abstract of
New England Journal of Medicine

www.lib.hukm.ukm.my       Volume 359, Number 7 & 8 - August 14 & 21, 2008
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On May 10, 2008, the Journal and the Massachusetts Medical Society brought together 13 panelists — physicians, academics, and business, insurance, and political leaders — for a seminar on U.S. health policy and health coverage. In a discussion moderated by Arthur R. Miller, J.D., of the New York University School of Law, the participants identified important challenges to the U.S. health care system and debated possible solutions. The group addressed the dissatisfaction among physicians in general and primary care providers in particular and considered its relationship to a reimbursement system that rewards high-tech procedures rather than cognitive work and time . . .


In the wake of Cyclone Nargis, which devastated the Myanmar delta in early May, and the seismic earthquake that shook China shortly thereafter, access to safe drinking water and proper sanitation have become top priorities among those attempting to prevent epidemic diseases. But even without catastrophic disasters, the lack of access to clean water and basic sanitation represents a silent crisis affecting more than a third of the world’s population.1 Some 443 million school days are lost annually to water-related illness, millions of women and girls spend up to 2 hours a day collecting water, and every day in . . .


In this issue of the Journal, Boucek et al. (pages 709–714) report on three cases of heart transplantation from infants who were pronounced dead on the basis of cardiac criteria. The three Perspective articles and a video roundtable discussion at www.nejm.org address key ethical aspects of organ donation after cardiac death. Bernat and Veatch comment on the cases described by Boucek et al.; Truog and Miller raise a fundamental question about the dead donor rule. In a related Perspective roundtable, moderator Atul Gawande, of Harvard Medical School, is joined by George Annas, of the Boston . . .


In the face of escalating costs, uneven quality of care, and the growth of the uninsured population, there is broad agreement that the U.S. health care system requires reform. However, Democrats and Republicans remain sharply divided over how to reform it, as evidenced by the health care plans offered by the parties’ presidential candidates. The ambitious reform agendas of Senators John McCain (R-AZ) and Barack Obama (D-IL) would take the U.S. health care system in very different directions. McCain’s plan embraces market forces and promotes individually purchased insurance (see red box). Its centerpiece is a change in the tax . . .


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In three infants awaiting orthotopic cardiac transplantation, transplantation was successfully performed with the use of organs from donors who had died from cardiocirculatory causes. The three recipients had blood group O and were in the highest-risk waiting-list category. The mean age of donors was 3.7 days, and the mean time to death after withdrawal from life support was 18.3 minutes. The 6-month survival rate was 100% for the 3 transplant recipients and 84% for 17 control infants who received transplants procured through standard organ donation. The mean number of rejection episodes among the three infants during the first 6 months after surgery was 0.3 per patient, as compared with 0.4 per patient among the controls. Echocardiographic measures of ventricular size and function at 6 months were similar among the three infants and the controls (left ventricular shortening fraction, 43.6% and 44.9%, respectively; P=0.73). No late deaths (within 3.5 years) have occurred in the three infants, and they have had functional and immunologic outcomes similar to those of controls. Mortality while awaiting a transplant is an order of magnitude higher in infants than in adults, and donors who died from cardiocirculatory causes offer an opportunity to decrease this waiting-list mortality.

Tibolone has estrogenic, progestogenic, and androgenic effects. Although tibolone prevents bone loss, its effects on fractures, breast cancer, and cardiovascular disease are uncertain. In this randomized study, we assigned 4538 women, who were between the ages of 60 and 85 years and had a bone mineral density T score of –2.5 or less and 84% for 17 control infants who received transplants procured through standard organ donation. The mean age of donors was 3.7 days, and the mean time to death after withdrawal from life support was 18.3 minutes. The 6-month survival rate was 100% for the 3 transplant recipients and 84% for 17 control infants who received transplants procured through standard organ donation. The mean number of rejection episodes among the three infants during the first 6 months after surgery was 0.3 per patient, as compared with 0.4 per patient among the controls. Echocardiographic measures of ventricular size and function at 6 months were similar among the three infants and the controls (left ventricular shortening fraction, 43.6% and 44.9%, respectively; P=0.73). No late deaths (within 3.5 years) have occurred in the three infants, and they have had functional and immunologic outcomes similar to those of controls. Mortality while awaiting a transplant is an order of magnitude higher in infants than in adults, and donors who died from cardiocirculatory causes offer an opportunity to decrease this waiting-list mortality.


Whether bivalirudin is superior to unfractionated heparin in patients with stable or unstable angina who undergo percutaneous coronary intervention (PCI) after pretreatment with clopidogrel is unknown. We enrolled 4570 patients with stable or unstable angina (with normal levels of troponin T and creatine kinase MB) who were undergoing PCI after pretreatment with a 600-mg dose of clopidogrel at least 2 hours before the procedure; 2289 patients were randomly assigned in a double-blind manner to receive bivalirudin, and 2281 to receive unfractionated heparin. The primary end point was the composite of death, myocardial infarction, urgent target-vessel revascularization due to myocardial ischemia within 30 days after randomization, or major bleeding during the index hospitalization (with a net clinical benefit defined as a reduction in the incidence of the end point). The secondary end point was the composite of death, myocardial infarction, or urgent target-vessel revascularization. The incidence of the primary end point was 8.3% (190 patients) in the bivalirudin group as compared with 8.7% (199 patients) in the unfractionated-heparin group (relative risk, 0.94; 95% confidence interval [CI], 0.77 to 1.15; P=0.57). The secondary end point occurred in 134 patients (5.9%) in the bivalirudin group and 115 patients (5.0%) in the unfractionated-heparin group (relative risk, 1.16; 95% CI, 0.91 to 1.49; P=0.23). The incidence of major bleeding was 3.1% (70 patients) in the bivalirudin group and 4.6% (104 patients) in the unfractionated-heparin group.
Tumor necrosis factor (TNF) has a pathogenic role in juvenile rheumatoid arthritis. We evaluated the efficacy and safety of adalimumab, a fully human monoclonal anti-TNF antibody, in children with polyarticular-course juvenile rheumatoid arthritis. Patients 4 to 17 years of age with active juvenile rheumatoid arthritis who had previously received treatment with nonsteroidal antiinflammatory drugs underwent stratification according to methotrexate use and received 24 mg of adalimumab per square meter of body-surface area (maximum dose, 40 mg) subcutaneously every other week for 16 weeks. We randomly assigned patients with an American College of Rheumatology Pediatric 30% (ACR Pedi 30) response at week 16 to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks. Seventy-four percent of patients not receiving methotrexate (64% of 86) and 94% of those receiving methotrexate (80 of 85) had an ACR Pedi 30 response at week 16 and were eligible for double-blind treatment. Among patients not receiving methotrexate, disease flares (the primary outcome) occurred in 43% of those receiving adalimumab and 71% of those receiving placebo (P=0.03). Among patients receiving methotrexate, flares occurred in 37% of those receiving adalimumab and 65% of those receiving placebo (P=0.02). At 48 weeks, the percentages of patients treated with methotrexate who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater for those receiving adalimumab than for those receiving placebo; the differences between patients not treated with methotrexate who received adalimumab and those who received placebo were not significant. Response rates were sustained after 104 weeks of treatment. Serious adverse events possibly related to adalimumab occurred in 14 patients. Adalimumab therapy seems to be an efficacious option for the treatment of children with juvenile rheumatoid arthritis.


Lowering low-density lipoprotein cholesterol with statin therapy results in substantial reductions in cardiovascular events, and larger reductions in cholesterol may produce larger benefits. In rare cases, myopathy occurs in association with statin therapy, especially when the statins are administered at higher doses and with certain other medications. We carried out a genomewide association study using approximately 300,000 markers (and additional fine-mapping) in 85 subjects with definite or incipient myopathy and 90 controls, all of whom were taking 80 mg of simvastatin daily as part of a trial involving 12,000 participants. Replication was tested in a trial of 40 mg of simvastatin daily involving 20,000 participants. The genomewide scan yielded a single strong association of myopathy with the rs4363657 single-nucleotide polymorphism (SNP) located within SLCO1B1 on chromosome 12 (P=4x10–9). SLCO1B1 encodes the organic anion–transporting polypeptide OATP1B1, which has been shown to regulate the hepatic uptake of statins. The noncoding rs4363657 SNP was in nearly complete linkage disequilibrium with the nonsynonymous rs4149056 SNP (r2=0.97), which has been linked to statin metabolism. The prevalence of the rs4149056 C allele in the population was 15%. The odds ratio for myopathy was 4.5 (95% confidence interval [CI], 2.6 to 7.7) per copy of the C allele, and 16.9 (95% CI, 4.7 to 61.1) in CC as compared with TT homozygotes. More than 60% of these myopathy cases could be attributed to the C variant. The association of rs4149056 with myopathy was replicated in the trial of 40 mg of simvastatin daily, which also showed an association between rs4149056 and the cholesterol-lowering effects of simvastatin. No SNPs in any other region were clearly associated with myopathy.


It is unknown whether preeclampsia is a risk marker for subsequent end-stage renal disease (ESRD). We linked data from the Medical Birth Registry of Norway, which contains data on all births in Norway since 1967, with data from the Norwegian Renal Registry, which contains data on all patients receiving a diagnosis of end-stage renal disease (ESRD) since 1980, to assess the association between preeclampsia in one or more pregnancies and the subsequent development of ESRD. The study population consisted of women who had had a first singleton birth between 1967 and 1991; we included data from up to three pregnancies. ESRD developed in 477 of 570,433 women a mean (±SD) of...
versus 72±23 for physical limitation (P=0.004), 77±28
3 months, these scores had increased in the PCI group,
treatment satisfaction, and 51±25 for quality of life. By
stability, 69±26 for angina frequency, 87±16 for
were 66±25 for physical limitations, 54±32 for angina
function (with the use of the RAND 36-item health
Questionnaire) and overall physical and mental
PCI group and 42% in the medical-therapy group were
free of angina. At 3 months, 53% of the patients in the
survey [RAND-36]. At baseline, 22% of the patients were
function (with the use of the RAND 36-item health
Questionnaire) and overall physical and mental
PCI plus optimal medical therapy or to optimal medical
assigned 2287 patients with stable coronary disease to
an incremental benefit in quality of life over that
provided by optimal medical therapy among patients
with chronic coronary artery disease. We randomly
assigned 2287 patients with stable coronary disease to
PCI plus optimal medical therapy or to optimal medical
therapy alone. We assessed angina-specific health
status (with the use of the Seattle Angina Questionnaire) and overall physical and mental
function (with the use of the RAND 36-item health
survey [RAND-36]). At baseline, 22% of the patients were
free of angina. At 3 months, 53% of the patients in the
PCI group and 42% in the medical-therapy group were
angina-free (P<0.001). Baseline mean (±SD) Seattle
Angina Questionnaire scores (which range from 0 to
100, with higher scores indicating better health status)
were 66±25 for physical limitations, 54±32 for angina
stability, 69±26 for angina frequency, 87±16 for
treatment satisfaction, and 51±25 for quality of life. By
3 months, these scores had increased in the PCI group,
versus 76±24 versus 72±23 for physical limitation (P=0.004), 77±28
51±25 for quality of life. By

versus 73±27 for angina stability (P=0.002), 85±22
versus 80±23 for angina frequency (P<0.001), 92±12
versus 90±14 for treatment satisfaction (P<0.001), and
73±22 versus 68±23 for quality of life (P<0.001). In
general, patients had an incremental benefit from PCI
for 6 to 24 months; patients with more severe angina
had a greater benefit from PCI. Similar incremental
benefits from PCI were seen in some but not all RAND-
36 domains. By 36 months, there was no significant
difference in health status between the treatment
groups. Among patients with stable angina, both those
treated with PCI and those treated with optimal medical
therapy alone had marked improvements in health
status during follow-up. The PCI group had small, but
significant, incremental benefits that disappeared by
36 months.

CLINICAL THERAPEUTICS
of alcohol dependence. *New England Journal of
Medicine*, 359 (7), 715-721.

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 44-year-old businessman
with a history of hypertension presents for evaluation
with a report of being under stress at work and home,
which has led to “unsatisfactory” sleep. Although there
is some despondency, screening for depression is
negative. His . . .

SPECIAL ARTICLE
economic implications of HPV vaccination in
the United States. *New England Journal of
Medicine*, 359 (8), 821-832.

The cost-effectiveness of prophylactic vaccination
against human papillomavirus types 16 (HPV-16) and
18 (HPV-18) is an important consideration for
guidelines for immunization in the United States. We
synthesized epidemiologic and demographic data using
models of HPV-16 and HPV-18 transmission and cervical
carcinogenesis to compare the health and economic
outcomes of vaccinating preadolescent girls (at 12 years
of age) and vaccinating older girls and women in catch-
up programs (to 18, 21, or 26 years of age). We examined
the health benefits of averting other HPV-16–related
and HPV-18–related cancers, the prevention of HPV-6–
related and HPV-11–related genital warts and juvenile-
onset recurrent respiratory papillomatosis by means
of the quadrivalent vaccine, the duration of immunity,
and future screening practices. On the assumption that
the vaccine provided lifelong immunity, the cost-
effectiveness ratio of vaccination of 12-year-old girls
was $43,600 per quality-adjusted life-year (QALY) gained, as compared with the current screening practice. Under baseline assumptions, the cost-effectiveness ratio for extending a temporary catch-up program for girls to 18 years of age was $97,300 per QALY; the cost of extending vaccination of girls and women to the age of 21 years was $120,400 per QALY, and the cost for extension to the age of 26 years was $152,700 per QALY.

**REVIEW ARTICLE**


Cytogenetic abnormalities are a characteristic attribute of cancer cells. To date, clonal chromosome aberrations have been found in all major tumor types from more than 54,000 patients (http://cgap.nci.nih.gov/Chromosomes/Mitelman), and their identification continues as a result of technical improvements in conventional and molecular cytogenetics. The World Health Organization Classification of Tumours recognizes a growing number of such genetic changes and uses them to define specific disease entities. Many of these aberrations have emerged as prognostic and predictive markers in hematologic cancers and certain types of solid tumors. Furthermore, the molecular characterization of cytogenetic abnormalities has provided insights into the . . .

**IMAGES IN CLINICAL MEDICINE**


A 23-year-old male Marine recruit passed out while bending over after a 2.4-km (1.5-mile) run. Chest radiography showed a mass in the anterior mediastinum (Panel A, arrow). His medical history was notable only for the removal of a benign thyroid cyst at the age of 12 years. He reported no use of medications or tobacco and no drug allergies. The physical examination and initial laboratory studies were unremarkable except for prominent varicocities noted on his chest (Panel B). Contrast-enhanced computed tomography of the chest revealed a large anterior mediastinal mass with fluid, fat, and calcific densities (Panel C, arrow) that . . .


A 63-year-old woman presented with a 1-year history of vague pelvic and back pain. She had undergone laparoscopic surgery of the fallopian tubes 27 years earlier owing to infertility. Computed tomography of the abdomen showed an 8-cm pelvic mass (Panel A). Because of concern about ovarian carcinoma, she underwent an exploratory laparoscopy, which revealed extensive adhesions of the lower abdomen and a yellow, dense mass involving the entire pouch of Douglas (Panel B). Attempts to dissect the mass led to its rupture, revealing contents that were suggestive of a dermoid cyst. However, on aspiration of the contents, an old swab . . .


A 55-year-old woman awoke with an acute onset of bilateral leg numbness and weakness. Initial evaluation and lumbar magnetic resonance imaging, which was performed to assess the patient for disk disease, showed no cause for her symptoms, but her ankle pulses were noted to be diminished. The patient smoked cigarettes and had untreated hyperlipidemia; she reported that during the previous year, she had had bilateral buttock and thigh pain on walking 300 m. Her renal function was normal. Computed tomographic angiography showed complete occlusion of the infrarenal abdominal aorta (Panel A, arrow). A lateral view showed collateral blood flow from . . .


During left ventriculography in a 46-year-old man with hypertrophic cardiomyopathy, we injected 20 ml of contrast material, using a power injector at a rate of 10 ml per second through a multipurpose catheter (MPA2). The left ventricle became opacified, and ventricular tachycardia subsequently developed, for which the patient underwent successful cardioversion. Initially, the catheter was free-floating. During the next beat, it was pulled in, resulting in cannulation. Contrast material was injected into what appeared to be thebesian veins (black arrows), with prompt visualization of cardiac veins (arrowheads) and the coronary sinus (white arrow). No persistent staining of the myocardium was . . .

**CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL**


Dr. Flavia V. Castelino (Rheumatology, Allergy, and Immunology): A 43-year-old man was seen in the neuro-oncology clinic of this hospital because of fatigue and lesions in the pituitary and cerebellum detected on radiography. He had been well until approximately 9 years earlier, when thirst, insomnia, fatigue, and arthralgias developed. On evaluation at another facility, a diagnosis of diabetes insipidus was made, and
desmopressin was prescribed. The symptoms resolved; however, during the next several years, he and his wife were unable to conceive a second child. Approximately 3 years earlier, insomnia, fatigue, and joint pain recurred, associated with cold intolerance. Evaluation . . .


Dr. Thomas J. Cummings, Jr. (Psychiatry): A 26-year-old woman was admitted to this hospital because of headache, behavioral changes, abnormal movements, and inability to communicate. The patient had been well, except for occasional migraine headaches, until 7 weeks earlier, when generalized, diffuse headache developed. It was most severe in the occipital region, with associated neck stiffness, sensitivity to sounds, intermittent blurred vision, nausea, and vomiting. There were no prodromal symptoms or visual scotoma, which had occurred routinely with her migraines, and the pain did not diminish in response to her usual migraine treatment. During the next 10 days, she . . .

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 healthy 58-year-old woman answers the telephone and realizes that her hearing is diminished on the left side. She notices aural fullness and loud tinnitus in the affected ear. Later that day she has several hours of mild vertigo that clears by the following morning. Over the next few days, repeated self-administered ear cleaning with the use of an over-the-counter kit does . . .