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PERSPECTIVES


Earlier this year, I was named the first female dean of the Duke University School of Medicine, an event that National Public Radio summed up in the headline: “Andrews Makes History at Duke Med School.” Why should the appointment of a woman dean still be big news in 2007? Perhaps because, with a few localized exceptions, there has been little change since the 1970s in the barriers to women’s full participation in academic medicine. I happen to believe strongly that diversifying all levels of academic medicine is not only politically correct, it is also the way to make our . . .


Colleagues offered congratulations when Mike and Anya announced that they were expecting a baby — due a few months before their expected graduation from residency programs in radiology and family medicine. Both had plum jobs lined up across the country, where grandparents could help with child care. Mike’s radiology program director told him he could take 8 weeks of parental leave and that the American Board of Radiology would exempt him from making up this time. Mike’s fellow residents were relieved that the extra on-call responsibility would not be distributed among them but rather would be covered by moonlighters. Unfortunately, . . .


The long-term fiscal balance of the United States will be determined primarily by the future rate of growth of health care costs, as we have recently noted.1 If costs per enrollee in Medicare and Medicaid continued to grow at the same rate as they have over the past four decades, federal spending on those two programs alone would increase from about 5% of the gross domestic product today to about 20% by 2050 — roughly the share of the economy now accounted for by the entire federal budget. Compounding the challenge for policymakers is the difficulty of controlling federal spending . . .
The cost of treating human immunodeficiency virus (HIV) infection is decreasing. Nonetheless, tenofovir–emtricitabine–efavirenz, the standard first-line treatment in North America and Europe, is prescribed rarely in low- and middle-income countries. The lowest annual cost for a generic stavudine–lamivudine–nevirapine, an effective but less safe alternative that has been largely abandoned in Western countries (see Figure 1).1

ABSTRACTS


Maintenance of long-term antibody responses is critical for protective immunity against many pathogens. However, the duration of humoral immunity and the role played by memory B cells remain poorly defined. We performed a longitudinal analysis of antibody titers specific for viral antigens (vaccinia, measles, mumps, rubella, varicella–zoster virus, and Epstein–Barr virus) and nonreplicating antigens (tetanus and diphtheria) in 45 subjects for a period of up to 26 years. In addition, we measured antigen-specific memory B cell frequencies to their corresponding serum antibody levels. Antiviral antibody responses were remarkably stable, with half-lives ranging from an estimated 50 years for varicella–zoster virus to more than 200 years for other viruses such as measles and mumps. Antibody responses against tetanus and diphtheria antigens waned more quickly, with estimated half-lives of 11 years and 19 years, respectively. B-cell memory was long-lived, but there was no significant correlation between peripheral memory B-cell numbers and antibody levels for five of the eight antigens tested. These studies provide quantitative analysis of serologic memory for multiple antigens in subjects followed longitudinally over the course of more than one decade. In cases in which multiple exposures or repeated vaccinations were common, memory B-cell numbers did not correlate with antibody titers. This finding suggests that peripheral memory B cells and antibody-secreting plasma cells may represent independently regulated cell populations and may play different roles in the maintenance of protective immunity.


The cost of treating human immunodeficiency virus (HIV) infection is decreasing. Nonetheless, tenofovir–emtricitabine–efavirenz, the standard first-line treatment in North America and Europe, is prescribed rarely in low- and middle-income countries. The lowest annual cost for a generic stavudine–lamivudine–nevirapine, an effective but less safe alternative that has been largely abandoned in Western countries (see Figure 1).1


Treatment of early-stage Hodgkin’s disease is usually tailored in line with prognostic factors that allow for reductions in the amount of chemotherapy and extent of radiotherapy required for a possible cure. From 1993 to 1999, we identified 1538 patients (age, 15 to 70 years) who had untreated stage I or II supradiaphragmatic Hodgkin’s disease with favorable prognostic features (the H8–F trial) or unfavorable features (the H8–U trial). In the H8–F trial, we compared three cycles of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) combined with doxorubicin, bleomycin, and vinblastine (ABV) plus involved-field radiotherapy with subtotal nodal radiotherapy alone (reference group). In the H8–U trial, we compared three regimens: six cycles of MOPP–ABV plus involved-field radiotherapy with subtotal nodal radiotherapy alone (reference group), four cycles of MOPP–ABV plus involved-field radiotherapy, and four cycles of MOPP–ABV plus subtotal nodal radiotherapy. The median follow-up was 92 months. In the H8–F trial, the estimated 5-year event-free survival rate was significantly higher after three cycles of MOPP–ABV plus involved-field radiotherapy than after subtotal nodal radiotherapy alone (98% vs. 74%, P<0.001). The 10-year overall survival estimates were 97% and 92%, respectively (P=0.001). In the H8–U trial, the estimated 5-year event-free survival rates were similar in the three treatment groups: 84% after six cycles of MOPP–ABV plus involved-field radiotherapy, 88% after four cycles of MOPP–ABV plus involved-field radiotherapy, and 87% after four cycles of MOPP–ABV plus subtotal nodal radiotherapy. The 10-year overall survival estimates were 88%, 85%, and 84%, respectively. Chemotherapy plus involved-field
radiotherapy should be the standard treatment for Hodgkin’s disease with favorable prognostic features. In patients with unfavorable features, four courses of chemotherapy plus involved-field radiotherapy should be the standard treatment.


The evolutionarily conserved 18-glycosyl-hydrolase family contains true chitinases and chitinase-like proteins that lack enzymatic activity. Acidic mammalian chitinase has recently been associated with animal models of asthma. The related chitinase-like protein, YKL-40 (also called human cartilage glycoprotein 39 [HCgp-39] and chitinase 3-like 1), can be readily measured in the serum. However, its relationship to asthma has not been evaluated. We quantified serum YKL-40 levels in three cohorts of patients with asthma — one recruited from the patient population at Yale University, one from the University of Paris, and one from the University of Wisconsin — as well as in controls from the surrounding communities. In the Paris cohort, immunohistochemical analysis and morphometric quantitation were used to evaluate the locus of expression of YKL-40 in the lung. The clinical characteristics of the patients with high serum or lung YKL-40 levels were also evaluated. Serum YKL-40 levels were significantly elevated in patients with asthma as compared with controls. In the Paris cohort, lung YKL-40 levels were elevated and were correlated with circulating YKL-40 levels (r=0.55, P<0.001) and with airway remodeling (measured as the thickness of the subepithelial basement membrane) (r=0.51, P=0.003). In all three cohorts, serum YKL-40 levels correlated positively with the severity of asthma and inversely with the forced expiratory volume in 1 second. Patients with elevated levels of YKL-40 had significantly more frequent rescue-inhaler use, greater oral corticosteroid use, and a greater rate of hospitalization than patients with lower levels. YKL-40 is found in increased quantities in the serum and lungs in a subgroup of patients with asthma, in whom expression of chitinase in both compartments correlates with the severity of asthma. The recovery of YKL-40 from these patients indicates either a causative or a sentinel role for this molecule in asthma.


Cetuximab, an IgG1 chimeric monoclonal antibody against epidermal growth factor receptor (EGFR), has activity against colorectal cancers that express EGFR. From December 2003 to August 2005, 572 patients who had colorectal cancer expressing immunohistochemically detectable EGFR and who had been previously treated with a fluoropyrimidine, irinotecan, and oxaliplatin or had contraindications to treatment with these drugs underwent randomization to an initial dose of 400 mg of cetuximab per square meter of body-surface area followed by a weekly infusion of 250 mg per square meter plus best supportive care (287 patients) or best supportive care alone (285 patients). The primary end point was overall survival. In comparison with best supportive care alone, cetuximab treatment was associated with a significant improvement in overall survival (hazard ratio for death, 0.77; 95% confidence interval [CI], 0.64 to 0.92; P=0.005) and in progression-free survival (hazard ratio for disease progression or death, 0.68; 95% CI, 0.57 to 0.80; P<0.001). These benefits were robust after adjustment in a multivariable Cox proportional-hazards model. The median overall survival was 6.1 months in the cetuximab group and 4.6 months in the group assigned to supportive care alone. Partial responses occurred in 23 patients (8.0%) in the cetuximab group but in none in the group assigned to supportive care alone (P<0.001); the disease was stable in an additional 31.4% of patients assigned to cetuximab and in 10.9% of patients assigned to supportive care alone (P<0.001). Quality of life was better preserved in the cetuximab group, with less deterioration in physical function and global health status scores (both P<0.05). Cetuximab treatment was associated with a characteristic rash; a rash of grade 2 or higher was strongly associated with improved survival (hazard ratio for death, 0.33; 95% CI, 0.22 to 0.50; P<0.001). The incidence of any adverse event of grade 3 or higher was 78.5% in the cetuximab group and 59.1% in the group assigned to supportive care alone (P<0.001). Cetuximab improves overall survival and progression-free survival and preserves quality-of-life measures in patients with colorectal cancer in whom other treatments have failed.

Congenital heart disease in newborns is associated with global impairment in development. We characterized brain metabolism and microstructure, as measures of brain maturation, in newborns with congenital heart disease before they underwent heart surgery. We studied 41 term newborns with congenital heart disease — 29 who had transposition of the great arteries and 12 who had single-ventricle physiology — with the use of magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) before cardiac surgery. We calculated the ratio of N-acetylaspartate to choline (which increases with brain maturation), the ratio of lactate to choline (which decreases with maturation), average diffusivity (which decreases with maturation), and fractional anisotropy of white-matter tracts (which increases with maturation). We compared these findings with those in 16 control newborns of a similar gestational age. As compared with control newborns, those with congenital heart disease had a decrease of 10% in the ratio of N-acetylaspartate to choline (P=0.003), an increase of 28% in the ratio of lactate to choline (P=0.08), an increase of 4% in average diffusivity (P<0.001), and a decrease of 12% in white-matter fractional anisotropy (P<0.001). Preoperative brain injury, as seen on MRI, was not significantly associated with findings on MRS or DTI. White-matter injury was observed in 13 newborns with congenital heart disease (32%) and in no control newborns.


Bisphosphonate therapy is the current standard of care for the prevention and treatment of glucocorticoid-induced osteoporosis. Studies of anabolic therapy in patients who are receiving long-term glucocorticoids and are at high risk for fracture are lacking. In an 18-month randomized, double-blind, controlled trial, we compared teriparatide with alendronate in 428 women and men with osteoporosis (ages, 22 to 89 years) who had received glucocorticoids for at least 3 months (prednisone equivalent, 5 mg daily or more). A total of 214 patients received 20 μg of teriparatide once daily, and 214 received 10 mg of alendronate once daily. The primary outcome was the change in bone mineral density at the lumbar spine. Secondary outcomes included changes in bone mineral density at the total hip and in markers of bone turnover, the time to changes in bone mineral density, the incidence of fractures, and safety. At the last measurement, the mean (±SE) bone mineral density at the lumbar spine had increased more in the teriparatide group than in the alendronate group (7.2±0.7% vs. 3.4±0.7%, P<0.001). A significant difference between the groups was reached by 6 months (P<0.001). At 12 months, bone mineral density at the total hip had increased more in the teriparatide group. Fewer new vertebral fractures occurred in the teriparatide group than in the alendronate group (0.6% vs. 6.1%, P=0.004); the incidence of nonvertebral fractures was similar in the two groups (5.6% vs. 3.7%, P=0.36). Significantly more patients in the teriparatide group had at least one elevated measure of serum calcium. Among patients with osteoporosis who were at high risk for fracture, bone mineral density increased more in patients receiving teriparatide than in those receiving alendronate.


Methylxanthine therapy is commonly used for apnea of prematurity but in the absence of adequate data on its efficacy and safety. It is uncertain whether methylxanthines have long-term effects on neurodevelopment and growth. We randomly assigned 2006 infants with birth weights of 500 to 1250 g to receive either caffeine or placebo until therapy for apnea of prematurity was no longer needed. The primary outcome was a composite of death, cerebral palsy, cognitive delay (defined as a Mental Development Index score of <85 on the Bayley Scales of Infant Development), deafness, or blindness at a corrected age of 18 to 21 months. Of the 937 infants assigned to caffeine for whom adequate data on the primary outcome were available, 377 (40.2%) died or survived with a neurodevelopmental disability, as compared with 431 of the 932 infants (46.2%) assigned to placebo for whom adequate data on the primary outcome were available (odds ratio adjusted for center, 0.77; 95% confidence interval [CI], 0.64 to 0.93; P=0.008). Treatment with caffeine as compared with placebo reduced the incidence
of cerebral palsy (4.4% vs. 7.3%; adjusted odds ratio, 0.58; 95% CI, 0.39 to 0.87; \( P=0.009 \)) and of cognitive delay (33.8% vs. 38.3%; adjusted odds ratio, 0.81; 95% CI, 0.66 to 0.99; \( P=0.04 \)). The rates of death, deafness, and blindness and the mean percentiles for height, weight, and head circumference at follow-up did not differ significantly between the two groups. Caffeine therapy for apnea of prematurity improves the rate of survival without neurodevelopmental disability at 18 to 21 months in infants with very low birth weight.


Dual-antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications of acute coronary syndromes and percutaneous coronary intervention. To compare prasugrel, a new thienopyridine, with clopidogrel, we randomly assigned 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose), for 6 to 15 months. The primary efficacy end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key safety end point was major bleeding. The primary efficacy end point occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (hazard ratio for prasugrel vs. clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; \( P<0.001 \)). We also found significant reductions in the prasugrel group in the rates of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; \( P<0.001 \)), urgent target-vessel revascularization (3.7% vs. 2.5%; \( P<0.001 \)), and stent thrombosis (2.4% vs. 1.1%; \( P<0.001 \)). Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; \( P=0.03 \)). Also greater in the prasugrel group was the rate of life-threatening bleeding (1.4% vs. 0.9%; \( P=0.01 \)), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; \( P=0.23 \)) and fatal bleeding (0.4% vs. 0.1%; \( P=0.002 \)). In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups.

SPECIAL ARTICLE


Although issues related to patenting by faculty at academic medical centers have been the source of much controversy, there is little systematic evidence of the growth of these activities, their distribution among academic departments, and their relationship to faculty research efforts. We pooled data on medical school faculty, National Institutes of Health (NIH) grant activity, and patenting to examine changes in the propensity to apply for a patent during the period from 1981 through 2000 that was subsequently granted, the distribution of these activities among departments, and the relationships between patenting and variables associated with individual faculty members. These variables included sex, academic degree, years since the last academic degree was earned, patenting by departmental peers, and NIH funding history. In addition to basic descriptive statistics, we estimated Poisson regression models based on the number of patents a faculty member applied for as a function of these variables.

CLINICAL THERAPEUTICS


This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author’s clinical recommendations. An 82-year-old widowed woman with a history of recurrent unipolar major depression is referred to the electroconvulsive therapy (ECT) service of an academic medical center. During her illness, she has had four episodes of major depression consisting of periods . . .
**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 author's clinical recommendations. A previously healthy 45-year-old man presents with severe lower abdominal pain on the left side, which started 36 hours earlier. He has noticed mild, periodic discomfort in this region before but has not sought medical treatment. He reports nausea, anorexia, and vomiting associated with any oral intake. On physical examination, his temperature is 38.5°C and his heart rate is 110 beats per . . .

**REVIEW ARTICLES**


In 1967, Northway et al. first described a new chronic respiratory disease, bronchopulmonary dysplasia, that developed in premature infants exposed to mechanical ventilation and oxygen supplementation.1 Two decades later, the same authors found that clinically significant respiratory symptoms and functional abnormalities persisted into adolescence and early adulthood in a cohort of survivors of bronchopulmonary dysplasia,2 suggesting that lung injuries early in life may have lifelong consequences. Bronchopulmonary dysplasia is now the most common chronic lung disease of infancy in the United States. Today, newborns consistently survive at gestational ages of 23 to 26 weeks — 8 to 10 weeks younger . . .

**VIDEOS IN CLINICAL MEDICINE**


Incision and drainage is the primary therapy for cutaneous abscess management, as antibiotic treatment alone is inadequate for treating many of these loculated collections of infectious material. Most localized skin abscesses without associated cellulitis can be managed with simple incision and drainage and do not require antibiotic treatment. Cutaneous abscesses have been described in all areas of the body, but are most commonly found in the axillae, buttocks, and extremities. This outpatient procedure is appropriate for many office settings, as well as for urgent care and emergency department practice environments. Diagnosis of a skin abscess is the first step . . .

**IMAGES IN CLINICAL MEDICINE**


A 39-year-old healthy, female aerobics instructor presented with a 6-week history of flushing on the left side of her face, neck, and upper trunk after 40 minutes of vigorous exercise, with a strict demarcation at the midline (Panel A). After 30 to 40 minutes of rest, her color returned to normal. Magnetic resonance imaging of the chest revealed a large extrapleural mass in the apex of the right thoracic cavity (Panel B, arrow) that was compressing the sympathetic chain (Panel C, arrow). She underwent thoracotomy and excision of the tumor, which was attached to the second sympathetic ganglion. Histopathological examination . . .
showed alveolar filling with amorphous, granular, eosinophilic, periodic . . .


An 81-year-old woman with rheumatoid arthritis, Sjögren’s syndrome, and hypertension presented with swelling and pain in the area of the left heel, which had developed suddenly a week after a short course of levofloxacin for acute bronchitis. She reported neither trauma to the area nor any excessive physical activity before the pain began. Examination revealed an ecchymotic area around the left posterior heel and a moderately swollen calf. A defect was palpable in the lateral side of the Achilles’ tendon; the medial side was still intact. Movement of the ankle was limited by severe pain. Magnetic resonance imaging (MRI) of . . .

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL


Dr. Patrick S. Yachimski (Gastroenterology): A 30-year-old Moroccan man was admitted to this hospital because of fever, abdominal pain, and bloody diarrhea. The patient had a history of inflammatory bowel disease but was in his usual state of health until 14 days before admission, when his temperature rose to 39.4°C and a nonproductive cough, rhinorrhea, and myalgia developed. He took acetaminophen as needed for fever. After approximately 5 days, his symptoms resolved except for intermittent fever. Six days before admission, he began having cramping lower abdominal pain and bloody diarrhea three to four times per day. The pain was not . . .


Today, generic drugs account for 63% of all U.S. prescriptions for drugs (see Figure 1). Since generic drugs sell at substantially lower prices than their brand-name counterparts, they save consumers and purchasers of prescription drugs tens of billions of dollars per year. Moreover, their expanded role has been linked to an attenuation of overall price increases for prescription drugs. Between 2007 and 2010, roughly 110 drugs will lose their patent protection — including well-known products such as Norvasc (amlodipine), Imitrex (sumatriptan), Fosamax (alendronate), and Risperdal (risperidone). Estimates suggest that these 110 drugs are currently responsible for $50 billion a . . .


A 77-year-old right-handed man was admitted to the hospital because of the recent onset of pain in the ear, difficulty speaking, and altered mental status. The patient had been well until the day before admission, when he awoke in the morning with nasal congestion and pain on the right side of his face. That evening, pain, accompanied by drainage, developed in the right ear; his wife administered ciprofloxacin eardrops. The next morning, the temperature was 37.8°C. At about 9 a.m., the patient’s wife noted that his speech was slurred. The patient said he was tired and retired to nap. Ninety . . .