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CLINICAL PROBLEM-SOLVING

A key miscommunication: an 81-year-old woman presented to the emergency department with increasing abdominal distention, nausea, and vomiting.
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When the Food and Drug Administration (FDA) approved the Medtronic Sprint Fidelis implantable cardioverter-defibrillator (ICD) lead in 2004 on the basis of bench testing but no human clinical data, there was no public outcry. Physicians rapidly incorporated the new electrode into their practice, welcoming its small diameter and ease of implantation. During the ensuing 3 years, 90% of Medtronic ICDs were implanted with this lead (see diagram). But in October 2007, after 38 months on the U.S. market and 268,000 implantations worldwide, the Fidelis was voluntarily recalled by Medtronic because of its propensity to fracture. The large number of . . .


The conflagration over the reauthorization of the State Children’s Health Insurance Program (SCHIP) offers a compelling example of Washington’s current inability to address even seemingly uncontroversial matters such as improved health care coverage for children. After the House failed to override President George W. Bush’s veto of a SCHIP expansion in October, Congressional leaders regrouped to develop a compromise measure that would address Bush’s claim that the original bill “moves the health care system in the wrong direction.” 1 SCHIP permits coverage of children in families whose incomes (according to evaluation methods developed by the states) are at or below 200% . . .


We’ve all heard about cases in which a patient presumed to have died from acute myocardial infarction was discovered at autopsy to have had an aortic dissection, or a patient who presented with decompensated liver failure from presumed alcoholic cirrhosis but proved at autopsy to have widely metastatic hepatocellular carcinoma. Indeed, an extensive literature documents the frequency with which autopsy reveals clinically significant diagnoses that were missed before death. 1 Autopsies also generate more accurate vital statistics, provide pathological descriptions of new diseases, and offer powerful tools for education and quality assurance (see Benefits of Nonforensic Autopsies). Yet despite these benefits, . . .


How, in this era of molecular diagnostic tests, can we best determine whether there is a causal relationship between the presence of a genetic signature of an infectious agent and disease? In recent years, molecular techniques have been applied successfully in the identification of infectious agents such as Borreliosis, Kaposi’s sarcoma–associated herpesvirus (human herpesvirus 8), West Nile virus, and the severe acute respiratory syndrome (SARS) coronavirus. 1 Currently, the majority of surveillance and discovery efforts use methods based on sequences of known agents — namely, competitive polymerase chain reaction (PCR) and microarrays. Such efforts fail, however, when the agents in . . .

**ARTICLES**


Autoimmune polyendocrine syndrome type 1 (APS-1) is a multiorgan autoimmune disorder caused by mutations in AIRE, the autoimmune regulator gene. Though recent studies concerning AIRE deficiency have begun to elucidate the molecular pathogenesis of organ-specific autoimmunity in patients with APS-1, the autoantigen responsible for hypoparathyroidism, a hallmark of APS-1 and its most common autoimmune endocrinopathy, has not yet been identified. We performed immunoscreening of a human parathyroid complementary DNA library, using serum samples from patients with APS-1 and hypoparathyroidism, to identify patients with reactivity to the NACHT leucine-rich repeat protein 5 (NALP5). Subsequently, serum samples from 87 patients with APS-1 and 293 controls, including patients with other autoimmune disorders, were used to determine the frequency and specificity of autoantibodies against NALP5. In addition, the expression of NALP5 was investigated in various tissues. NALP5-specific autoantibodies were detected in 49% of the patients with APS-1 and hypoparathyroidism but were absent in all patients with APS-1 but without hypoparathyroidism, in all patients with other autoimmune endocrine disorders, and in all healthy controls. NALP5 was predominantly expressed in the cytoplasm of parathyroid chief cells. NALP5 appears to be a tissue-specific
autoantigen involved in hypoparathyroidism in patients with APS-1. Autoantibodies against NALP5 appear to be highly specific and may be diagnostic for this prominent component of APS-1.


Severe anemia is a major cause of sickness and death in African children, yet the causes of anemia in this population have been inadequately studied. We conducted a case–control study of 381 preschool children with severe anemia (hemoglobin concentration, <5.0 g per deciliter) and 757 preschool children without severe anemia in urban and rural settings in Malawi. Causal factors previously associated with severe anemia were studied. The data were examined by multivariate analysis and structural equation modeling. Bacteremia (adjusted odds ratio, 5.3; 95% confidence interval [CI], 2.6 to 10.9), malaria (adjusted odds ratio, 2.3; 95% CI, 1.6 to 3.3), hookworm (adjusted odds ratio, 4.8; 95% CI, 2.0 to 11.8), human immunodeficiency virus infection (adjusted odds ratio, 2.0; 95% CI, 1.0 to 3.8), the G6PD–202/–376 genetic disorder (adjusted odds ratio, 2.4; 95% CI, 1.3 to 4.4), vitamin A deficiency (adjusted odds ratio, 2.8; 95% CI, 1.3 to 5.8), and vitamin B12 deficiency (adjusted odds ratio, 2.2; 95% CI, 1.4 to 3.6) were associated with severe anemia. Folate deficiency, sickle cell disease, and laboratory signs of an abnormal inflammatory response were uncommon. Iron deficiency was not prevalent in case patients (adjusted odds ratio, 0.37; 95% CI, 0.22 to 0.60) and was negatively associated with bacteremia. Malaria was associated with severe anemia in the urban site (with seasonal transmission) but not in the rural site (where malaria was holoendemic). Seventy-six percent of hookworm infections were found in children under 2 years of age. There are multiple causes of severe anemia in Malawian preschool children, but folate and iron deficiencies are not prominent among them. Even in the presence of malaria parasites, additional or alternative causes of severe anemia should be considered.


Systemic lupus erythematosus (SLE) is a clinically heterogeneous disease in which the risk of disease is influenced by complex genetic and environmental contributions. Alleles of HLA-DRB1, IRF5, and STAT4 are established susceptibility genes; there is strong evidence for the existence of additional risk loci. We genotyped more than 500,000 single-nucleotide polymorphisms (SNPs) in DNA samples from 1311 case subjects with SLE and 1783 control subjects; all subjects were North Americans of European descent. Genotypes from 1557 additional control subjects were obtained from public data repositories. We measured the association between the SNPs and SLE after applying strict quality-control filters to reduce technical artifacts and to correct for the presence of population stratification. Replication of the top loci was performed in 793 case subjects and 857 control subjects from Sweden. Genetic variation in the region upstream from the transcription initiation site of the gene encoding B lymphoid tyrosine kinase (BLK) and C8orf13 (chromosome 8p23.1) was associated with disease risk in both the U.S. and Swedish case–control series (rs13277113; odds ratio, 1.39; P=1x10–10) and also with altered levels of messenger RNA in B-cell lines.


Three patients who received visceral-organ transplants from a single donor on the same day died of a febrile illness 4 to 6 weeks after transplantation. Culture, polymerase-chain-reaction (PCR) and serologic assays, and oligonucleotide microarray analysis for a wide range of infectious agents were not informative. We evaluated RNA obtained from the liver and kidney transplant recipients. Unbiased high-throughput sequencing was used to identify microbial sequences not found by means of other methods. The specificity of sequences
Genetic variants of the enzyme that metabolizes warfarin, cytochrome P-450 2C9 (CYP2C9), and of a key pharmacologic target of warfarin, vitamin K epoxide reductase (VKORC1), contribute to differences in patients’ responses to various warfarin doses, but the role of these variants during initial anticoagulation is not clear. In 297 patients starting warfarin therapy, we assessed CYP2C9 genotypes (CYP2C9 *1, *2, and *3), VKORC1 haplotypes (designated A and non-A), clinical characteristics, response to therapy (as determined by the international normalized ratio [INR]), and bleeding events. The study outcomes were the time to the first INR within the therapeutic range, the time to the first INR of more than 4, the time above the therapeutic INR range, the INR response over time, and the warfarin dose requirement. As compared with patients with the non-A/non-A haplotype, patients with the A/A haplotype of VKORC1 had a decreased time to the first INR within the therapeutic range (P=0.01) and to the first INR of more than 4 (P=0.003). In contrast, the CYP2C9 genotype was not a significant predictor of the time to the first INR within the therapeutic range (P=0.57) but was a significant predictor of the time to the first INR of more than 4 (P=0.03). Both the CYP2C9 genotype and VKORC1 haplotype had a significant influence on the required warfarin dose after the first 2 weeks of therapy. Initial variability in the INR response to warfarin was more strongly associated with genetic variability in the pharmacologic target of warfarin, VKORC1, than with CYP2C9.

Vasopressin is commonly used as an adjunct to catecholamines to support blood pressure in refractory septic shock, but its effect on mortality is unknown. We hypothesized that low-dose vasopressin as compared with norepinephrine would decrease mortality among patients with septic shock who were being treated with conventional (catecholamine) vasopressors. In this multicenter, randomized, double-blind trial, we assigned patients who had septic shock and were receiving a minimum of 5 µg of norepinephrine per minute to receive either low-dose vasopressin (0.01 to 0.03 U per minute) or norepinephrine (5 to 15 µg per minute) in addition to open-label vasopressors. All vasopressor infusions were titrated and tapered according to protocols to maintain a target blood pressure. The primary end point was the mortality rate 28 days after the start of infusions. A total of 778 patients underwent randomization, were infused with the study drug (396 patients received vasopressin, and 382 norepinephrine), and were included in the analysis. There was no significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate (35.4% and 39.3%, respectively; P=0.26) or in 90-day mortality (43.9% and 49.6%, respectively; P=0.11).

A distinctive extrapyramidal syndrome has been observed in intravenous methcathinone (ephedrine) users in Eastern Europe and Russia. We studied 23 adults in Latvia who had extrapyramidal symptoms and who had injected methcathinone for a mean (±SD) of 6.7±5.1 years. The methcathinone was manufactured under home conditions by potassium permanganate oxidation of ephedrine or pseudoephedrine. All patients were positive for hepatitis C virus, and 20 were also positive for the human immunodeficiency virus (HIV). The patients reported that the onset of their first neurologic symptoms (gait disturbance in 20 and hypophonia in 3) occurred after a mean of 5.8±4.5 years of methcathinone use. At the time of neurologic evaluation, all 23 patients had gait disturbance and difficulty walking backward; 11 patients were falling daily, and 1 of these patients used a wheelchair. Twenty-one patients had hypophonic speech in addition to gait disturbance, and one of these patients was mute. No pa-
tient reported decline in cognitive function. T1-weighted magnetic resonance imaging (MRI) showed symmetric hyperintensity in the globus pallidus and in the substantia nigra and innominate in all 10 active methcathinone users. Among the 13 former users (2 to 6 years had passed since the last use), lesser degrees of change in the MRI signal were noted. Whole-blood manganese levels (normal level, <209 nmol per liter) averaged 831 nmol per liter (range, 201 to 2102) in the active methcathinone users and 346 nmol per liter (range, 114 to 727) in former users. The neurologic deficits did not resolve after patients discontinued methcathinone use. Our observation of a distinctive extrapyramidal syndrome, changes in the MRI signal in the basal ganglia, and elevated blood manganese levels in methcathinone users suggests that manganese in the methcathinone solution causes a persistent neurologic disorder.


Single-nucleotide polymorphisms (SNPs) in five chromosomal regions — three at 8q24 and one each at 17q12 and 17q24.3 — have been associated with prostate cancer. Each SNP has only a moderate association, but when SNPs are combined, the association may be stronger. We evaluated 16 SNPs from five chromosomal regions in a Swedish population (2893 subjects with prostate cancer and 1781 control subjects) and assessed the individual and combined association of the SNPs with prostate cancer. Multiple SNPs in each of the five regions were associated with prostate cancer in single SNP analysis. When the most significant SNP from each of the five regions was selected and included in a multivariate analysis, each SNP remained significant after adjustment for other SNPs and family history. Together, the five SNPs and family history were estimated to account for 46% of the cases of prostate cancer in the Swedish men we studied. The five SNPs plus family history had a cumulative association with prostate cancer (P for trend, 3.93x10–28). In men who had any five or more of these factors associated with prostate cancer, the odds ratio for prostate cancer was 9.46 (P=1.29x10–8), as compared with men without any of the factors. The cumulative effect of these variants and family history was independent of serum levels of prostate-specific antigen at diagnosis. SNPs in five chromosomal regions plus a family history of prostate cancer have a cumulative and significant association with prostate cancer.

**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 authors’ clinical recommendations. A male infant weighing 3400 g was born at 37 weeks’ gestation after an uncomplicated pregnancy. The mother is a 24-year-old primipara who has type A Rh-positive blood. The infant’s course in the hospital nursery was uncomplicated. Although his . . .

**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 woman reports losing urine with coughing, laughing, or sneezing since the birth of her last baby. She has been unable to lose the 25 lb (11 kg) that she gained after her pregnancy 6 years ago. She voids every 3 hours and reports no urinary urgency or nocturia. Her incontinence keeps her from participating in her exercise class, and she . . .

**REVIEW ARTICLES**


To the clinician, systemic lupus erythematosus is important because it is a potentially fatal disease that is easily confused with many other disorders. To the immunologist, lupus is intriguing because all the key components of the immune system are involved in the underlying mechanisms of the disease. This review describes these mechanisms and shows how knowledge of the pathogenesis of lupus facilitates its treatment. The prevalence of lupus ranges from approximately 40 cases per 100,000 persons among Northern Europeans to more than 200 per 100,000 persons among blacks.1 In the United States, the number of patients with lupus exceeds 250,000. . . .

Pulmonary embolism, most commonly originating from deep venous thrombosis of the legs, ranges from asymptomatic, incidentally discovered emboli to massive embolism causing immediate death. Chronic sequelae of venous thromboembolism (deep venous thrombosis and pulmonary embolism) include the post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. Acute pulmonary embolism may occur rapidly and unpredictably and may be difficult to diagnose. Treatment can reduce the risk of death, and appropriate primary prophylaxis is usually effective. Patients treated for acute pulmonary embolism appear to be almost four times as likely to die of recurrent thromboembolism in the next year as patients treated for deep . . .

**IMAGES IN CLINICAL MEDICINE**


A 65-year-old woman with a 15-year history of diabetes presented with fever (temperature, 38.5°C), chills, malaise, and a rash on the medial surface of the right thigh, vulva, and lower abdominal wall (Panel A). The symptoms had progressed during the previous 48 hours. Three days earlier, she had visited a general practitioner for recurrent vulvar pruritus accompanied by excoriations due to scratching. A yeast infection was diagnosed, and she was treated with a topical antifungal agent. On admission, the physical examination revealed crepitus of the abdominal wall, with no vaginal discharge or evidence of a perianal abscess. Laboratory results included . . .


A 70-year-old woman was referred by her general practitioner for evaluation of an ulcerative lesion on her lower right leg. Subcutaneous white calcifications were seen (Panel A, arrow). She had worn compression stockings for several years because of bilateral recurrent ulcers caused by venous stasis. Chronic venous insufficiency was seen on duplex ultrasonography. The patient had no other associated illnesses and had normal levels of C-reactive protein, parathyroid hormone, calcium, phosphorus, serum creatinine, and 25-hydroxycholecalciferol. Chronic venous insufficiency may be accompanied by subcutaneous calcifications. These calcifications are often discovered by chance on plain radiographs (Panel B, arrows) or on ultrasonographic . . .

**CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL**


Dr. Mary Shannon Fracchia (Pediatrics): A 17-year-old girl was transferred to this hospital because of chest pain and hemoptysis. She had been well except for mild asthma until 4 months earlier, when pedal edema developed; testing revealed 3+ proteinuria, hematuria, and hyperlipidemia. One month later, a renal biopsy was performed at another facility, and a diagnosis of membranous glomerulonephritis was made. Testing for antibodies to hepatitis B and hepatitis C, as well as antiribonuclear protein, antitopoisomerase I, anti-Smith, anti-Ro (SS-A), anti-La (SS-B), anti-double-stranded DNA, and antinuclear antibody was negative. The levels of serum C3 and C4 complement were normal. Enalapril, . . .

**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. An 81-year-old woman presented to the emergency department with increasing abdominal distention, nausea, and vomiting. She also reported increasing shortness of breath and fatigue, which had become worse over the past several weeks. She had a history of congestive heart failure, mitral regurgitation, hypertension, atrial fibrillation, hypothyroidism, peptic ulcer disease, and depression. She had no history of coronary artery disease or cardiac . . .