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**PERSPECTIVE**

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


In 1937, an article in the Journal describing 10 years of births at Boston City Hospital revealed an overall rate of cesarean delivery of about 3%. Recently released 2005 data on cesarean deliveries show that contemporary rates are 10 times as high, having climbed above 30% (see graph). Indeed, of the 20th century’s many changes in obstetrical care — the wholesale move from home to hospital delivery, increasing use of anesthesia, the advent of in vitro fertilization — few have generated more attention and debate or had a greater effect on the process of delivery than this . . .


In the light of recent studies suggesting that drug-eluting stents may pose a risk of thrombosis that was not observed during pre-market testing, the Food and Drug Administration (FDA) convened a meeting of its Circulatory System Devices Advisory Panel on December 7 and 8, 2006, to examine the safety of these devices. The FDA will carefully consider the information and views presented at the meeting in deciding on future actions. An understanding of the mechanisms of neointimal growth within bare-metal stents led to the development of drug-eluting stents designed to reduce restenosis rates. Both drug-eluting stents approved by the FDA . . .


After recognizing coronary drug-eluting stents as a “breakthrough technology” and granting them expedited review status, the Food and Drug Administration (FDA) approved two such devices for use in 2003 (Cordis’s sirolimus-eluting Cypher stent) and 2004 (Boston Scientific’s paclitaxel-eluting Taxus stent). Cardiologists quickly embraced the new technology; by the end of 2004, drug-eluting stents were used in nearly 80% of percutaneous coronary interventions in the United States, and within 3 years, several million drug-eluting stents had been implanted worldwide. Recently, however, concerns about an increased risk of late stent thrombosis have arisen and have been exacerbated by insufficient and conflicting information . . .


In 1949, Ackroyd reported the abrupt onset of severe thrombocytopenia and purpura in patients receiving the sedative allylisonpropylacetylcarbamide (Sedormid). All the patients had taken Sedormid previously and had become sensitized to it. Today, this classic picture of drug-induced, immune-mediated thrombocytopenia is most often caused by quinine in outpatients and by vancomycin in hospitalized patients, as discussed by Von Drygalski et al. in this issue of the Journal (pages 904–910). In 1973, Rhodes, Dixon, and Silver described thrombocytopenia and thrombosis occurring a week after the initiation of heparin therapy and provided evidence of an immune pathogenesis for this complication of . . .


The gynecology clinic is often a discouraging learning environment for medical students. Although those who complete a third-year clerkship in obstetrics and gynecology may take histories from plenty of women, many find they rarely get an opportunity to perform a pelvic examination: either their preceptors are reluctant to ask patients whether a medical student can examine them or the patients decline.

In contrast to ambulatory care, the gynecologic operating room has historically provided medical students with an opportunity to learn this exam: they could perform it in anesthetized patients immediately before surgery. The examination under anesthesia is typically done to . . .

**ORIGINAL ARTICLES**


Vancomycin has only rarely been implicated as a cause of thrombocytopenia, and there is only limited evidence that this complication is caused by immune mechanisms. We conducted a study to determine whether thrombocytopenia is caused by vancomycin-dependent antibodies in patients being treated with vancomycin. We identified and characterized vancomycin-dependent, platelet-reactive antibodies in patients who had been referred for testing during a 5-year period because of a clinical suspicion of vancomycin-induced thrombocytopenia.

We obtained clinical information about the patients from their referring physicians. Drug-dependent, platelet-reactive antibodies of the IgG class, the IgM class, or both were identified in 34 patients, and clinical follow-up information was obtained from 29 of these patients. The mean nadir platelet count in these patients was 13,600 per cubic millimeter, and severe bleeding occurred in 10 patients (34%). Platelet levels returned to baseline in all 26 surviving patients after vancomycin was stopped. In 15 patients, the drug was continued for 1 to 14 days while other possible causes of thrombocytopenia were investigated. Vancomycin-dependent antibodies were not found in 25 patients who had been given vancomycin and in whom thrombocytopenia did not develop.

Severe bleeding can occur in patients with vancomycin-induced immune thrombocytopenia. The detection of vancomycin-dependent antiplatelet antibodies in patients receiving the
antibiotic in whom thrombocytopenia develops, and the absence of antibodies in patients given the drug in whom platelet counts remain stable, indicate that these antibodies are the cause of the thrombocytopenia.


The long-term effects of treatment with sirolimus-eluting stents, as compared with bare-metal stents, have not been established. We performed an analysis of individual data on 4958 patients enrolled in 14 randomized trials comparing sirolimus-eluting stents with bare-metal stents (mean follow-up interval, 12.1 to 58.9 months). The primary end point was death from any cause. Other outcomes were stent thrombosis, the composite end point of death or myocardial infarction, and the composite of death, myocardial infarction, or reintervention. The overall risk of death (hazard ratio, 1.03; 95% confidence interval [CI], 0.80 to 1.30) and the combined risk of death or myocardial infarction (hazard ratio, 0.97; 95% CI, 0.81 to 1.16) were not significantly different for patients receiving sirolimus-eluting stents versus bare-metal stents. There was a significant reduction in the combined risk of death, myocardial infarction, or reintervention (hazard ratio, 0.43; 95% CI, 0.34 to 0.54) associated with the use of sirolimus-eluting stents. There was no significant difference in the overall risk of stent thrombosis with sirolimus-eluting stents versus bare-metal stents (hazard ratio, 1.09; 95% CI, 0.64 to 1.86). However, there was evidence of a slight increase in the risk of stent thrombosis associated with sirolimus-eluting stents after the first year. The use of sirolimus-eluting stents does not have a significant effect on overall long-term survival and survival free of myocardial infarction, as compared with bare-metal stents. There is a sustained reduction in the need for reintervention after the use of sirolimus-eluting stents. The risk of stent thrombosis is at least as great as that seen with bare-metal stents.


Recent reports have indicated that there may be an increased risk of late stent thrombosis with the use of drug-eluting stents, as compared with bare-metal stents. We evaluated 6033 patients treated with drug-eluting stents and 13,738 patients treated with bare-metal stents in 2003 and 2004, using data from the Swedish Coronary Angiography and Angioplasty Registry. The outcome analysis covering a period of up to 3 years was based on 1424 deaths and 2463 myocardial infarctions and was adjusted for differences in The two study groups did not differ significantly in the composite of death and myocardial infarction during 3 years of follow-up. At 6 months, there was a trend toward a lower unadjusted event rate in patients with drug-eluting stents than in those with bare-metal stents, with 13.4 fewer such events per 1000 patients. However, after 6 months, patients with drug-eluting stents had a significantly higher event rate, with 12.7 more events per 1000 patients per year (adjusted relative risk, 1.20; 95% confidence interval [CI], 1.05 to 1.37). At 3 years, mortality was significantly higher in patients with drug-eluting stents (adjusted relative risk, 1.18; 95% CI, 1.04 to 1.35), and from 6 months to 3 years, the adjusted relative risk for death in this group was 1.32 (95% CI, 1.11 to 1.57). Drug-eluting stents were associated with an increased rate of death, as compared with bare-metal stents. This trend appeared after 6 months, when the risk of death was 0.5 percentage point higher and a composite of death or myocardial infarction was 0.5 to 1.0 percentage point higher per year. The long-term safety of drug-eluting stents needs to be ascertained in large, randomized trials.


Definitions of stent thrombosis that have been used in clinical trials of drug-eluting stents have been restrictive and have not been used in a uniform manner. We applied a hierarchical classification of stent thrombosis set by the Academic Research Consortium (ARC) across randomized trials involving 878 patients treated with sirolimus-eluting stents, 1400 treated with paclitaxel-eluting stents, and 2267 treated with bare-metal stents. We then pooled 4 years of follow-up data. All events were adjudicated by an independent clinical-events committee. The cumulative incidence of stent thrombosis according to the original protocol definitions was 1.2% in the sirolimus-stent group versus 0.6% in the bare-metal–stent group (P=0.20; 95% confidence interval [CI], –0.4 to 1.5) and 1.3% in the paclitaxel-stent group versus 0.8% in the bare-metal–stent group (P=0.24; 95% CI, –0.3 to 1.4). The incidence of definite or probable stent thrombosis as defined by the ARC was 1.5% in the sirolimus-stent group versus 1.7% in the bare-metal–stent group (P=0.70; 95% CI, –1.5 to 1.0) and 1.8% in the paclitaxel-stent group versus 1.4% in the bare-metal–stent group (P=0.52; 95% CI, –0.7 to 1.4). The incidence of definite or probable events occurring 1 to 4 years after implantation was 0.9% in the sirolimus-stent group versus 0.4% in the bare-metal–stent group and 0.9% in the paclitaxel-stent group versus 0.6% in the bare-metal–stent group. The incidence of stent thrombosis did not differ significantly between patients with drug-eluting stents and those with bare-metal stents in randomized clinical trials, although the power to detect small differences in rates was limited.


Although randomized studies have shown a beneficial effect of drug-eluting stents in reducing the risk of repeated
revascularization, these trials were underpowered to compare rates of death and myocardial infarction. The long-term safety of drug-eluting stents has been questioned recently. We performed a pooled analysis of 1748 patients in four randomized trials evaluating the safety of sirolimus-eluting stents as compared with bare-metal stents. Patient-level data were obtained and analyzed by independent statisticians at two academic institutions. The primary safety end point was survival at 4 years. We tested for heterogeneities in treatment effect in patient subgroups. The survival rate at 4 years was 93.3% in the sirolimus-stent group, as compared with 94.6% in the bare-metal–stent group (hazard ratio for death, 1.24; 95% confidence interval [CI], 0.84 to 1.83; P=0.28). In the 428 patients with diabetes, a significant difference in the survival rate was observed in favor of the bare-metal–stent group over the sirolimus-stent group (95.6% vs. 87.8%; hazard ratio for death in the sirolimus-stent group, 2.9; 95% CI, 1.38 to 6.10; P=0.008). The lower survival rate among patients with diabetes who were treated with sirolimus-eluting stents was due to increased numbers of deaths from both cardiovascular and noncardiovascular causes. No difference in survival rate was detected among the patients without diabetes. Rates of myocardial infarction and stent thrombosis were similar in the two groups. In a pooled analysis of data from four trials comparing sirolimus-eluting stents and bare-metal stents, no significant differences were found between the two treatments in rates of death, myocardial infarction, or stent thrombosis.


Hepatitis E virus (HEV) is an important cause of viral hepatitis. We evaluated the safety and efficacy of an HEV recombinant protein (rHEV) vaccine in a phase 2, randomized, double-blind, placebo-controlled trial. In Nepal, we studied 2000 healthy adults susceptible to HEV infection who were randomly assigned to receive three doses of either the rHEV vaccine or placebo at months 0, 1, and 6. Active (including hospital) surveillance was used to identify acute hepatitis and adverse events. The primary end point was the development of hepatitis E after three vaccine doses. A total of 1794 subjects (898 in the vaccine group and 896 in the placebo group) received three vaccine doses; the total vaccinated cohort was followed for a median of 804 days. After three vaccine doses, hepatitis E developed in 69 subjects, of whom 66 were in the placebo group. The vaccine efficacy was 95.5% (95% confidence interval [CI], 85.6 to 98.6). In an intention-to-treat analysis that included all 87 subjects in whom hepatitis E developed after the first vaccine dose, 9 subjects were in the vaccine group, with a vaccine efficacy of 88.5% (95% CI, 77.1 to 94.2). Among subjects in a subgroup randomly selected for analysis of injection-site findings and general symptoms (reactogenicity subgroup) during the 8-day period after the administration of any dose, the proportion of subjects with adverse events was similar in the two study groups, except that injection-site pain was increased in the vaccine group (P=0.03). In a high-risk population, the rHEV vaccine was effective in the prevention of hepatitis E.


The safety of drug-eluting stents has been called into question by recent reports of increased stent thrombosis, myocardial infarction, and death. Such studies have been inconclusive because of their insufficient size, the use of historical controls, a limited duration of follow-up, and a lack of access to original source data. We performed a pooled analysis of data from four double-blind trials in which 1748 patients were randomly assigned to receive either sirolimus-eluting stents or bare-metal stents and five double-blind trials in which 3513 patients were randomly assigned to receive either paclitaxel-eluting stents or bare-metal stents; we then analyzed the major clinical end points of the trials. The 4-year rates of stent thrombosis were 1.2% in the sirolimus-stent group versus 0.6% in the bare-metal–stent group (P=0.20) and 1.3% in the paclitaxel-stent group versus 0.9% in the bare-metal–stent group (P=0.30). However, after 1 year, there were five episodes of stent thrombosis in patients with sirolimus-eluting stents versus none in patients with bare-metal stents (P=0.025) and nine episodes in patients with paclitaxel-eluting stents versus two in patients with bare-metal stents (P=0.028). The 4-year rates of target-lesion revascularization were markedly reduced in both the sirolimus-stent group and the paclitaxel-stent group, as compared with the bare-metal–stent groups. The rates of death or myocardial infarction did not differ significantly between the groups with drug-eluting stents and those with bare-metal stents. Stent thrombosis after 1 year was more common with both sirolimus-eluting stents and paclitaxel-eluting stents than with bare-metal stents. Both drug-eluting stents were associated with a marked reduction in target-lesion revascularization. There were no significant differences in the cumulative rates of death or myocardial infarction at 4 years.


Systemic inflammation may impair vascular function, and epidemiologic data suggest a possible link between periodontitis and cardiovascular disease. We randomly assigned 120 patients with severe periodontitis to community-based periodontal care (59 patients) or intensive periodontal treatment (61). Endothelial function, as assessed by measurement of the diameter of the
brachial artery during flow (flow-mediated dilatation), and inflammatory biomarkers and markers of coagulation and endothelial activation were evaluated before treatment and 1, 7, 30, 60, and 180 days after treatment. Twenty-four hours after treatment, flow-mediated dilatation was significantly lower in the intensive-treatment group than in the control-treatment group (absolute difference, 1.4%; 95% confidence interval [CI], 0.5 to 2.3; P=0.002), and levels of C-reactive protein, interleukin-6, and the endothelial-activation markers soluble E-selectin and von Willebrand factor were significantly higher (P<0.05 for all comparisons). However, flow-mediated dilatation was greater and the plasma levels of soluble E-selectin were lower in the intensive-treatment group than in the control-treatment group 60 days after therapy (absolute difference in flow-mediated dilatation, 0.9%; 95% CI, 0.1 to 1.7; P=0.02) and 180 days after therapy (difference, 2.0%; 95% CI, 1.2 to 2.8; P<0.001). The degree of improvement was associated with improvement in measures of periodontal disease (r=0.29 by Spearman rank correlation, P=0.003). There were no serious adverse effects in either of the two groups, and no cardiovascular events occurred. Intensive periodontal treatment resulted in acute, short-term systemic inflammation and endothelial dysfunction. However, 6 months after therapy, the benefits in oral health were associated with improvement in endothelial function.

SPECIAL ARTICLE


The Health Disparities Collaboratives of the Health Resources and Services Administration (HRSA) were designed to improve care in community health centers, where many patients from ethnic and racial minority groups and uninsured patients receive treatment. We performed a controlled preintervention and postintervention study of community health centers participating in quality-improvement collaboratives (the Health Disparities Collaboratives sponsored by the HRSA) for the care of patients with diabetes, asthma, or hypertension. We enrolled 9658 patients at 44 intervention centers that had participated in the collaboratives and 20 centers that had not participated (external control centers). Each intervention center also served as an internal control for another condition. Quality measures were abstracted from medical records at each health center. We created overall quality scores by standardizing and averaging the scores from all of the applicable measures. Changes in quality were evaluated with the use of hierarchical regression models that controlled for patient characteristics. Overall, the intervention centers had considerably greater improvement than the external and internal control centers in the composite measures of quality for the care of patients with asthma and diabetes, but not for those with hypertension. As compared with the external control centers, the intervention centers had significant improvements in the measures of prevention and screening, including a 21% increase in foot examinations for patients with diabetes, and in disease treatment and monitoring, including a 14% increase in the use of antiinflammatory medication for asthma and a 16% increase in the assessment of glycated hemoglobin. There was no improvement, however, in any of the intermediate outcomes assessed (urgent care or hospitalization for asthma, control of glycated hemoglobin levels for diabetes, and control of blood pressure for hypertension).

The Health Disparities Collaboratives significantly improved the processes of care for two of the three conditions studied. There was no improvement in the clinical outcomes studied.

CLINICAL IMPLICATION OF BASIC RESEARCH


Targeting drugs to tumors has been a key goal of cancer pharmacology for decades. Newer technologies such as monoclonal antibodies engineered to target tumors, as well as liposomal or nanoparticle drug carriers, represent important steps toward this goal, but they have limitations. A recent study by Cheong and colleagues1 provides a new twist on tumor-targeted drugs: the authors use bacteria to release liposomal drugs within the tumor..

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 3-year-old boy presents with a 6-month history of strabismus in his left eye. The visible inward deviation of the eye began intermittently but is now constant. His visual acuity is 20/20 in the right eye but only 20/100 in the left eye. The physical examination is otherwise normal. How should he be treated?

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 73-year-old man with stable coronary artery disease, hypertension, and chronic renal insufficiency presents with recurrent atrial fibrillation at 80 to 90 beats per minute. His symptoms include shortness of breath and fatigue. He has had atrial fibrillation twice
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 79-year-old woman presented with a 1-month history of dyspnea and a cough productive of yellow sputum. She reported no chest pain, hemoptysis, night sweats, or fever. The patient’s symptoms are probably caused by a respiratory tract infection...

IMAGES IN CLINICAL MEDICINE


A healthy 69-year-old man with osteoarthritis of the knees presented with a 2-week history of mottled darkening of the skin on the left thigh. On examination, there was a reticular, reddish-brown, pruritic, nontender, macular, nonblanching discoloration around the medial aspect of his left knee, with a few superficial erosions. He had no fever, chills, or other constitutional symptoms. For several weeks before this event, the patient had applied a heating pad repeatedly to his left knee to relieve the discomfort from the osteoarthritis. The reticular, hyperpigmented erythema is a typical presentation of erythema ab igne, a phenomenon caused by chronic...


A 51-year-old woman with a history of hypertension and chronic constipation presented with abdominal pain of 2 weeks’ duration. The pain was continuous, worsened with eating, was associated with nausea, and radiated to her back. She reported no vomiting, fever, diarrhea, or weight loss, and her vital signs were normal. Her abdomen was distended, diffusely tender on palpation, and tympanic on percussion on the upper half and dull on the lower half. Bowel sounds were missing on the left side, and a large mass was palpated in that area. Laboratory evaluation was unremarkable. Computed tomography (CT) showed massive dilatation...


A 48-year-old man with multiple myeloma and a history of a repaired umbilical hernia and four thromboembolic events was admitted for cramping abdominal pain associated with back pain and a weight loss of 5 kg (11 lb) during the previous month. Physical examination showed a distended abdomen and no lower-extremity edema. Laboratory evaluation was notable for a creatinine level of 1.2 mg per deciliter (108 µmol per liter), an albumin level of 3.3 g per deciliter, and normal urinary sediment. Contrast-enhanced computed tomography showed well-defined cystic retroperitoneal masses in which the kidneys appeared to be floating, extending...


A 21-year-old woman with a history of rheumatic fever at 7 years of age presented with left-sided weakness. A large ischemic infarction involving the territory of the right middle cerebral artery was diagnosed. Cardiac evaluation revealed atrial fibrillation. Echocardiography showed normal aortic, pulmonic, and tricuspid valves, severe mitral stenosis with a valve area of 0.9 cm², and a large free-floating ball-valve thrombus in the dilated (to 5 cm in diameter) left atrium (Panels A and B, arrows), which partially obstructed the mitral valve intermittently (Panels C and D, arrows, and video). After initial stabilization, the patient was...

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL


A 59-year-old woman was admitted to the hospital because of a nonhealing ulcer on the right heel and painful ulcers on the right thigh and hip. The patient had been morbidly obese since early childhood; she had had type 2 diabetes mellitus and hypertension for 30 years and chronic renal insufficiency for 6. Painless ulcers had developed on the plantar surfaces of both heels 6 years earlier; those on the left side had healed with wound care and decreased weight bearing, but those on the right recurred when she resumed weight bearing. Four years before...