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Editor’s Note: On February 15, 2008, after this article had gone to press, the Office for Human Research Protections (OHRP) issued a statement (www.hhs.gov/ohrp/news/recentnews.html#20080215) expressing its new conclusion that Michigan hospitals may continue to implement the checklist developed by Pronovost et al. “without falling under regulations governing human subjects research,” since it “is now being used . . . solely for clinical purposes, not medical research or experimentation.” OHRP further stated that in the research phase, the project “would likely have been eligible for both expedited IRB review and a waiver of the informed consent requirement.” About 80,000 catheter-related blood stream . . .


With health care once again a leading issue in a presidential race, candidates have offered plans for controlling spiraling costs while enhancing the quality of care. A popular component of such plans involves greater promotion of preventive health measures. The first element in Hillary Clinton’s plan is to “focus on prevention: wellness not sickness.” John Edwards has stated that “studies after study shows that primary and preventive care greatly reduces future health care costs, as well as increasing patients’ health.” Mike Huckabee has said that a focus on prevention “would save countless lives, pain and suffering by the victims of . . .


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A phase 2 clinical trial of rituximab in the treatment of multiple sclerosis reported by Hauser et al. in this issue of the Journal (pages 676-688) provides important insights into the biology of the disease. The study showed that rituximab reduces disease activity in patients with relapsing-remitting multiple sclerosis; patients treated with rituximab had a substantial reduction in the number of new relapses and the number of contrast-enhancing lesions detected on magnetic resonance imaging (MRI). It is generally accepted that the MRI equivalent of an acute relapse is the disruption of the blood–brain barrier evidenced by increased signal after the . . .

ORIGINAL ARTICLES


There is increasing evidence that B lymphocytes are involved in the pathogenesis of multiple sclerosis, and they may be a therapeutic target. Rituximab, a monoclonal antibody, selectively targets and depletes CD20+ B lymphocytes. In a phase 2, double-blind, 48-week trial involving 104 patients with relapsing-remitting multiple sclerosis, we assigned 69 patients to receive 1000 mg of intravenous rituximab and 35 patients to receive placebo on days 1 and 15. The primary end point was the total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse. As compared with patients who received placebo, patients who received rituximab had reduced counts of total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 (P<0.001) and of total new gadolinium-enhancing lesions over the same period (P<0.001); these results were sustained for 48 weeks (P<0.001). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5% vs. 34.3%, P=0.02) and week 48 (20.3% vs. 40.0%, P=0.04). More patients in the rituximab group than in the placebo group had adverse events within 24 hours after the first infusion, most of which were mild-to-moderate events; after the second infusion, the numbers of events were similar in the two groups. A single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. This trial was not designed to assess long-term safety or to detect uncommon adverse events. The data provide evidence of B-cell involvement in the pathophysiology of relapsing-remitting multiple sclerosis.

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Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated amino transferase levels, serum HEV RNA, and histologic features of chronic hepatitis. The time from transplantation to diagnosis was significantly shorter and the total counts of lymphocytes and of CD2, CD3, and CD4 T cells were significantly lower in patients in whom chronic disease developed.

Morley, C.J., Peter G. Davis, Lex W. Doyle, Luc P. Brion, Jean-Michel Hascoet, John B. Carlin. (2008). Nasal CPAP or intubation at birth for very preterm infants. New England Journal of Medicine, 358 (7), 700-708. Bronchopulmonary dysplasia is associated with ventilation and oxygen treatment. This randomized trial investigated whether nasal continuous positive airway pressure (CPAP), rather than intubation and ventilation, shortly after birth would reduce the rate of death or bronchopulmonary dysplasia in very preterm infants. We randomly assigned 610 infants who were born at 25- to 28-weeks' gestation to CPAP or intubation and ventilation at 5 minutes after birth. We assessed outcomes at 28 days of age, at 36 weeks' gestational age, and before discharge. At 36 weeks' gestational age, 33.9% of 307 infants who were assigned to receive CPAP had died or had bronchopulmonary dysplasia, as compared with 38.9% of 303 infants who were assigned to receive intubation (odds ratio favoring CPAP, 0.80; 95% confidence interval [CI], 0.58 to 1.12; P=0.19). At 28 days, there was a lower risk of death or need for oxygen therapy in the CPAP group than in the intubation group (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). There was little difference in overall mortality. In the CPAP group, 46% of infants were intubated during the first 5 days, and the use of surfactant was halved. The incidence of pneumothorax was 9% in the CPAP group, as compared with 3% in the intubation group (P<0.001). There were no other serious adverse events. The CPAP group had fewer days of ventilation. In infants born at 25- to 28-weeks' gestation, early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, as compared with intubation. Even though the CPAP group had more incidences of pneumothorax, fewer infants received oxygen at 28 days, and they had fewer days of ventilation.


Aprotinin (Trasylol) is used to mitigate bleeding during coronary-artery bypass grafting (CABG). Accumulating evidence suggests that this practice increases mortality. Using electronic administrative records of the Premier Perspective Comparative Database, we studied hospitalized patients with operating-room charges for the use of aprotinin (33,517 patients) or aminocaproic acid (44,682 patients) on the day CABG was performed. We tabulated the numbers of patients with a hospital-discharge status of death and performed three types of analyses: a multivariable logistic-regression analysis (primary analysis); propensity-score matching in the highly selected subgroup of patients who received full amounts of the study drug, who underwent CABG by surgeons who performed 50 or more CABG surgeries during the study period, and for whom information on 10 additional covariates was available because the surgery occurred on hospital day 3 or later; and an instrumen
tal-variable analysis of data from patients whose surgeons showed a strong preference for one of the two study drugs. In all, 1512 of the 33,517 aprotinin recipients (4.5%) and 1101 of the 44,682 aminocaproic acid recipients (2.5%) died. After adjustment for 41 characteristics of patients and hospitals, the estimated risk of death was 64% higher in the aprotinin group than in the aminocaproic acid group (relative risk, 1.64; 95% confidence interval [CI], 1.50 to 1.78). In the first 7 days after surgery, the adjusted relative risk of in-hospital death in the aprotinin group was 1.78 (95% CI, 1.56 to 2.02). The relative risk in a propensity-score–matched analysis was 1.32 (95% CI, 1.08 to 1.63). In the instrumental-variable analysis, the use of aprotinin was found to be associated with an excess risk of death of 1.59 per 100 patients (95% CI, 0.14 to 3.04). Postoperative revascularization and dialysis were more frequent among recipients of aprotinin than among recipients of aminocaproic acid.


Aprotinin has recently been associated with adverse outcomes in patients undergoing cardiac surgery. We reviewed our experience with this agent in patients undergoing cardiac surgery at Duke University Medical Center. We retrieved data on 10,275 consecutive patients undergoing surgical coronary revascularization at Duke between January 1, 1996, and December 31, 2005. We fit data to a logistic-regression model predicting each patient’s likelihood of receiving aprotinin on the basis of preoperative characteristic and to models pre-
dicting long-term survival (up to 10 years) and decline in renal function, as measured by increases in serum creatinine levels. A total of 1343 patients (13.2%) received aprotinin, 6776 patients (66.8%) received aminocaproic acid, and 2029 patients (20.0%) received no antifibrinolytic therapy. All patients underwent coronary-artery bypass grafting, and 1181 patients (11.5%) underwent combined coronary-artery bypass grafting and valve surgery. In the risk-adjusted model, survival was worse among patients treated with aprotinin, with a main-effects hazard ratio for death of 1.32 (95% confidence interval [CI], 1.12 to 1.55) for the comparison with patients receiving no antifibrinolytic therapy (P=0.003) and 1.27 (95% CI, 1.10 to 1.46) for the comparison with patients receiving aminocaproic acid (P=0.004). As compared with the use of aminocaproic acid or no antifibrinolytic agent, aprotinin use was also associated with a larger risk-adjusted increase in the serum creatinine level (P<0.001) but not with a greater risk-adjusted incidence of dialysis (P=0.56).


Drug-eluting stents reduce restenosis in coronary arteries, but clinical trials have failed to prove their efficacy in peripheral arteries. We investigated the use of paclitaxel-coated angioplasty balloons and paclitaxel dissolved in the angiographic contrast medium during angioplasty of the leg. In a small, multicenter trial, we randomly assigned 154 patients with stenosis or occlusion of a femoropopliteal artery to treatment with standard balloon catheters coated with paclitaxel, uncoated balloons with paclitaxel dissolved in the contrast medium, or uncoated balloons without paclitaxel (control). The primary endpoint was late lumen loss at 6 months. The mean (±SD) age of the patients was 68±8 years; 24% were smokers, and 49% had diabetes. Twenty-seven percent of the lesions were total occlusions, and 36% were restenotic lesions. The mean lesion length was 7.4±6.5 cm. There were no significant differences in baseline characteristics between the groups. There were no adverse events attributed to the paclitaxel-coated balloons. At 6 months, the mean late lumen loss was 1.7±1.8 mm in the control group, as compared with 0.4±1.2 mm (P<0.001) in the group treated with paclitaxel-coated balloons and 2.2±1.6 mm (P=0.11) in the group treated with paclitaxel in the contrast medium. The rate of revascularization of target lesions at 6 months was 20 of 54 (37%) in the control group, 2 of 48 (4%) in the group treated with paclitaxel-coated balloons (P<0.001 vs. control), and 15 of 52 (29%) in the group treated with paclitaxel in the contrast medium (P=0.41 vs. control); at 24 months, the rate increased to 28 of 54 (52%), 7 of 48 (15%), and 21 of 52 (40%), respectively. Use of paclitaxel-coated angioplasty balloons during percutaneous treatment of femoropopliteal disease is associated with significant reductions in late lumen loss and target-lesion revascularization.


Surgical treatment for spinal stenosis is widely performed, but its effectiveness as compared with nonsurgical treatment has not been shown in controlled trials. Surgical candidates with a history of at least 12 weeks of symptoms and spinal stenosis without spondylolisthesis (as confirmed on imaging) were enrolled in either a randomized cohort or an observational cohort at 13 U.S. spine clinics. Treatment was decompressive surgery or usual nonsurgical care. The primary outcomes were measures of bodily pain and physical function on the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) and the modified Oswestry Disability Index at 6 weeks, 3 months, 6 months, and 1 and 2 years. A total of 289 patients were enrolled in the randomized cohort, and 365 patients were enrolled in the observational cohort. At 2 years, 67% of patients who were randomly assigned to surgery had undergone surgery, whereas 43% of those who were randomly assigned to receive nonsurgical care had also undergone surgery. Despite the high level of nonadherence, the intention-to-treat analysis of the randomized cohort showed a significant treatment effect favoring surgery on the SF-36 scale for bodily pain, with a mean difference in change from baseline of 7.8 (95% confidence interval, 1.5 to 14.1); however, there was no significant difference in scores on physical function or on the Oswestry Disability Index.


Autism spectrum disorder is a heritable developmental disorder in which chromosomal abnormalities are thought to play a role. As a first component of a genomewide association study of families from the Autism Genetic Resource Exchange (AGRE), we used two novel algorithms to search for recurrent copy-number variations in genotype data from 751 multiplex families with autism. Specific recurrent de novo events were further evaluated in clinical-testing data from Children’s
A 43-year-old woman presented with pain, swelling, and stiffness in the hands and feet; she reported having had the symptoms for the previous 5 years. Possible rheumatoid arthritis had been diagnosed and was treated with nonsteroidal antiinflammatory agents and prednisone. Pulmonary sarcoidosis had been diagnosed 14 years earlier. On examination, the patient had dactylitis of the second and third fingers of the right hand and the fifth finger of the left hand. The second and fourth toes of both feet were swollen. The erythrocyte sedimentation rate and level of angiotensin-converting enzyme were elevated. Test results for rheumatoid factor and anti-cyclic . . .


A 59-year-old man with a medical history of hypertension, hyperlipidemia, and coronary artery disease presented with transient, painless visual obscuration in the left eye, and he was referred for retinal evaluation. Two months earlier, he had undergone placement of a stent in the left carotid artery for severe stenosis. He was receiving antiplatelet therapy. Two years earlier, an eye examination had been unremarkable. Retinal examination of the left eye showed multiple, tiny refractile retinal arteriolar cholesterol emboli and a saddle embolus superior to the optic nerve (Panel A, arrow). Two months later, repeat examination showed an increase in the number . . .

REVIEW ARTICLE


Acute lower respiratory tract infections are a persistent and pervasive public health problem. They cause a greater burden of disease worldwide than human immunodeficiency virus infection, malaria, cancer, or heart attacks.1 In the United States, they cause more disease and death than any other infection, and there has been little change in mortality due to respiratory tract infection for more than five decades.1,2 The outcome of an acute lower respiratory tract infection depends on the virulence of the organism and the inflammatory response in the lung. When small numbers of low-virulence microbes are deposited in the lungs, an effective . . .

IMAGE IN CLINICAL MEDICINE


A 43-year-old woman presented with a 10-month history of an urticarial rash induced by cold, particularly when she was swimming. A clinical diagnosis of cold-induced urticaria was made. The diagnosis was confirmed by inducing an urticarial weal with an ice cube placed on the forearm for 5 minutes (Panel A). Initially, only erythema was apparent, but as the skin warmed, a typical urticarial lesion developed (Panel B and close-up view in Panel C), gradually filling in from the periphery of the cooled area (Panel D). The patient was treated with daily nonsedating antihistamines and was warned of the risk of . . .
Dr. Nancy Cibotti-Granof (Medicine): A 46-year-old woman with end-stage renal disease was seen by a rheumatology consultant because of stiffness of her joints and skin. The patient had been well except for mild asthma until 7 years earlier, when group A streptococcal pneumonia developed, complicated by septic shock, with acute respiratory distress syndrome; septic emboli to the lungs, brain, and kidney; renal failure requiring dialysis; flaccid quadriplegia; and coma. On the 25th day after initial admission to another hospital, she was transferred to this hospital while she was receiving mechanical ventilation. As part of the evaluation during admission, computed tomography . . .


An 18-month-old girl was transferred from a hospital in China to the Shriners Hospital for Children in Boston for management of a life-threatening neck contracture. The child had been well until 12 months of age, when she sustained a burn to the face and upper body from boiling cooking oil. She was transferred from her rural village to the burn unit of a regional hospital, where a tracheotomy was performed to protect the airway; the wounds eventually healed with topical care. The tracheotomy tube was removed, and the child was discharged from the hospital. In the ensuing 4 months, . . .

CLINICAL PRACTICE


This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations. A 72-year-old woman with hypertension presents with a 4-month history of lower back discomfort that radiates to both buttocks and lateral thighs. Previously, she had walked 2 miles (3.2 km) a day; now she has difficulty walking 2 blocks and standing up for more than 15 minutes at a time. Her physical examination is notable only for a slightly stooped posture and . . .