: Martin J. London. Image: J. P. Rathmell.)*

Take home message: Extracorporeal membrane oxygenation use in patients with severe ARDS was not associated with improved mortality at 60 days. Early trial termination and a large percentage of crossover patients complicate interpretation of the results.

Secondary attention-deficit/hyperactivity disorder in children and adolescents 5 to 10 years after traumatic brain injury. JAMA Pediatr 2018; 172:437–43.

Traumatic brain injury in early childhood is associated with an increased risk for developing psychiatric disorders later in life. Among them, the prevalence of attention-deficit/hyperactivity disorder is approximately 2.5-fold higher in children with traumatic brain injury but the risk factors are poorly understood. In this cohort study, the authors examined the development of attention-deficit/hyperactivity disorder during 5 to 10 yr after injury in children with traumatic brain injury (n = 81) in comparison to a cohort of children with orthopedic injury (n = 106). They found that 62% of children with severe traumatic brain injury developed attention-deficit/hyperactivity disorder within this time frame compared to 15% of children in the orthopedic injury group (hazard ratio 3.62; 95% CI, 1.59 to 8.26). Higher level of maternal education was independently associated with lower risk for developing posttraumatic brain injury attention-deficit/hyperactivity disorder (hazard ratio 0.33; 95% CI, 0.17 to 062), whereas family dysfunction was associated with increased risk (hazard ratio 4.24; 95% CI, 1.91 to 9.43) in the traumatic brain injury group but not in the orthopedic injury group (hazard ratio 1.32; 95% CI, 0.36 to 4.91). These findings underscore the need for long-term monitoring of postinjury attention problems. They also emphasize the interaction between injury and environmental factors in developing attention-deficit/hyperactivity disorder in children with traumatic brain injury. *(Summary: Laszlo Vutskits. Image: J. P. Rathmell.)*

Take home message: A substantial proportion of children develop attention-deficit/hyperactivity disorder within 10 yr after traumatic brain injury. Identification of environmental factors that may interact with injury characteristics, such as family dysfunction, is important when planning clinical follow-up strategies in these populations.

Accurate pain reporting training diminishes the placebo response: Results from a randomised, double-blind, crossover trial. PLoS ONE 2018; 13:e0197844.

The rate of failed clinical trials for candidate analgesic molecules, including antidepressants and other drugs, is very high. A major contributor to this high rate of trial failure is believed to be the high rate of response to placebo treatments when assessed using subjective outcome measures. In this study, the authors attempted to reduce placebo responses by providing pain reporting training before randomization in a study designed to compare efficacy of pregabalin *versus* placebo for treatment of painful diabetic neuropathy with 24-h average pain intensity as the primary outcome. Up to four training sessions were conducted in which participants were exposed to standardized painful pressure stimuli. After randomization and treatment in the evaluation stage of the trial, it was observed that placebo responses were diminished (mean difference ± SD, –1.19 ± 1.73; $P = 0.02$), while responses to the active medication, pregabalin, were unchanged among those who received pain reporting training. These results suggest that pain reporting training may improve the power of analgesic trials and increase the number of positive studies. *(Summary: J. David Clark. Image: ©ThinkStock.)*

Take home message: Pain reporting training may remove some positive placebo responses and improve the power of analgesic trials to detect treatment-specific improvements in pain.

Postoperative ERAS interventions have the greatest impact on optimal recovery: Experience with implementation of ERAS across multiple hospitals. Ann Surg 2018; 267:992–7.

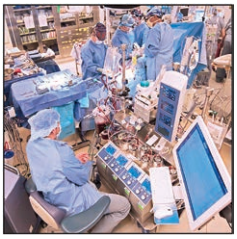
The specific components of enhanced recovery after surgery that are associated with the greatest improvements in patient outcomes are unknown. This study was designed to address this issue in 15 academic medical centers by identifying compliance to the protocol and determining those components of the enhanced recovery after surgery program that were associated with optimal recovery (discharge within 5 days after surgery; no major complications, hospital readmissions, or mortality). Among the 2,876 patients enrolled, only 20% had compliance with all components of the protocol. Interestingly, the least compliant component of the protocol was for postoperative interventions (40%). However, compliance with the postoperative component of the protocol (early enteral feeding and ambulation, chewing gum 3 times per day, and reductions in Foley catheters) was associated with optimal recovery (relative risk 2.12; 95% CI, 1.81 to 2.47). Regardless of whether the surgery was performed as a laparoscopic or open procedure, enhanced recovery after surgery was associated with improved outcomes ($P < 0.001$). Postoperative compliance with enhanced recovery after surgery protocol was associated with optimal recovery. *(Summary: Deborah J. Culley. Image: ©ThinkStock.)*

Take home message: Compliance with the postoperative component of an enhanced recovery after surgery protocol was associated with optimal recovery.

Association of mental health conditions and treatments with long-term opioid analgesic receipt among adolescents. JAMA Pediatr 2018; 172:423–30.

Long-term opioid therapy is common in adults with mental health comorbidities. In this study, the authors used a cohort of more than one million commercially insured adolescents receiving opioids between January 1, 2003, and December 31, 2014, to investigate whether long-term opioid therapy is more likely in adolescents with preexisting mental health conditions, as identified in the medical record, when compared to adolescents without those conditions. They found that the cumulative incidence of long-term opioid therapy was 3.0 (95% CI, 2.8 to 3.1) per 1,000 recipients at 3 yr after first opioid receipt. Importantly, all preexisting mental health conditions were strongly associated with higher rates of long-term opioid therapy and included an adjusted hazard ratio of 1.73 (95% CI, 1.54 to 1.95) for attention-deficit/hyperactivity disorder and 8.90 (95% CI, 5.85 to 13.54) for opioid use disorder. *(Summary: Laszlo Vutskits. Image: ©ThinkStock.)*

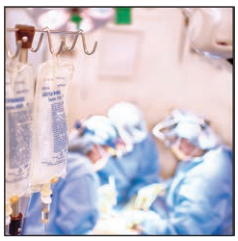
Take home message: Long-term opioid consumption is very rare among adolescent opioid recipients. However, the incidence is much higher in the subgroup of this population with preexisting mental health conditions and treatments.



High-target versus low-target blood pressure management during cardiopulmonary bypass to prevent cerebral injury in cardiac surgery patients: A randomized controlled trial. Circulation 2018; 137:1770–80.

Overt stroke occurs in 1 to 2% of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) while silent infarction is found in up to 50%. The role of perfusion pressure during CPB on these outcomes is unclear. In the Perfusion Pressure Cerebral Infarcts trial, patients were randomized to a high (70 to 80 mmHg, n = 99) or low (40 to 50 mmHg, n = 98) mean arterial pressure target during CPB. Pump flow was fixed at 2.4 $l \cdot min^{-1} \cdot m^{-2}$, phenylephrine boluses up to 2.0 mg followed by a 0.4 mcg $\cdot kg^{-1} \cdot min^{-1}$ infusion of norepinephrine was allowed during CPB with normothermia (temperature more than 36.5°C). No vasodilators were used in the low target group. The primary outcome was change in volume of ischemic cerebral lesions preoperatively to postoperative day 3 to 6. There was no difference in the primary outcome between the two groups (infarct volumes 25 mm^3 in the low group and 29 mm^3 in the high group; difference estimate 0; 95% CI, −25 to 0.028; P = 0.99). No significant differences were noted in the frequency of severe adverse events. *(Summary: Martin J. London. Image: J. P. Rathmell.)*

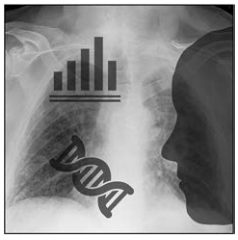
Take home message: Targeting a higher *versus* lower mean arterial pressure during normothermic CPB did not affect the volume of new cerebral infarcts.



Effects of intraoperative fluid management on postoperative outcomes: A hospital registry study. Ann Surg 2018; 267:1084–92.

Questions remain regarding optimal intraoperative fluid management. This study describes a retrospective analysis of 92,094 patients who underwent noncardiac surgery between 2007 and 2014 under general anesthesia and investigated whether the total volume of fluid administered was a predictor of 30-day mortality (primary outcome). When compared to patients in the moderately restrictive range (more than 900 to 1,100 ml), patients in the restrictive (less than 900 ml; hazard ratio 1.41; 95% CI, 1.03 to 1.93; P = 0.03) and liberal (more than 2,700 ml; hazard ratio 1.65; 95% CI, 1.04 to 2.00) fluid management range had a higher 30-day mortality. For the secondary outcomes, respiratory complications were greater in the liberal fluid management group when compared to patients in the moderately restrictive range (hazard ratio 1.27; 95% CI, 1.08 to 1.48; P = 0.003), whereas for acute kidney injury the risk was lowest in the moderately liberal group (more than 1,750 to 2,700 ml) and highest in patients in both the restrictive (hazard ratio 1.66; 95% CI, 1.37 to 2.01; P < 0.001) and liberal (hazard ratio 1.29; 95% CI, 1.14 to 1.46; P < 0.001) fluid administration groups. *(Summary: Deborah J. Culley. Image: J. P. Rathmell.)*

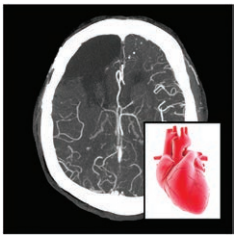
Take home message: Overly zealous or restrictive intraoperative fluid administration may increase the risk of 30-day mortality.



Integration of multi-omics datasets enables molecular classification of COPD. Eur Respir J 2018; 51:1701930.

Diagnosis of chronic obstructive pulmonary disease (COPD) is currently driven by symptoms and lung function testing. A number of factors, including multiple etiologies, genetic predisposition, developmental factors, and genetic predisposition lead to a large number of COPD subphenotypes. While clinical characteristics are similar within such a subgroup, molecular aspects may vary and may preclude proper diagnosis and targeted therapy. The primary objective of this study was to determine whether a large-scale data analysis would increase the accuracy of molecular classifications of COPD. Omics data, including messenger RNA, micro RNA, proteomes, and metabolomes from pulmonary and serum samples from 52 female subjects (12 COPD, 20 healthy, 20 smokers) were collected. Data were integrated using similarity network fusion. The results clearly demonstrate that integration of five to seven omics data blocks allow correct classification of COPD patients. A combination of multiple molecular biomarkers (micro RNA, proteomes, metabolomes, and eicosanoids) and multiple sampling locations including bronchoalveolar lavage and serum datasets were necessary to reach more than 95% accuracy of prediction. *(Summary: Beatrice Beck-Schimmer. Illustration: J. P. Rathmell.)*

Take home message: This study highlights a role for utilization of multiple biomarkers in complex diseases such as COPD that may lead to enhanced targeted therapy.



Association of surgical left atrial appendage occlusion with subsequent stroke and mortality among patients undergoing cardiac surgery. JAMA 2018; 319:2116–26.

Surgical occlusion of the left atrial appendage during cardiac surgery is commonly performed in patients with preexisting atrial fibrillation. Using administrative data from the OptumLabs Data Warehouse covering private insurance or Medicare Advantage patients between January 2009 and March 2017, the authors identified 75,782 patients undergoing first-time coronary artery bypass graft or valve surgery and whether a left atrial appendage occlusion had been performed (5.8%). The primary outcomes were stroke and all-cause mortality. Propensity score matching (1:1) was used to balance patients on 76 dimensions stratified by history of previous atrial fibrillation at the time of surgery. In the 8,590 matched patients, left atrial appendage occlusion was associated with reduced risk of stroke (hazard ratio 0.73; 95% CI, 0.56 to 0.96; $P = 0.03$) and all-cause mortality (hazard ratio 0.71; 95% CI, 0.60 to 0.84; $P < 0.001$). In the 25% of patients without a previous history of atrial fibrillation, the primary outcomes were not significant but a significant increase in risk of postoperative atrial fibrillation was noted (hazard ratio 1.46; 95% CI, 1.22 to 1.73; $P = < 0.001$). *(Summary: Martin J. London. Image: J. P. Rathmell [Heart Illustration ©ThinkStock].)*

Take home message: Left atrial appendage occlusion during cardiac surgery may be associated with a decreased risk of stroke and all-cause mortality.

Child mortality in England compared with Sweden: A birth cohort study. Lancet 2018; 391:2008–18.

Important differences in child mortality persist within different countries of Europe. In this birth cohort study, the authors aimed to establish the extent to which adverse birth characteristics (birthweight, gestational age, congenital anomalies, sex) and socioeconomic factors (maternal age and socioeconomic status) contribute to the high child mortality observed in England when compared to Sweden. The authors analyzed mortality using nationally representative cohorts between 2003 and 2012 from the Hospital Episode Statistics in England and the Swedish Medical Birth Register. The unadjusted hazard ratios of mortality for England compared to Sweden were 1.66 (95% CI, 1.53 to 1.81) at 2 to 27 days, 1.59 (95% CI, 1.47 to 1.71) at 28 to 364 days, and 1.27 (95% CI, 1.15 to 1.40) at 1 to 4 yr. Before 1 month of age, 77% of excess risk of death in England was related to adverse birth characteristics and 3% to socioeconomic factors. Between 1 month and 1 yr of age, 68% of excess risk of death in England was explained by adverse birth characteristics and 11% by socioeconomic factors. The risk of child mortality in England relative to Sweden declined by 70 to 80% when adjusted for birth characteristics in the two populations. At 1 to 4 yr of age, the differences in mortality were negligible between the two countries. *(Summary: Laszlo Vutskits. Image: ©ThinkStock.)*

Take home message: Reducing the prevalence of low birth weight, prematurity, and congenital anomalies could largely reduce child mortality in Europe. This could be achieved through implementing universal programs to improve the health of women and to reduce health inequalities before and during pregnancy.