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September 12, 2007, marked the 50th anniversary of E. Donnell (Don) Thomas's initial report of a radical new approach to cancer treatment: radiation and chemotherapy followed by the intravenous infusion of bone marrow. That publication represented the beginning of a long series of laboratory and clinical investigations; more than a decade would pass before the procedure achieved its first successes. Yet Thomas's persistence in the face of criticism and clinical failure ultimately paid off in a new form of therapy that was used to treat approximately 50,000 people worldwide in 2006 (see timeline).


As increasing numbers of promising but expensive biologic agents are introduced for use as medical treatments, drug pricing has become a high-profile issue. Earlier this year, pricing practices took a new turn in Britain, when the National Institute for Health and Clinical Excellence (NICE), the evaluative agency that applies cost-effectiveness analysis in making recommendations concerning drug coverage, declined to support coverage of the proteasome inhibitor bortezomib (Velcade) by the British National Health Service (NHS) for the treatment of multiple myeloma. It concluded that the price was too high relative to NICE’s estimates of its average benefits for the population to...


A cell’s ability to give to rise to all the cell types of the embryo and the adult organism is called pluripotency. Pluripotent cells are found within mammalian blastocysts and persist briefly in embryos after implantation. Embryonic stem cells, derived from the inner cell mass of blastocysts, are a renewable source of pluripotent stem cells that are proving valuable in basic science studies and may eventually become a source of cells for safe, effective cell-based therapies. Much embryonic stem-cell research has focused on determining the molecular signature of pluripotency, and a picture is emerging of a complex interaction among transcription...


A couple of years ago, Jennifer Gardiner and Pamela Matovich, who work in the Information Systems Division at the Minneapolis headquarters of General Mills, were at risk for serious medical problems. The women, both in their 30s and mothers of young children, were obese and had diabetes. Gardiner weighed over 200 lb, smoked heavily, and avoided physical activity. Matovich weighed 230 lb, took insulin several times a day, had had episodes of severe hypoglycemia, and could not lift her babies because of pain from herniated lumbar disks. Both wanted to feel better and to reduce their risk of future illness...


To defuse physicians’ and hospitals’ opposition to the creation of Medicare back in 1965, the program’s congressional architects selected payment mechanisms designed to preserve the status quo. But as Medicare has expanded and problems of affordability and quality of care have grown, such an approach has become untenable. Recently, the Centers for Medicare and Medicaid Services (CMS) announced its decision to cease paying hospitals for some of the care made necessary by “preventable complications” — conditions that result from medical errors or improper care and that can reasonably be expected to be averted. This rule, which implements a congressionally mandated...


The West of Scotland Coronary Prevention Study was a randomized clinical trial comparing pravastatin with placebo in men with hypercholesterolemia who did not have a history of myocardial infarction, with an average follow-up of approximately 5 years. The combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction was reduced from 7.9 to 5.5% (P<0.001) in the treatment group. Extended follow-up data were obtained for...
approximately 10 years after completion of the trial. For the survivors of the trial, all deaths, hospitalizations and deaths due to coronary events and stroke, and incident cancers and deaths from cancer were tracked with the use of a national computerized record-linkage system. The results were analyzed with time-to-event analyses and use of Cox proportional-hazards models. Five years after the trial ended, 38.7% of the original statin group and 35.2% of the original placebo group were being treated with a statin. In the period approximately 10 years after completion of the trial, the risk of death from coronary heart disease or nonfatal myocardial infarction was 10.3% in the placebo group and 8.6% in the pravastatin group (P=0.02); over the entire follow-up period, the rate was 15.5% in the placebo group and 11.8% in the pravastatin group (P<0.001). Similar percentage reductions were seen in the combined rate of death from coronary heart disease and hospitalization for coronary events for both periods. The rate of death from cardiovascular causes was reduced (P=0.01), as was the rate of death from any cause (P=0.03), over the entire follow-up period. There were no excess deaths from noncardiovascular causes or excess fatal or incident cancers. In this analysis, 5 years of treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolemia who did not have a history of myocardial infarction.


Corticosteroids and antiviral agents are widely used to treat the early stages of idiopathic facial paralysis (i.e., Bell’s palsy), but their effectiveness is uncertain. Methods We conducted a double-blind, placebo-controlled, randomized, factorial trial involving patients with Bell’s palsy who were recruited within 72 hours after the onset of symptoms. Patients were randomly assigned to receive 10 days of treatment with prednisolone, acyclovir, both agents, or placebo. The primary outcome was recovery of facial function, as rated on the House–Brackmann scale. Secondary outcomes included quality of life, appearance, and pain. Final outcomes were assessed for 496 of 551 patients who underwent randomization. At 3 months, the proportions of patients who had recovered facial function were 83.0% in the prednisolone group as compared with 63.6% among patients who did not receive prednisolone (P<0.001) and 71.2% in the acyclovir group as compared with 75.7% among patients who did not receive acyclovir (adjusted P=0.50). After 9 months, these proportions were 94.4% for prednisolone and 81.6% for no prednisolone (P=0.001) and 85.4% for acyclovir and 90.8% for no acyclovir (adjusted P=0.10). For patients treated with both drugs, the proportions were 79.7% at 3 months (P<0.001) and 92.7% at 9 months (P<0.001). There were no clinically significant differences between the treatment groups in secondary outcomes. There were no serious adverse events in any group. In patients with Bell’s palsy, early treatment with prednisolone significantly improves the chances of complete recovery at 3 and 9 months. There is no evidence of a benefit of acyclovir given alone or an additional benefit of acyclovir in combination with prednisolone.


Pathological features of the airway in young children with severe recurrent wheeze suggest an association between bacterial colonization and the initiating events of early asthma. We conducted a study to investigate a possible association between bacterial colonization of the hypopharynx in asymptomatic neonates and later development of recurrent wheeze, asthma, and allergy during the first 5 years of life. Methods The subjects were children from the Copenhagen Prospective Study on Asthma in Childhood birth cohort who were born to mothers with asthma. Aspirates from the hypopharyngeal region of asymptomatic 1-month-old infants were cultured for Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus. Wheeze was monitored prospectively on diary cards during the first 5 years of life. Blood eosinophil count and total IgE and specific IgE were measured at 4 years of age. Lung function was measured and asthma was diagnosed at 5 years of age. Results Hypopharyngeal samples were cultured from 321 neonates at 1 month of age. Twenty-one percent of the infants were colonized with S. pneumoniae, M. catarrhalis, H. influenzae, or a combination of these organisms; colonization with one or more of these organisms, but not colonization with S.
aureus, was significantly associated with persistent wheeze (hazard ratio, 2.40; 95% confidence interval [CI], 1.45 to 3.99), acute severe exacerbation of wheeze (hazard ratio, 2.99; 95% CI, 1.66 to 5.39), and hospitalization for wheeze (hazard ratio, 3.85; 95% CI, 1.90 to 7.79). Blood eosinophil counts and total IgE at 4 years of age were significantly increased in children colonized neonatally with S. pneumoniae, M. catarrhalis, H. influenzae, or a combination of these organisms, but specific IgE was not significantly affected. The prevalence of asthma and the reversibility of airway resistance after agonist administration at 5 years of age were significantly increased in the children colonized neonatally with these organisms as compared with the children without such colonization (33% vs. 10% and 23% vs. 18%, respectively).

Conclusions Neonates colonized in the hypopharyngeal region with S. pneumoniae, H. influenzae, or M. catarrhalis, or with a combination of these organisms, are at increased risk for recurrent wheeze and asthma early in life.


The status of human epidermal growth factor receptor type 2 (HER2) in breast-cancer cells predicts clinical outcomes in women who receive adjuvant anthracycline-based chemotherapy. We hypothesized that HER2 positivity predicts a benefit from adjuvant doxorubicin doses above standard levels, from the addition of paclitaxel after adjuvant chemotherapy with doxorubicin plus cyclophosphamide, or from both. We randomly selected 1500 women from 3121 women with node-positive breast cancer who had been randomly assigned to receive doxorubicin (60, 75, or 90 mg per square meter of body-surface area) plus cyclophosphamide (600 mg per square meter) for four cycles, followed by four cycles of paclitaxel (175 mg per square meter) or observation. Tissue blocks from 1322 of these 1500 women were available. Immunohistochemical analyses of these tissue specimens for HER2 with the CB11 monoclonal antibody against HER2 or with a polyclonal-antibody assay kit and fluorescence in situ hybridization for HER2 amplification were performed. No interaction was observed between HER2 positivity and doxorubicin doses above 60 mg per square meter. HER2 positivity was, however, associated with a significant benefit from paclitaxel. The interaction between HER2 positivity and the addition of paclitaxel to the treatment was associated with a hazard ratio for recurrence of 0.59 (P=0.01). Patients with a HER2-positive breast cancer benefited from paclitaxel, regardless of estrogen-receptor status, but paclitaxel did not benefit patients with HER2-negative, estrogen-receptor–positive cancers. The expression or amplification, or both, of HER2 by a breast cancer is associated with a benefit from the addition of paclitaxel after adjuvant treatment with doxorubicin (<60 mg per square meter) plus cyclophosphamide in node-positive breast cancer, regardless of estrogen-receptor status. Patients with HER2-negative, estrogen-receptor–positive, node-positive breast cancer may gain little benefit from the administration of paclitaxel after adjuvant chemotherapy with doxorubicin plus cyclophosphamide.
monocyte chemoattractant protein 1 in response to the presence of interleukin-6 (P=0.03), suggesting a defect in interleukin-6 signaling through its downstream mediators, one of which is STAT3. We identified missense mutations and single-codon in-frame deletions in STAT3 in 50 familial and sporadic cases of the hyper-IgE syndrome. Eighteen discrete mutations, five of which were hot spots, were predicted to directly affect the DNA-binding and SRC homology 2 (SH2) domains. Mutations in STAT3 underlie sporadic and dominant forms of the hyper-IgE syndrome, an immunodeficiency syndrome involving increased innate immune response, recurrent infections, and complex somatic features.


Storage of glycogen is essential for glucose homeostasis and for energy supply during bursts of activity and sustained muscle work. We describe three siblings with profound muscle and heart glycogen deficiency caused by a homozygous stop in the muscle glycogen synthase gene. The oldest brother died from sudden cardiac arrest at the age of 10.5 years. Two years later, an 11-year-old brother showed muscle fatigability, hypertrophic cardiomyopathy, and an abnormal heart rate and blood pressure while exercising; a 2-year-old sister had no symptoms. In muscle-biopsy specimens obtained from the two younger siblings, there was lack of glycogen, predominance of oxidative fibers, and mitochondrial proliferation. Glucose tolerance was normal.


To determine whether testing for DNA of oncogenic human papillomaviruses (HPV) is superior to the Papanicolaou (Pap) test for cervical-cancer screening, we conducted a randomized trial comparing the two methods. We compared HPV testing, using an assay approved by the Food and Drug Administration, with conventional Pap testing as a screening method to identify high-grade cervical intraepithelial neoplasia in women ages 30 to 69 years in Montreal and St. John’s, Canada. Women with abnormal Pap test results or a positive HPV test (at least 1 pg of high-risk HPV DNA per milliliter) underwent colposcopy and biopsy, as did a random sample of women with negative tests. Sensitivity and specificity estimates were corrected for verification bias. A total of 10,154 women were randomly assigned to testing. Both tests were performed on all women in a randomly assigned sequence at the same session. The sensitivity of HPV testing for cervical intraepithelial neoplasia of grade 2 or 3 was 94.6% (95% confidence interval [CI], 84.2 to 100), whereas the sensitivity of Pap testing was 55.4% (95% CI, 33.6 to 77.2; P=0.01). The specificity was 94.1% (95% CI, 93.4 to 94.8) for HPV testing and 96.8% (95% CI, 96.3 to 97.3; P<0.001) for Pap testing. Performance was unaffected by the sequence of the tests. The sensitivity of both tests used together was 100%, and the specificity was 92.5%. Triage procedures for Pap or HPV testing resulted in fewer referrals for colposcopy than did either test alone but were less sensitive. No adverse events were reported.


Screening for cervical cancer based on testing for human papillomavirus (HPV) increases the sensitivity of detection of high-grade (grade 2 or 3) cervical intraepithelial neoplasia, but whether this gain represents overdiagnosis or protection against future high-grade cervical epithelial neoplasia or cervical cancer is unknown. In a population-based screening program in Sweden, 12,527 women 32 to 38 years of age were randomly assigned at a 1:1 ratio to have an HPV test plus a Papanicolaou (Pap) test (intervention group) or a Pap test alone (control group). Women with a positive HPV test and a normal Pap test result were offered a second HPV test at least 1 year later, and those who were found to be persistently infected with the same high-risk type of HPV were then offered colposcopy with cervical biopsy. A similar number of double-blinded Pap smears and colposcopies with biopsy were performed in randomly selected women in the control group. Comprehensive registry data were used to follow the women for a mean of 4.1 years. The relative rates of grade 2 or 3 cervical intraepithelial neoplasia or cancer detected at enrollment and at subsequent screening examinations were calculated. At enrollment, the proportion of women in the intervention group who were found to have lesions of grade 2 or 3
cervical intraepithelial neoplasia or cancer was 51% greater (95% confidence interval [CI], 13 to 102) than the proportion of women in the control group who were found to have such lesions. At subsequent screening examinations, the proportion of women in the intervention group who were found to have grade 2 or 3 lesions or cancer was 42% less (95% CI, 4 to 64) and the proportion with grade 3 lesions or cancer was 47% less (95% CI, 2 to 71) than the proportions of control women who were found to have such lesions. Women with persistent HPV infection remained at high risk for grade 2 or 3 lesions or cancer after referral for colposcopy.

SPECIAL ARTICLE


Little is known about the magnitude of deficits in the quality of care delivered to children, since comprehensive studies have been lacking. We assessed the extent to which care processes recommended for pediatric outpatients are delivered. Quality indicators were developed with the use of the RAND–UCLA modified Delphi method. Parents of 1536 children who were randomly selected from 12 metropolitan areas provided written informed consent to obtain medical records from all providers who had seen the children during the 2-year period before the date of study recruitment. Trained nurses abstracted these medical records. Composite quality scores were calculated by dividing the number of times indicated care was documented as having been ordered or delivered by the number of times a care process was indicated. On average, according to data in the medical records, children in the study received 46.5% (95% confidence interval [CI], 44.5 to 48.4) of the indicated care. They received 67.6% (95% CI, 63.9 to 71.3) of the indicated care for acute medical problems, 53.4% (95% CI, 50.0 to 56.8) of the indicated care for chronic medical conditions, and 40.7% (95% CI, 38.1 to 43.4) of the indicated preventive care. Quality varied according to the clinical area, with the rate of adherence to indicated care ranging from 92.0% (95% CI, 89.9 to 94.1) for upper respiratory tract infections to 34.5% (95% CI, 31.0 to 37.9) for preventive services for adolescents. Deficits in the quality of care provided to children appear to be similar in magnitude to those previously reported for adults. Strategies to reduce these apparent deficits are needed.

REVIEW ARTICLE


Early administration of reperfusion therapy improves survival in patients with ST-elevation myocardial infarction by reestablishing coronary blood flow within the occluded infarct-related artery.1 Primary percutaneous coronary intervention (PCI) is superior to fibrinolytic therapy when performed rapidly by expert teams,2 but its effectiveness may be limited by delays in delivery.3 Recent national efforts are drawing attention to the importance of door-to-balloon time as a key indicator of quality of care for patients with ST-elevation myocardial infarction who are treated with primary PCI.4 The American College of Cardiology (ACC), in collaboration with the American Heart Association (AHA), the American College of Emergency . . .

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. A 52-year-old woman presents with a 1-year history of fatigue and itching. Several months before presentation, her primary care physician noted abnormal liver-function tests, and levels have been persistently elevated since that time. A test for antimitochondrial antibodies was . . .

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 45-year-old white woman . . .
presents with a 1-year history of scalp-hair loss. She was hospitalized with appendicitis 14 months ago. She has been a vegetarian for 20 years. She takes no medications. Her father was bald. On physical examination, she has diffuse, nonscarring hair thinning with a widened part over the central portion of the scalp. How should this problem be evaluated . . .

VIDEOS IN CLINICAL MEDICINE

Dev, S.P., Bartolomeu Nascimiento, Carmine Simone, and Vincent Chien. (2007). Chest-Tube Insertion. New England Journal of Medicine, 357 (15), e15. The insertion of a pleural chest tube is often done in a setting where immediate action is required. Nonetheless, adherence to sterility, analgesia, sound technique, and safety are always warranted. Indications The most common indications for chest-tube drainage are: Pneumothorax that is recurrent, persistent, under tension, or bilateral; any pneumothorax in a patient on positive-pressure ventilation; hemothorax; recurrent or symptomatic large pleural effusion; empyema; and chylothorax. Contraindications There are relative contraindications, mainly based on hematologic abnormalities such as bleeding diatheses or coagulopathy. Blood products or coagulation factors may need to be transfused in order to reduce the . . .

IMAGES IN CLINICAL MEDICINE

Cornner, J.C., and V.S. Bebarta. (2007). White phosphorus dermal burns. New England Journal of Medicine, 357 (15), 1530. A 19-year-old man presented with painful burns on his posterior scalp after exposure to an incendiary agent. Smoke emanated from the wounds on removal of the dressing that had been applied during prehospital treatment. The wounds appeared waxy and yellow under natural light (Panel A) and fluorescent under ultraviolet light (i.e., Wood’s lamp) (Panel B), consistent with a white phosphorus burn. Remaining particles were brushed off the wound, and the burns were irrigated with copious saline. His pain diminished, but the persistent presence of white phosphorus on examination under ultraviolet light required surgical débridement. White phosphorus is an incendiary agent . . .

Thornton, K.A., and M. Levis. (2007). FLT3 mutation and acute myelogenous leukemia with leukostasis. New England Journal of Medicine, 357 (16), 1639. A 59-year-old man presented with a sudden onset of abdominal pain in the left upper quadrant, associated with low-grade fever and shortness of breath. He had had a recent relapse of acute myelogenous leukemia and had an internal-tandem-duplication mutation of Fms-like tyrosine kinase 3 (FLT3). His white-cell count at admission was 15,900 per cubic millimeter, with 60% monoblasts. Over the next 24 hours, his leukocyte count increased from 29,000 to 102,340 per cubic millimeter, and his monoblast count increased from 5510 to 55,264 per cubic millimeter, despite the administration of cyclophosphamide. The patient’s hypoxemia worsened. Mechanical ventilation was initiated, but . . .

Sinnamon, K., and R. Mullan. (2007). Aneurysmal arteriovenous fistula. New England Journal of Medicine, 357 (15), e16. A 50-year-old man had a 30-year history of end-stage renal disease associated with idiopathic membranoproliferative glomerulonephritis. His medical history included immune thrombocytopenic purpura, with platelet counts that were persistently less than 15,000 per cubic millimeter. After a second renal transplant failed 8 years ago, the patient began to undergo dialysis through a left brachiocephalic arteriovenous fistula, which became severely aneurysmal over the next 6 years (Panel A), with no evidence of a proximal venous stenosis. There was no evidence of complications — such as infection, embolism, rupture, or high-output congestive heart failure — from this aneurysmal arteriovenous fistula. The patient . . .

Young, T.-H., and H.-S. Lee. (2007). Recanalized umbilical vein. New England Journal of Medicine, 357 (16), e17. A 72-year-old woman with a 10-year history of compensated cirrhosis due to hepatitis C infection presented with swelling of the lower leg. Physical examination showed splenomegaly, spider angiomata, and visible tortuous vessels on the abdominal wall. Axial magnetic resonance imaging through the liver (Panel A) showed a connection (arrow) between the umbilical vein (UV) and the left portal vein (LPV), as well as esophageal varices (arrowhead). Coronal T2-weighted imaging (Panel B) showed a recanalized umbilical vein (arrow) coursing in the anterior abdominal wall to the umbilicus. Normally, after interruption of the placental circulation at birth, the umbilical vein collapses . . .

Dr. David A. Barbie (Medical Oncology): A 62-year-old woman came to this hospital for management of breast cancer. Six years earlier, a routine mammogram had revealed calcifications in the left breast. Specimens from a stereotactically guided core biopsy showed atypical cells, and an excisional biopsy with needle localization showed a grade 1 invasive ductal carcinoma of the left breast, 0.7 cm in maximal diameter, associated with intermediate-grade ductal carcinoma in situ. The tumor extended within 0.2 cm of the margin; there was no lymphovascular invasion. The tumor cells expressed estrogen and progesterone receptors and did not overexpress human epidermal growth . . .


A 41-year-old man was admitted to this hospital because of abdominal pain, nausea, and an elevated serum creatinine level. He had been in good health until 6 days before admission, when chills and malaise developed. At that time, his body felt warm to the touch, but the temperature was not measured. He took ibuprofen (at a dose of 400 mg) orally every 6 hours for three or four doses, with some improvement in his symptoms. Weakness and nausea developed, and he took one dose of an over-the-counter medication that included acetaminophen, dextromethorphan, and pseudoephedrine, with improvement in his symptoms.