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Perspective

(As these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


In a ceremony held at the New York Public Library on June 26, 2006, Microsoft founder and global health philanthropist Bill Gates expressed his belief that “there is no reason we can’t cure the top 20 diseases.”

To achieve this ambitious objective, however, international health organizations will need to greatly expand their efforts, especially in low-income countries, to prevent and treat noncommunicable chronic diseases…


Globally, the prevalence of chronic, noncommunicable diseases is increasing at an alarming rate. About 18 million people die every year from cardiovascular disease, for which diabetes and hypertension are major predisposing factors. Propelling the upsurge in cases of diabetes and hypertension is the growing prevalence of overweight and obesity — which have, during the past decade, joined underweight, malnutrition, and infectious diseases as major health problems threatening the developing world. Today, more than 1.1 billion adults worldwide are overweight, and 312 million of them are obese. In addition, at least 155 million children worldwide are overweight or obese, according to the International Obesity Task Force…


Under ideal conditions, large clinical trials would be designed so that they satisfied the marketing needs of the pharmaceutical manufacturers that generally sponsor them and, at the same time, answered important clinical questions that may have a major influence on public health. In practice, however, alternative choices in trial design often favor one of these two goals. The choice of the reference treatment in active-comparator studies is an excellent example. For nonsteroidal antiinflammatory drugs (NSAIDs), which all relieve…


The rapidly increasing global burdens of cardiovascular disease and diabetes call for interventions that have a population-wide effect, as well as interventions that identify and protect individual patients who have a high risk of major adverse events. Such actions are especially needed in low-income and middle-income countries, which can ill afford the huge losses in human and financial resources that will result from unchecked development of clinical disease.1 Many drugs have been found to be highly effective in the primary or secondary prevention of cardiovascular disease. These include aspirin, angiotensin-converting–enzyme (ACE) inhibitors, statins, beta-blockers, and calcium-channel blockers…


Last September, a firestorm was ignited over drug-eluting stents when data were released showing an increase in the risk of late stent thrombosis. In response, the Food and Drug Administration (FDA) held an open meeting of its Circulatory System Devices Panel on December 7 and 8, 2006.1 The advisory group of about 20 academics and clinicians was sharply divided on the ramifications of the findings: a thoracic surgeon, on one side, argued that the new data necessitate a black-box warning; an interventional cardiologist, on the other side, said these data would barely change his practice. In part, the frequent…


Clinical practice guidelines are systematically developed statements that aim to help physicians and patients reach the best health care decisions. Good guidelines have many attributes, including validity, reliability, reproducibility, clinical applicability and flexibility, clarity, development through a multidisciplinary process, scheduled reviews, and documentation.1 More than 2000 guidelines are currently represented in the National Guideline Clearinghouse (www.guideline.gov). Medical specialty societies are their most common sponsors. Guidelines rely on both evidence and opinion; they are neither infallible nor a substitute for clinical judgment. They do, however, go beyond systematic reviews to recommend what should and should not be done…

Original Articles


Extensive mammographic density is associated with an increased risk of breast cancer and makes the detection of cancer by mammography difficult, but the influence of density on risk according to method of cancer detection is unknown. We carried out three nested case-control studies in screened populations with 1112 matched case-control pairs. We examined the association of the measured percentage of density in the baseline mammogram with risk of breast cancer, according to method of cancer detection, time since the initiation of screening, and age. As compared with women with density in less than 10% of the mammogram, women with density in 75% or more had an increased risk of breast cancer (odds ratio, 4.7; 95% confidence interval [CI], 3.0 to 7.4), whether detected by screening (odds ratio, 3.5; 95% CI, 2.0 to 6.2) or less than 12 months after a negative screening examination (odds ratio, 17.8; 95% CI, 4.8 to 65.9). Increased risk of breast cancer, whether detected by screening or other means, persisted for at least 8 years after study entry and was greater in younger than in older women. For women younger than the median age of 56 years, 26% of all breast cancers and 50% of cancers detected less than 12 months after a negative screening test were attributable to density in 50% or more of the mammogram.


Patients with neutropenia resulting from chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome are at high risk for difficult-to-treat and often fatal invasive fungal infections. In this randomized, multicenter study involving evaluators who were unaware of treatment assignments, we compared the efficacy and safety of posaconazole with those of fluconazole or itraconazole.
as prophylaxis for patients with prolonged neutropenia. Patients received prophylaxis with each cycle of chemotherapy until recovery from neutropenia and complete remission, until occurrence of an invasive fungal infection, or for up to 12 weeks, whichever came first. We compared the incidence of proven or probable invasive fungal infections during treatment (the primary end point) between the posaconazole and fluconazole or itraconazole groups; death from any cause and time to death were secondary end points. A total of 304 patients were randomly assigned to receive posaconazole, and 298 patients were randomly assigned to receive fluconazole (240) or itraconazole (58). Proven or probable invasive fungal infections were reported in 7 patients (2%) in the posaconazole group and 25 patients (8%) in the fluconazole or itraconazole group (absolute reduction in the posaconazole group, –6.6%; 95% confidence interval, –9.7 to –2.5%; P < 0.001), fulfilling statistical criteria for superiority. Significantly fewer patients in the posaconazole group had invasive aspergillosis (2 [1%] vs. 20 [7%]; P < 0.001). Survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole (P = 0.04). Serious adverse events possibly or probably related to treatment were reported by 19 patients (6%) in the posaconazole group and 6 patients (2%) in the fluconazole or itraconazole group (P = 0.01). The most common treatment-related adverse events were myelogenous leukemia and the myelodysplastic syndrome, posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival. There were more serious adverse events possibly or probably related to treatment in the posaconazole group. (ClinicalTrials.gov number, NCT00044486)


A single family has been described in which obesity results from a mutation in the leptin-receptor gene (LEPR), but the prevalence of such mutations in severe, early-onset obesity has not been systematically examined. We sequenced LEPR in 300 subjects with hyperphagia and severe early-onset obesity, including 90 probands from consanguineous families, and investigated the extent to which mutations cosegregated with obesity and affected receptor function. We evaluated metabolic, endocrine, and immune function in probands and affected relatives. Of the 300 subjects, 8 (3%) had nonsense or missense LEPR mutations — 7 were homozygotes, and 1 was a compound heterozygote. All missense mutations resulted in impaired receptor signaling. Affected subjects were characterized by hyperphagia, severe obesity, alterations in immune function, and delayed puberty due to hypogonadotropic hypogonadism. Serum leptin levels were within the range predicted by the elevated fat mass in these subjects. Their clinical features were less severe than those of subjects with congenital leptin deficiency. The prevalence of pathogenic LEPR mutations in a cohort of subjects with severe, early-onset obesity was 3%. Circulating levels of leptin were not disproportionately elevated, suggesting that serum leptin cannot be used as a marker for leptin-receptor deficiency. Congenital leptin-receptor deficiency should be considered in the differential diagnosis in any child with hyperphagia and severe obesity in the absence of developmental delay or dysmorphism.


Patients with a single episode of neurologic dysfunction and brain magnetic resonance imaging (MRI) scans suggestive of multiple sclerosis are at high risk for clinically definite multiple sclerosis, but the outcome for individual patients is unpredictable. An increased risk of progression to clinically definite multiple sclerosis in patients with serum antibodies against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) has been reported. We measured serum anti-MOG and anti-MBP IgG and IgM antibodies in 462 patients with a first clinical event suggestive of multiple sclerosis and at least two clinically silent lesions on brain MRI. The patients were participating in a multicenter trial of treatment with interferon beta-1b. Antibodies were assessed by Western blot analysis at baseline, and the results compared with the time and rate of progression to clinically definite multiple sclerosis or a diagnosis of multiple sclerosis as defined by an international panel (the McDonald criteria). Regular visits were scheduled for the assessment of neurologic impairment and for MRI before treatment and at months 3, 6, 9, 12, 18, and 24. No associations were found between the presence of anti-MOG and anti-MBP IgM and IgG antibodies and progression to clinically definite multiple sclerosis or a diagnosis of multiple sclerosis according to the McDonald criteria, either in the entire cohort or in any subgroups of the study population. Serum antibodies against MOG and MBP, as detected by Western blot analysis, are not associated with an increased risk of progression to clinically definite multiple sclerosis in patients who have had a clinically isolated syndrome suggestive of multiple sclerosis.


Breast cancers contain a minority population of cancer cells characterized by CD44 expression but low or undetectable levels of CD24 (CD44+CD24−/low) that have higher tumorigenic capacity than other subtypes of cancer cells. We compared the gene-expression profile of CD44+CD24−/low tumorigenic breast-cancer cells with that of normal breast epithelium. Differentially expressed genes were used to generate a 186-gene “invasiveness” gene signature (IGS), which was evaluated for its association with overall survival and metastasis-free survival in patients with breast cancer or other types of cancer. There was a significant association between the IGS and both overall and metastasis-free survival (P < 0.001, for both) in patients with breast cancer, which was independent of established clinical and pathological variables. When combined with the prognostic criteria of the National Institutes of Health, the IGS was used to stratify patients with high-risk early breast cancer into prognostic categories (good or poor); among patients with a good prognosis, the 10-year rate of metastasis-free survival was 81%, and among those with a poor prognosis, it was 57%. The IGS was also associated with the prognosis in medulloblastoma (P = 0.004), lung cancer (P = 0.03), and prostate cancer (P = 0.01). The prognostic power of the IGS was increased when combined with the wound-response (WR) signature. Conclusions The IGS is strongly associated with metastasis-free survival and overall survival for four different types of tumors. This genetic signature of tumorigenic breast-cancer cells was even more strongly associated with clinical outcomes when combined with the WR signature in breast cancer.
Developmental impairments in children have been attributed to persistent middle-ear effusion in their early years of life. Previously, we reported that among children younger than 3 years of age with persistent middle-ear effusion, prompt as compared with delayed insertion of tympanostomy tubes did not result in improved cognitive language, speech, or psychosocial development at 3, 4, or 6 years of age. However, other important components of development could not be assessed until the children were older. We enrolled 6350 infants soon after birth and evaluated them regularly for middle-ear effusion. Before 3 years of age, 429 children with persistent effusion were randomly assigned to undergo the insertion of tympanostomy tubes either promptly or up to 9 months later if effusion persisted. We assessed literacy, attention, social skills, and academic achievement in 391 of these children at 9 to 11 years of age. Mean (±SD) scores on 48 developmental measures in the group of children who were assigned to undergo early insertion of tympanostomy tubes did not differ significantly from the scores in the group that was assigned to undergo delayed insertion. These measures included the Passage Comprehension subtest of the Woodcock Reading Mastery Tests (mean score, 98±12 in the early-treatment group and 99±12 in the delayed-treatment group); the Spelling, Writing Samples, and Calculation subtests of the Woodcock–Johnson III Tests of Achievement (96±13 and 97±16; 104±14 and 105±15; and 99±13 and 99±13, respectively); and inattention ratings on visual and auditory continuous performance tests. In otherwise healthy young children who have persistent middle-ear effusion, as defined in our study, prompt insertion of tympanostomy tubes does not improve developmental outcomes up to 9 to 11 years of age.


Invasive fungal infections are an important cause of morbidity and mortality after allogeneic hematopoietic stem-cell transplantation. In an international, randomized, double-blind trial, we compared oral posaconazole with oral fluconazole for prophylaxis against invasive fungal infections in patients with graft-versus-host disease (GVHD) who were receiving immunosuppressive therapy. The primary end point was the incidence of proven or probable invasive fungal infections from randomization to day 112 of the fixed treatment period of the study. Of a total of 600 patients, 301 were assigned to posaconazole and 299 to fluconazole. At the end of the fixed 112-day treatment period, posaconazole was found to be as effective as fluconazole in preventing all invasive fungal infections (incidence, 5.3% and 9.0%, respectively; odds ratio, 0.56; 95 percent confidence interval [CI], 0.30 to 1.07; P=0.07) and was superior to fluconazole in preventing proven or probable invasive aspergillosis (2.3% vs. 7.0%; odds ratio, 0.31; 95% CI, 0.13 to 0.75; P=0.006). While patients were receiving study medications (exposure period), in the posaconazole group, as compared with the fluconazole group, there were fewer breakthrough invasive fungal infections (2.4% vs. 7.6%, P=0.004), particularly invasive aspergillosis (1.0% vs. 5.9%, P=0.001). Overall mortality was similar in the two groups, but the number of deaths from invasive fungal infections was lower in the posaconazole group (1%, vs. 4% in the fluconazole group; P=0.046). The incidence of treatment-related adverse events was similar in the two groups (36% in the posaconazole group and 38% in the fluconazole group), and the rates of treatment-related serious adverse events were 13% and 10%, respectively. Posaconazole was similar to fluconazole for prophylaxis against fungal infections among patients with GVHD. It was superior in preventing invasive aspergillosis and reducing the rate of deaths related to fungal infections.

CLINICAL PRACTICE

(REVIEW ARTICLES


In one way or another, most practicing physicians are involved in assessing the competence of trainees, peers, and other health professionals. As the example above suggests, however, they may not be as comfortable using educational assessment tools as they are using more clinically focused diagnostic tests. This article provides a conceptual framework for and a brief update on commonly used and emerging methods of assessment, discusses the strengths and limitations of each method, and identifies several challenges in the assessment of physicians’ professional competence and performance.


Worldwide, when the needs of injured or ill patients exceed what local clinics and hospitals can provide, urgent evacuation by air to the nearest well-equipped medical facility becomes the key to preserving function and saving lives. The international aeromedical evacuation industry is expanding, in part because of two recent trends: increasing travel to regions where road trauma and infectious diseases are endemic but dependable medical care is unavailable and...
an increasing number of travelers who are predisposed to injury or illness by advancing age or underlying medical conditions...

**IMAGES IN CLINICAL MEDICINE**

(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


An 85-year-old woman with newly diagnosed metastatic non–small-cell lung cancer was admitted for pain control. Two days after admission, bluish discoloration of the left great toe was noted. Doppler ultrasonography revealed a left femoropopliteal deep-vein thrombosis. Anticoagulation with heparin was initiated, but there was progressive swelling and cyanosis of the leg (Panels A and B). The patient was referred for prophylactic placement of an inferior vena cava filter. Fluoroscopy revealed that the clot had extended into the left iliac vein and lower inferior vena cava. Filter placement was successful. However, despite continued intravenous anticoagulation and attempts at mechanical thrombectomy, the clinical findings progressed to venous gangrene. Phlegmasia cerulea dolens (blue, painful leg) is an uncommon manifestation of deep-vein thrombosis and results from massive thrombosis compromising venous outflow, which causes ischemia...


A 60-year-old Somali woman presented to the emergency department with pain in the upper abdomen. Her medical history was notable for the placement of an intrauterine device (IUD) while she was living in Somalia. After the placement of the IUD, she continued to have children. Radiography of the abdomen showed an IUD in the left upper quadrant. Further evaluation revealed that she had cholecystitis. The IUD was easily removed during the laparoscopic cholecystectomy. The incidence of uterine perforation and migration of IUDs is approximately 1 to 2 cases per 1000 insertions. During pueroerium, when the uterus is small and thin...


A 19-year-old woman underwent five cycles of chemotherapy for acute myelomonocytic leukemia that had been diagnosed 7 months earlier. During the last cycle of chemotherapy, neutropenia developed, lasting 22 days, during which she had fever that was treated with empirical antibacterial therapy. When the neutrophil count increased, the fever persisted. Her evaluation was notable for a peak temperature of 39.5°C and an increase in the serum alkaline phosphatase level to 335 U per liter. An abdominal computed tomographic (CT) scan showed multiple hypodense lesions in the liver...


A previously healthy 56-year-old woman had spontaneous eruption of a lacy, net-like erythema of her entire skin, which was especially pronounced on her arms and legs (Panel A). The erythema of her lower arms disappeared within 2 minutes after immersion into a water bath at exactly 37°C. Her blood clumped immediately after being drawn and placed in a Petri dish (Panel B). Microscopic examination showed large red-cell agglutinates (Panel C). Results on electrocardiography, echocardiography, radiography, and skin biopsy (Panel A, arrow) were normal, as were the differential blood count and kidney function. There was no evidence of vasculitis or the...

**CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL**

(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


A 3-year-old boy was admitted to the hospital because of recurrent episodes of respiratory insufficiency, pulmonary infiltrates, and anemia. He was treated with antibiotics and levalbuterol and budesonide by inhalation at 9, 12, and 23 months of age. At 24 months of age, the patient was seen by his pediatrician because of increased work of breathing. He was sent to the emergency department of this hospital and admitted.


A 49-year-old woman was seen in the outpatient surgical clinic of this hospital because of a diagnosis of melanoma. The patient had noted a flat, pigmented lesion on her left upper arm approximately 1 year earlier. Three months later, it began to itch and became slightly raised. Approximately 3 months before the current evaluation, the lesion began to bleed when she scratched it. She saw a dermatologist at another facility, who performed a punch biopsy. Pathological examination was reported to show an atypical Spitz tumor; reexcision was recommended. The lesion was reexcised; pathological examination disclosed a superficial, spreading malignant melanoma, 0.91 mm in thickness, with a vertical growth phase and dermal mitoses, extending to within 1.5 mm of the nearest margin. Her dermatologist referred her to this hospital for further care. The patient had no history of skin cancers, and she felt well. An ovarian cystectomy had been performed at the age of 25 years. She had smoked for 10 years but quit at the age of 29 years, and she drank alcohol occasionally. She had siblings with nonmelanoma skin cancers. Her maternal grandmother had breast cancer at 76 years of age, her aunt at 65 years of age, and a cousin at 45 years of age. Her maternal grandfather had throat cancer in his 70s. Her four children were well.

**EDITORIALS**

(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


Retrospective studies carried out in the 1950s, 1960s, and 1970s suggested an association between otitis media early in life and subsequent developmental impairments in children. Although these studies were not designed to establish a cause-and-effect relationship, many prominent physicians, audiologists, and speech pathologists thought that a cause-and-effect relationship did exist, because severe, bilateral sensorineural hearing loss was known to cause irreversible developmental impairments. Therefore, aggressive intervention to restore normal hearing became the standard of care, and the placement of tympanostomy tubes became the second most frequent surgical procedure performed in the United States (after neonatal circumcision). In July 1994, the...

Invasive fungal diseases contribute substantially to death and illness associated with the prolonged, profound neutropenia resulting from intensive chemotherapy for hematologic cancers and from myeloablation for allogeneic hematopoietic stem-cell transplantation. In addition, the development of graft-versus-host disease (GVHD) puts transplant recipients at risk for infection for several weeks or months after engraftment. Given the high mortality associated with invasive fungal diseases and our inability to recognize active cases reliably, it is not surprising that prophylaxis is perceived as a sensible therapeutic approach. More than a decade ago, fluconazole was shown to be effective for preventing candida infection.


That mammographic density is an important risk factor for breast cancer was first recognized by Wolfe in the 1970s. His pioneering observation has since been confirmed in more than 42 studies, the vast majority of which have shown an association between increased mammographic density and the risk of breast cancer. Women in the highest quartile of mammographic density have a risk of breast cancer that is approximately four to six times as high as that among women of similar age who are in the lowest quartile. Only two other factors increase the risk of breast cancer more than mammographic density.


A fair amount of scrutiny has been given recently to the assessment of medical students’ competence before they enter practice. In this issue of the Journal, Epstein provides a timely summary of advances in this arena. In contrast, little attention has been paid to the assessment of doctors who are already in practice. As Epstein points out, far from being a fixed attribute or trait, competence comprises multidimensional sets of behaviors that are dependent on both environmental and individual factors. As a result, the assessment of competence must go beyond the identification of who practitioners are, on the basis of evidence of their personal attributes or dated credentials, ...


The advent of technology for the analysis of human tissue samples for the activity of the entire genome initiated a quest for the molecular profiling of tumors. The aim of this quest was a better system for classifying cancers, a clarification of the origin of these diseases, a more accurate prognostic capacity than was previously available, and an improved ability to choose among possible therapies. Progress in the molecular profiling of solid tumors began with the identification of sets of genes whose expression can be used to classify ... 


In the early 1990s, Jacques H. Ravina first applied the technique of embolization of uterine arteries to treat uterine fibroids in women at high risk for complications during surgery in an effort to control uterine bleeding. Embolization was then expanded for the treatment of patients who were undergoing myomectomy in order to decrease intraoperative bleeding. In 1993, Ravina and colleagues started using uterine-artery embolization as a primary treatment for uterine fibroids. Today, interventional radiologists worldwide perform uterine-artery embolization. Most of them embolize the uterine arteries bilaterally and not only the branch supplying blood to a particular fibroid (Figure ...