Expanding the black box: depression, antidepressants, and the risk of suicide
Friedman, R.A., and Andrew C. Leon.

Weighing the hazards of erythropoiesis stimulation in patients with cancer
Khuri, F.P.

In the dark: the case for electronic health records
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Do Cancer Cells Express Functional Erythropoietin Receptors?
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The stem-cell market: patents and the pursuit of scientific progress
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Erythropoietin, the FDA, and Oncology
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Communication between physicians and patients in the era of e-medicine
Stone, J.H.

Discovery of new infectious diseases: bartonella species
Wormser, G.P.

Eprodisate for the treatment of renal disease in AA Amyloidosis

Brief report: bacteremia, fever, and splenomegaly caused by a newly recognized bartonella species

Natural history and outcome in systemic AA Amyloidosis

A Multicenter, randomized trial of prophylactic fluconazole in preterm neonates

Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes
Nissen, S.E., and Kathy Wolski.

Anidulafungin versus fluconazole for invasive candidiasis

Adjuvant mitotane treatment for adrenocortical carcinoma

Explaining the decrease in U.S. deaths from coronary disease, 1980–2000

Relationship between number of medical conditions and quality of care

Local therapy and survival in breast cancer
Punglia, R.S., Monica Morrow, Eric P. Winer, and Jay R. Harris.

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Peripheral Smear with Malassezia furfur
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Amyloid Purpura
Eder, L., and H. Bitterman

Diffuse chemoradiotherapy-related enterocolitis

A hand-carried diagnosis: A 34-year-old black woman presented to a walk-in clinic with a 3-day history of malaise

Follow-up of Patients with Early Breast Cancer
Hayes, D.F.

Why does rheumatoid arthritis involve the joints?
Lipsky, P.E.

Case 18-2007: a 54-year-old man with early-stage prostate cancer

Information technology comes to medicine
Blumenthal, D., and John P. Glaser.
PERSPECTIVES
(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


On May 2, 2007, the Food and Drug Administration (FDA) ordered that all antidepressant medications carry an expanded black-box warning incorporating information about an increased risk of suicidal symptoms in young adults 18 to 24 years of age. Since October 2004, antidepressants have been required to have a black-box warning indicating that they are associated with an increased risk of suicidal thinking, feeling, and behavior in children and adolescents. The new warning also states that there is no evidence of an increased risk for adults older than 24 years of age and that the risk is actually decreased for adults . . .


On May 10, 2007, the Food and Drug Administration (FDA) convened a meeting of its Oncology Drug Advisory Committee to discuss concerns about risks associated with the erythropoiesis-stimulating agents (ESAs) used to treat anemia caused by chemotherapy. The principal ESAs under scrutiny were epoetin alfa (Procrit, Eprex, and Epogen) and darbepoetin alfa (Aranesp), and the risks — actual or potential — were thromboembolic disease, promotion of tumor growth, and decreased survival. The actual risk of thromboembolic events was shown in two phase 3 clinical trials, reported in the Journal in 2006, that unequivocally showed an increased risk of death or . . .


sighed as I flipped again through the paperwork sent with my first admission of the night. All I found was a partially legible discharge summary. The patient, a young man who was ventilator dependent and in a vegetative state since receiving a gunshot injury 6 months previously, had been transferred from a nursing home after a workup revealed a new deep venous thrombosis in his leg. From the limited notes provided by the nursing home, I ascertained that the gunshot had initially caused a subarachnoid hemorrhage. It was my job, as a night-float admitting resident, to determine whether it . . .


When erythropoietin won market approval in 1988, it was hailed as a wonder drug because of the selectivity of its action and its resulting relative freedom from untoward effects. This selective action was due largely to the restricted expression of its receptor on erythroid progenitors. As is common with "wonder" drugs, however, things turned out not to be quite so simple. Over the ensuing years, functional erythropoietin receptors have been shown to be present on other types of cells, but these findings have had little effect on the therapeutic uses of erythropoietin — although some of them could be advantageous . . .


University of Wisconsin researcher James Thomson and his colleagues wowed the scientific community when they reported in November 1998 that they had isolated and cultured human embryonic stem cells.1 They also precipitated intense debate. Although moral dilemmas and federal funding of stem-cell research have received the most media attention, behind-the-scenes concern has centered on the market for stem cells — the ownership, control, pricing, and availability of stem-cell lines. For many academic researchers hoping to build on Thomson’s discovery, the difficulty of obtaining stem cells was immensely frustrating. This difficulty arose because not only did Wisconsin have material rights to . . .


As has been the case for patients with chronic renal failure, treatment with erythropoiesis-stimulating agents (ESAs) has substantially raised the hemoglobin concentrations of hundreds of thousands of patients with cancer, diminishing their need for red-cell transfusions during chemotherapy. At the same time, use of these agents has raised safety concerns because they can cause thromboembolic events and increase "the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL," according to the black-box warning that the Food and Drug Administration (FDA) added to the prescribing information in March 2007.1 Therefore, the . . .
Amyloidogenic proteins and glycosaminoglycans designed to interfere with interactions between fibrils. Amyloid deposition in the kidney causes proteinuria, reduction in creatinine clearance, and deposition of the fibrils in tissues. We performed a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of eprodisate in patients with AA amyloidosis and kidney involvement. We randomly assigned 183 patients from 27 centers to receive eprodisate or placebo for 24 months. The primary composite end point was an assessment of renal function or death. Disease was classified as worsened if any one of the following occurred: doubling of the serum creatinine level, reduction in creatinine clearance by 50% or more, progression to end-stage renal disease, or death. At 24 months, disease was worsened in 24 of 89 patients who received eprodisate (27%) and 38 of 94 patients given placebo (40%; P=0.06); the hazard ratio for worsening disease with eprodisate treatment was 0.58 (95% confidence interval, 0.37 to 0.93; P=0.02). The mean rates of decline in creatinine clearance were 10.9 and 15.6 ml per minute per 1.73 m2 of body-surface area per year in the eprodisate and the placebo groups, respectively (P=0.02). The drug had no significant effect on progression to end-stage renal disease (hazard ratio, 0.54; P=0.20) or risk of death (hazard ratio, 0.95; P=0.94). The incidence of adverse events was similar in the two groups. Eprodisate slows the decline of renal function in AA amyloidosis.


This year, my clinic began inviting patients to use a secure Internet link to communicate with physicians and staff members. Self-preservation was high on our list of reasons for establishing online communication. Our patients had become accustomed to contacting us through myriad routes: the clinic telephone, our individual office lines, the hospital paging system, our cell phones, the clinic fax machine, and in some cases, our home telephones. Secure Web messaging about routine issues was an attempt to direct round-the-clock communication into a manageable channel. Even before we initiated such messaging within a broader model of e-medicine, many patients . . .


Careful microbiologic evaluation of patients with various illnesses has led to the discovery of many important pathogens in recent decades, including human immunodeficiency virus (HIV), legionella species, Borrelia burgdorferi (the agent of Lyme disease), human herpesvirus 8 (HHV-8), and numerous others. Success in these endeavors, however, was critically dependent on the availability of the appropriate technology for both the detection of the microorganism and its characterization to the level necessary to permit clear differentiation from already recognized pathogens. The delay between the recognition of a particular clinical syndrome and the identification of its causative agent has been highly variable. Whereas . . .

**ARTICLES**


Amyloid A (AA) amyloidosis is a complication of chronic inflammatory conditions that develops when proteolytic fragments of serum amyloid A protein (SAA) are deposited in tissues as amyloid fibrils. Amyloid deposition in the kidney causes progressive deterioration in renal function. Eprodisate is a member of a new class of compounds designed to interfere with interactions between amyloidogenic proteins and glycosaminoglycans and thereby inhibit polymerization of amyloid fibrils and deposition of the fibrils in tissues. Bartonella species cause serious human infections globally, including bacillary angiomatosis, Oroya fever, trench fever, and endocarditis. We describe a patient who had fever and splenomegaly after traveling to Peru and also had bacteremia from an organism that resembled Bartonella bacilliformis, the causative agent of Oroya fever, which is endemic to Peru. However, genetic analyses revealed that this fastidious bacterium represented a previously uncultured and unnamed bartonella species, closely related to B. clarridgeiae and more distantly related to B. bacilliformis. We characterized this isolate, including its ability to cause fever and sustained bacteremia in a rhesus macaque. The route of infection and burden of human disease associated with this newly described pathogen are currently unknown.


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Deposition of amyloid fibrils derived from circulating acute-phase reactant serum amyloid A protein (SAA) causes systemic AA amyloidosis, a serious complication of many chronic inflammatory disorders. Little is known about the natural history of AA amyloidosis or its response to treatment. We evaluated clinical features, organ function, and survival among 374 patients with AA amyloidosis who were followed for a median of 86 months. The SAA concentration was measured serially, and the amyloid burden was estimated with the use of whole-body serum amyloid P component scintigraphy. Therapy for inflammatory diseases was administered to suppress the production of SAA. Median survival after diagnosis was 133 months; renal dysfunction was the predominant disease manifestation. Mortality, amyloid burden, and renal prognosis all significantly correlated with the SAA concentration during follow-up. The median SAA concentration during follow-up was 6 mg per liter in patients in whom renal function improved and 28 mg per liter in those in whom it deteriorated (P < 0.001). Amyloid deposits regressed in 60% of patients who had a median SAA concentration of less than 10 mg per liter, and survival among these patients was superior to survival among those in whom amyloid deposits did not regress (P = 0.04). The effects of renal dysfunction dominate the course of AA amyloidosis, which is associated with a relatively favorable outcome in patients with SAA concentrations that remain in the low-normal range (<4 mg per liter).

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined. We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes. Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction and death from cardiovascular causes was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P = 0.03), and the odds ratio for death from cardiovascular causes was 1.03 (95% CI, 0.86 to 1.23; P = 0.74).
was 1.64 (95% CI, 0.98 to 2.74; P=0.06). Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.


Anidulafungin, a new echinocandin, has potent activity against candida species. We compared anidulafungin with fluconazole in a randomized, double-blind, noninferiority trial of treatment for invasive candidiasis. Adults with invasive candidiasis were randomly assigned to receive either intravenous anidulafungin or intravenous fluconazole. All patients could receive oral fluconazole after 10 days of intravenous therapy. The primary efficacy analysis assessed the global response (clinical and microbiologic) at the end of intravenous therapy in patients who had a positive baseline culture. Efficacy was also assessed at other time points. Eighty-nine percent of the 245 patients in the primary analysis had candidemia only. Candida albicans was isolated in 62% of the 245 patients. In vitro fluconazole resistance was infrequent. Most of the patients (97%) did not have neutropenia. At the end of intravenous therapy, treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole (difference, 15.4 percentage points; 95% confidence interval [CI], 3.9 to 27.0). The results were similar for other efficacy end points. The statistical analyses failed to show a “center effect”; when data from the site enrolling the largest number of patients were removed, success rates at the end of intravenous therapy were 73.2% in the anidulafungin group and 61.1% in the fluconazole group (difference, 12.1 percentage points; 95% CI, −1.1 to 25.3). The frequency and types of adverse events were similar in the two groups. The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group (P=0.13). Anidulafungin was shown to be noninferior to fluconazole in the treatment of invasive candidiasis.


Adrenocortical carcinoma is a rare neoplasm characterized by a high risk of recurrence after radical resection. Whether the use of mitotane is beneficial as an adjuvant treatment has been controversial. Our aim was to evaluate the efficacy of adjuvant mitotane in prolonging recurrence-free survival. We performed a retrospective analysis involving 177 patients with adrenocortical cancer who had undergone radical surgery at 8 centers in Italy and 47 centers in Germany between 1985 and 2005. Adjuvant mitotane was administered to 47 Italian patients after radical surgery (mitotane group), whereas 55 Italian patients and 75 German patients (control groups 1 and 2, respectively) did not receive adjuvant treatment after surgery. Baseline features in the mitotane group and the control group from Italy were similar; the German patients were significantly older (P=0.03) and had more stage I or II adrenocortical carcinomas (P=0.02) than did patients in the mitotane group. Recurrence-free survival was significantly prolonged in the mitotane group, as compared with the two control groups (median recurrence-free survival, 42 months, as compared with 10 months in control group 1 and 25 months in control group 2). Hazard ratios for recurrence were 2.91 (95% confidence interval [CI], 1.77 to 4.78; P<0.001) and 1.97 (95% CI, 1.21 to 3.20; P=0.005), respectively. Multivariate analysis indicated that mitotane treatment had a significant advantage for recurrence-free survival. Adverse events associated with mitotane were mainly of grade 1 or 2, but temporary dose reduction was needed in 13% of patients. Adjuvant mitotane may prolong recurrence-free survival in patients with radically resected adrenocortical carcinoma.

SPECIAL ARTICLES
Mortality from coronary heart disease in the United States has decreased substantially in recent decades. We conducted a study to determine how much of this decrease could be explained by the use of medical and surgical treatments as opposed to changes in cardiovascular risk factors. We applied a previously validated statistical model, IMPACT, to data on the use and effectiveness of specific cardiac treatments and on changes in risk factors between 1980 and 2000 among U.S. adults 25 to 84 years old. The difference between the observed and expected number of deaths from coronary heart disease in 2000 was distributed among the treatments and risk factors included in the analyses. From 1980 through 2000, the age-adjusted death rate for coronary heart disease fell from 542.9 to 266.8 deaths per 100,000 population among men and from 263.3 to 134.4 deaths per 100,000 population among women, resulting in 341,745 fewer deaths from coronary heart disease in 2000. Approximately 47% of this decrease was attributed to treatments, including secondary preventive therapies after myocardial infarction or revascularization (11%), initial treatments for acute myocardial infarction or unstable angina (10%), treatments for heart failure (9%), revascularization for chronic angina (5%), and other therapies (12%). Approximately 44% was attributed to changes in risk factors, including reductions in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%), although these reductions were partially offset by increases in the body-mass index and the prevalence of diabetes, which accounted for an increased number of deaths (8% and 10%, respectively). Approximately half the decline in U.S. deaths from coronary heart disease from 1980 through 2000 may be attributable to reductions in major risk factors and approximately half to evidence-based medical therapies.


There is emerging concern that the methods used to measure the quality of care unfairly penalize providers caring for patients with multiple chronic conditions. We therefore sought to study the relationship between the quality of care and the number of medical conditions a patient has. We assessed measurements of the quality of medical care received in three cohorts of community-dwelling adult patients in the Community Quality Index study, the Assessing Care of Vulnerable Elders study, and the Veterans Health Administration project (7680 patients in total). We analyzed the relationship between the quality of care that patients received, defined as the percentage of quality indicators satisfied among those for which patients were eligible, and the number of chronic medical conditions each patient had. We further explored the roles of characteristics of patients, use of health care (number of office visits and hospitalizations), and care provided by specialists as explanations for the observed relationship. The quality of care increased as the number of medical conditions increased. Each additional condition was associated with an increase in the quality score of 2.2% (95% confidence interval [CI], 1.7 to 2.7) in the Community Quality Index cohort, of 1.7% (95% CI, 1.1 to 2.4) in the Assessing Care of Vulnerable Elders cohort, and of 1.7% (95% CI, 0.7 to 2.8) in the Veterans Health Administration cohort. The relationship between the quality of care and the number of conditions was little affected by adjustment for the difficulty of delivering the care recommended in a quality indicator and for the fact that, because of multiple conditions requiring the same care, a patient could be eligible to receive the same care process more than once. Adjustment for characteristics of patients, use of health care, and care provided by specialists diminished the relationship, but it remained positive. The quality of care, measured according to whether patients were offered recommended services, increases as a patient’s number of chronic conditions increases.

REVIEW ARTICLE


The effect of local therapy on the survival of patients with breast cancer has been debated for decades. Three viewpoints have been proposed on the basis of various hypotheses concerning the biology of breast cancer. Is breast cancer a local disease that spreads predictably over time to develop distant metastases? Is it a systemic disease from the outset, with distant metastases present well before diagnosis? Or is the truth somewhere in between, with many cancers being localized at diagnosis and, if untreated or recurrent, acquiring the ability to metastasize and kill? These differing views have vastly different implications for the . . .
IMAGES IN CLINICAL MEDICINE


A 40-year-old man with a 4-year history of diabetes mellitus and no history of gallstones was admitted to the health center after acute alcohol intoxication. He had been consuming about 200 ml of whiskey a day for over 15 years. No one in his immediate family had diabetes mellitus. On further questioning, he reported passing bulky, foul-smelling stools, which were difficult to flush, for more than 3 months. He also reported decreased night vision, although his visual acuity was normal. The serum lipase level was 468 U per liter, and the glucose level was 432 mg per deciliter (24 mmol


A 53-year-old man with Crohn’s disease, short-bowel syndrome that required total parenteral nutrition, a history of recurrent catheter infections, hypertension, chronic renal insufficiency, and mitral regurgitation presented with fevers of 2 weeks’ duration. He had elevated liver enzyme levels (aspartate aminotransferase, 45 U per liter; alanine aminotransferase, 97 U per liter; alkaline phosphatase, 679 U per liter; and total bilirubin, 7.3 mg per deciliter [125 µmol per liter]). Abdominal ultrasonography and endoscopic retrograde cholangiopancreatography showed no abnormalities. Blood was obtained for culture, and the patient was discharged while receiving intravenous levofloxacin. He returned after 5 days because of continued fevers . . .


A 73-year-old woman presented with new-onset periorbital purpuric, nonblanching, nonpruritic lesions. The lesions appeared spontaneously and were not associated with any recent trauma. She did not take aspirin, nonsteroidal antiinflammatory drugs, or any other anticoagulant agents. On physical examination, no similar skin lesions were found elsewhere. In addition, laboratory studies revealed mild impairment of renal function and nephritic-range proteinuria. The blood count showed mild thrombocytopenia (platelet count, 80,000 per cubic millimeter), whereas the prothrombin time and partial-thromboplastin time were normal. Approximately 3 years earlier, the patient had received a diagnosis of multiple myeloma and acquired monoclonal immunoglobulin light-chain amyloidosis, for . . .


An 86-year-old man received a diagnosis of stage IV adenocarcinoma of the rectum, with metastatic disease noted below the aortic bifurcation. He had no history of inflammatory bowel disease. He was treated with 4500 cGy of radiation delivered to the whole pelvis in 25 fractions by means of a four-field box technique, in conjunction with fluorouracil and folic acid. Five weeks after the initiation of the radiotherapy, severe diarrhea developed, increasing to 11 episodes per day. No infectious pathogens were found. Computed tomography of the abdomen showed diffuse bowel changes that involved most of the ileum . . .

CLINICAL PROBLEM-SOLVING


In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows. A 34-year-old black woman presented to a walk-in clinic with a 3-day history of malaise. Her colleagues had noticed yellowing of her eyes over the past few days. Scleral icterus, which is usually apparent when total serum bilirubin levels exceed 3 mg per deciliter (51 µmol per liter), is frequently first noticed not by the patient but by others. It may result . . .

CLINICAL PRACTICES


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. An otherwise healthy 53-year-old woman is seen for routine care after completing treatment several months earlier for stage II estrogen-receptor–positive, HER2-positive breast cancer. The treatment consisted of lumpectomy, irradiation, adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel), and
trastuzumab. Her only current medication is an aromatase inhibitor. She is amenorrheic. She reports fatigue, hot flashes, arthralgias, and sexual difficulties and is concerned . . .

**CLINICAL IMPLICATIONS OF BASIC RESEARCH**


A long-standing question in rheumatology is why inflammatory arthritides such as rheumatoid arthritis involve the joints. Many studies have addressed this question; a recent article by Lee et al.1 provides a new answer that is both obvious and intriguing. Rheumatoid arthritis affects the joints because of the essential role of the synovium in regulating inflammation. The normal synovial membrane is a thin, glistening tissue that lines the diarthrodial joints. Its name (which contains the root “ovum”) derives from its visual similarity to the thin lining under the shell of a chicken egg. The membrane normally consists of a lining layer . . .

**CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL**


A 54-year-old man was seen in consultation at the Multidisciplinary Genitourinary Clinic of the Cancer Center of this hospital because of a recent diagnosis of prostate cancer. Approximately 3 years earlier, the serum prostate-specific antigen (PSA) level obtained during an annual physical examination was 5.2 ng per milliliter. One month later, transrectal ultrasonography-guided biopsy of the prostate was performed; pathological examination showed no evidence of carcinoma. Repeated PSA testing was performed on multiple occasions thereafter (Table 1). Fourteen months before the consultation, examination of another ultrasonography-guided biopsy specimen of the prostate revealed no evidence of carcinoma.

**HEALTH POLICY REPORTS**


Judging from the excited rhetoric of some of its enthusiasts, health information technology (HIT) has the power to transport us to almost a dreamlike world of health care perfection in which the work of doctors and the care of patients proceed with barely imaginable quality and efficiency. For many physicians, however, especially those in solo or small practices, HIT conjures a very different image — that of a waiting room full to bursting, a crashed computer, and a frantic clinician on hold with IT support in Bangalore. With these two starkly different fantasies animating so much discussion about HIT, the . . .