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INSIDE

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Toxic Shock Syndrome After Medical Abortion

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Rare cases of fatal toxic shock syndrome associated with* Clostridium sordellii *have been reported; clinicians are urged to be aware of warning signals.*

Source: Fischer M, et al. Fatal toxic shock syndrome associated with *Clostridium sordellii* after medical abortion. *N Engl J Med.* 2005;353:2352-2360.

THE CDC REPORTED 4 CASES OF FATAL TOXIC SHOCK SYNdrome in California associated with *Clostridium sordellii* that occurred within one week after medical abortions (induced with 200 mg of oral mifepristone and 800 µg of vaginal misoprostol).[1]

Patient 1: A healthy 18-year-old woman underwent medical abortion at 47 days gestation and 4 days later was seen in an emergency ward with abdominal cramping. She was afebrile and there was no tenderness on physical examination. No laboratory studies or cultures were obtained. Three days later, the patient returned with nausea, vomiting, and weakness. She was again afebrile, but now had tachycardia, hypotension, an extremely elevated white count, blood cultures that later were negative, and bilateral infiltrates on chest X-ray. She still had no positive findings on physical examination. Despite treatment with antibiotics, the patient rapidly developed respiratory distress and died 10 hours after admission.

Patient 2: A healthy 21-year-old woman underwent medical abortion at 43 days gestation and became unresponsive 6 days later. Resuscitation was unsuccessful. No laboratory studies or cultures were performed.

Patient 3: A healthy 22-year-old woman underwent medical abortion at 53 days gestation and presented to an emergency ward 5 days later with nausea, vomiting, diarrhea, and abdominal pain.

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The patient had normal vital signs except for mild tachycardia. The patient was admitted to rule out an ectopic pregnancy, and the next day developed hypotension, diffuse abdominal tenderness, a white count of 120,200 cells/μL, and metabolic acidosis. Blood cultures before antibiotic treatment were negative. Within a few hours, the patient had a cardiopulmonary arrest. Emergency laparotomy revealed a large amount of serous peritoneal fluid that failed to grow aerobic or anaerobic bacteria. The patient died during surgery, 23 hours after coming to the hospital.

Patient 4: This healthy 34-year-old woman had her medical abortion at 45 days gestation and presented to an emergency ward 4 days later with nausea, vomiting, and abdominal pain. Vital signs were normal and the only finding on physical examination was abdominal tenderness. Her white count was elevated and cultures of blood and urine were later negative. Despite antibiotic treatment, the patient went into refractory hypotension and died 12 hours after presenting to the hospital.

The autopsies revealed pleural, pericardial, and peritoneal effusions, inflammation of endometrium and myometrium with multiple small abscesses, necrosis, and hemorrhage without gas formation. There were no retained fetal or placental tissues. Formalin-fixed tissues were obtained by the CDC and *Clostridium sordellii* was identified in uterine tissues by a nonspecific polyclonal anti-clostridium antibody, followed by specific polymerase-chain-reaction assays on extracted DNA.

COMMENTARY

Clostridium sordellii is a Gram-positive anaerobic bacillus that has been previously identified as a cause of fatal toxic shock syndrome in 10 cases in the United States, 8 within 1 week after delivery of live-born infants, 1 within a week after a medical abortion, and 1 not associated with pregnancy (and 1 more case in Canada following medical abortion). The clinical and pathological findings (responses to exotoxins) in the 4 new cases and the 10 previous cases were similar. Clostridium species are known to colonize the vagina and to be associated with postpartum endometritis and septic abortion. Recognized infections with *Clostridium sordellii*, however, are very rare, although this rare prevalence may be partly due to the difficulty in the isolation and identification of this organism. The usual anaerobic culture techniques seem to be insufficient for timely diagnosis. The FDA has reported that testing the manufacturing lots of mifepristone and misoprostol has indicated no evidence of bacterial contamination.

How great is the risk? The 4 patients in this report and the 1 previous case (whose death was attributed to a ruptured ectopic pregnancy) represent the only fatal cases recognized after nearly 500,000 uses of medical abortion in the United States since mifepristone was approved in 2000. The mortality rate is estimated to be from 1.0 to 1.5 per 100,000, a rate that would be higher than that associated with legal surgical abortions. The number of American women reported as dying from abortion declined from nearly 300 deaths in 1961, to only 6 in 1985, 10 in 1992, and 4 in 1999, or about 0.6 deaths for every 100,000 legal abortions.[2,3] The risk of death from any cause associated with pregnancy is higher. For comparison, in 1990, the maternal death rate for childbirth in the United States was 10 per 100,000 births, and for ectopic pregnancy, approximately 50 per 100,000 cases,[4-6] and, in 1992, 17 deaths were associated with spontaneous miscarriage.[2]

Why haven't similar cases been reported in Europe? Philip Darney has speculated regarding the possibilities.[7] Because of equivalent efficacy and safety, the currently accepted method of medical abortion, supported by the recommendation of the World Health Organization, uses 200 mg mifepristone orally followed the next day by 800 μg misoprostol vaginally; this differs from the FDA-approved regimen of 600 mg mifepristone orally followed by 400 μg misopros-

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VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Gerard Gernazian.
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tol also given orally. Thus, one might suspect different American and European experiences to reflect the different dose of mifepristone; however, American clinicians have not followed the FDA-approved regimen, but instead, used the European lower-dose regimen that has solid clinical trial support. The use of self-administered vaginal misoprostol in America is different compared with the European practice of administering misoprostol by health care personnel in a clinic setting. Darney questions whether the misoprostol oral route with its equivalent pharmacokinetic behavior might be preferable.

Is there an alteration in immunity secondary to one of the drugs. McGregor and Equiles suggest that mifepristone may impair stress responses by blocking both progesterone and glucocorticoid receptors.[8] On the other hand, Grimes points out that infection with *Clostridium sordellii* has occurred without exposure to mifepristone.[9]

At this point in time, no changes have been suggested in the regimen used for medical abortion. The best prevention of fatal toxic shock with this rare infection is awareness of the possibility and early recognition. Abdominal cramping as a presenting complaint makes the diagnosis difficult because this is a common symptom following medical abortion. Unique characteristics include: the absence of fever, markedly elevated white counts, fluid effusions sufficient to produce hemoconcentration, and eventually tachycardia and hypotension. Specific antibiotics with demonstrated efficacy against *Clostridium sordellii* have not been identified. Early recognition of this rare infection would mandate consideration of aggressive surgery with hysterectomy, a lesson learned from the experience with septic abortions in the years before legalized abortion. ■

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Umbilical Cord Stem Cells

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Issues related to cost, quality control, and the need for ethnic diversity in public banks preclude the universal collection of units from all obstetric deliveries. Directed donation of cord blood should be considered when there is a specific diagnosis of a disease within a family known to be amenable to stem cell transplantation.*

Source: Moise K. Umbilical Cord Stem Cells. *Obstet Gynecol*. 2005; 106:1393-1407.

In the December Green Journal there was an excellent review by Ken Moise on the current status of umbilical cord blood stem cells. Since this is a topic patients frequently ask about, this month I will depart from the usual alert format to abstract this informative article.

Presently more than 5 million peripheral blood samples from potential bone marrow donors are being stored under the auspices of the National Marrow Donor Program. These libraried samples have been "typed" by compulsive and comprehensive HLA antigen testing. Currently, more than 70 hematopoietic, autoimmune, metabolic, and oncologic disorders lend themselves to treatment with bone marrow stem cells from donors registered in this ambitious and successful program.

Treatment consists of first ablating the affected recipient's bone marrow to give a fresh start to a unit of implanted hematopoietic stem cells capable of developing into normal mature blood cells. Success of

the method is based on how long it takes for the patient to obtain adequate concentrations of neutrophils, platelets, and erythrocytes in the his/her peripheral blood (the recovery time).

There are some drawbacks to this type of therapy. Not every potential recipient will have a HLA matching donor in the system. For example, 12% of Caucasians, 20% of Hispanics, 22% of Asians, and 41% of African Americans were unmatchable as of 2003 figures. Also, as of 2003 the average time taken to find a match was about 53 days and then another 4-6 weeks have been required to find the donor, evaluate his or her suitability and to schedule a bone marrow aspiration.

Another problem is the unfortunate tendency in some cases for graft-vs-host (GVH) reactions in which transplanted T-lymphocytes, found among the progenitor cells earmarked for therapy, attack the tissue of the recipient. Interestingly, the T-lymphocytes may also have a beneficial effect by attacking residual malignant cells in the recipient's system (graft-vs-leukemic effect—GVL).

Umbilical cord blood contains hematopoietic stem cells that have some advantages over bone marrow cells. These stem cells appear be more robust, replicating better in in vitro settings. Also, there is less GVH activity and they survive better if the HLA match is not perfect. Surprisingly, these cells have the same GVL capacity.

Other advantages involve the logistics of the process. For example, banked cord blood samples are all "typed" and ready to go when needed, which only translates into an average 2-week lag time. Also it is a painless process, avoiding the discomfort of a donor marrow aspiration.

The greatest disadvantage is that the cord blood yields fewer stem cells per unit, simply because of the limited volume of blood that can be aspirated from the umbilical cord after birth. This results in longer recovery times for new blood cells to appear in the recipient's circulation (7 days longer then neutrophils, 30 days longer for platelets).

Presently there are 22 public cord blood banks participating in the National Marrow Donor Program that are processing samples across the United States. These centers operate under very strict guidelines and the samples have been collected compulsively under strict aseptic conditions.

Since there are more advantages then disadvantages of cord blood stem cells, this may well be the way of the future for some hematopoietic diseases. Now there is evidence that totipotential fetal mesenchymal cells from cord blood could be used for tissue transplantation, thereby opening up the potential of treatment for Parkinson's disease, spinal cord injury, and myocardial infarction, among many other conditions.

COMMENTARY

Fetal stem cell therapy is not only an extremely exciting area but also a highly polarized one—certainly regarding embryonic stem cells. However, a common issue that confronts clinicians today emanates from a spin off potential benefit from cord blood banking- autologous transplants. This is a concept that also has appealed to entrepreneurs. Twenty four private cord banks have sprung up offering *biologic insurance* for infants against possible conditions to come. Storing these cord bloods comes at a cost to the parents of about $1100-$1700 for initial processing and an additional cost of about $120 a year for storage. Since these bloods are earmarked for possible use only by their *owners*, HLA typing is not being done.

Interestingly, one company advertises that currently 1 out of 27 infants would benefit from their cord bloods and, with future progress in stem cell therapy, 1 out of 2 could possibly use their banked samples. With this type of hype it would seem uncaring for parents not to make this investment in their child's future. However, many genetic mutations are already in stem cells, rendering these autologous cells unsuitable for treating many types of conditions, including leukemia. Also, most importantly, current objective assessments indicate that the real chance of needing one's own stem cells is about 1 in 2,700, although this figure could improve somewhat if use of mesenchymal cells from the umbilical cord pans out. Also, other problems include incomplete knowledge about the lifespan or even usefulness of stem cells stored for more then 15 years, the legal aspects of ownership, or, frankly, how long these presently unregulated companies will survive.

For the above reasons, the American College of Obstetrics and Gynecology, the American Academy of Pediatrics, and the Royal College of Obstetricians and Gynecologists have not recommended this pathway for parents. In fact, in Italy these types of commercial banks are interdicted by law.

Here in the United States, patients obviously are free to choose this option, but at least when asked, we can give them objective advice regarding its advantages and disadvantages. ■

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Intraperitoneal Chemotherapy: Coming of Age?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *As compared with intravenous paclitaxel plus cisplatin, intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer.*

Source: Armstrong DK, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354:34-43.

THE STANDARD APPROACH TO ADJUVANT THERAPY in women with advanced ovarian cancer is intravenous platinum-based chemotherapy, usually in combination with a taxane. Since the disease is largely characterized by a disseminated intraperitoneal spread pattern, investigators have been interested as whether the disease may respond to therapy administered in the same route. Armstrong and colleagues from the Gynecologic Oncology Group addressed this hypothesis by conducting a randomized phase III trial of standard intravenous platinum and taxane chemotherapy vs a regimen which combined intravenous (IV) paclitaxel with intraperitoneal (IP) cisplatin and intraperitoneal paclitaxel. This latter regimen required infusion on 3 separate days each 21-day cycle. Both progression-free and overall survival were primary end points of the study. In all, 429 patients with optimally cytoreduced (defined as residual disease < 1 cm) were randomized. Grade 3 and 4 pain fatigue and hematologic, GI, metabolic and neurotoxicity were greater in the IP-therapy group. In fact, just 42% of patients randomized to receive IP therapy finished all 6 cycles via IP administration. Nonetheless, both primary end points were favorably longer in the IP arm vs IV (standard) therapy. The differences were 5.5 months gained in PFS (median, 18.3 vs 23.8 mos) and nearly 16 months in OS (median, 49.7 vs 65.6 mos). Quality of life was lower on the IP arm but the difference disappeared at 12 months post-treatment. The authors concluded that the IP regimen improved survival in optimally debulked advanced stage ovarian cancer patients.

COMMENTARY

Advanced ovarian cancer remains the most lethal of the gynecologic malignancies because of its late stage at diagnosis and frequent relapse after primary treatment. It is commonly found at primary surgery that diffusely metastatic disease coats the intraperitoneal surfaces, sometimes with great tumor bulk, challenging the ability to completely remove the tumor. As has been presented in *OB/GYN Clinical Alert* previously, optimal cytoreduction at this juncture appears to levy the greatest impact on subsequent chemotherapy response. To date, that regimen of choice has been intravenously administered platinum-based and taxane chemotherapy combinations. Little has changed in the primary intravenous recommendation over the last decade although many modifications have been made; most therapeutic additions to the platinum/taxane backbone have not altered survival parameters.

The current report joins 2 previously conducted trials evaluating the merits of administering chemotherapy into the cavity where the disease is largely distrib-

uted—intraperitoneal. The concept has been under investigation for several decades and has been favorably considered, as IP drug administration is associated with superior pharmacokinetics relative to intravenous administration. In this manner high-dose drug exposure can be accomplished without the commensurate systemic toxicity. Limited surface diffusion into tumors, however, meant smaller volume residual status would be necessary. Nonetheless, in the last 10 years, there have been 3 large phase III clinical trials in ovarian cancer patients, which appear to confirm that the strategy is valid.[1-3] The first trial simply compared IV cisplatin and cyclophosphamide to IP cisplatin and IV cyclophosphamide. The dosing of both agents was the same; of note, the platinum was 100 mg/m^2—a dose on the upper limit of patient tolerance without marrow support. Patients were enrolled if they had 2 cm or less of residual disease from surgery. The intent was 6 courses of therapy. While PFS was not reported in the study, OS was significantly improved by approximately 8 months in the IP arm (41 vs 49 mos). Since the study appeared about the time results from a trial demonstrating the superiority of paclitaxel over cyclophosphamide in combination with platinum, the findings were not incorporated into standard care. A second trial used the IV platinum/taxane standard as a control against a regimen combining relatively high-dose carboplatin for 2 cycles followed by IP cisplatin (same dose as above) and IV paclitaxel in patients with optimal cytoreduction (defined as residual less than 1 cm). The induction chemotherapy was incorporated to help reduce the volume of post-operative residual disease but led to therapy discontinuation due to toxicity. Despite these criticisms, the IP arm was superior in both PFS and OS. For the latter variable, the gain was nearly a year and represented the first study in which overall survival in this cohort extended beyond 5 years. While the data caught the eye of many, toxicity was significant enough that the authors hesitated to recommend the regimen as "standard" for patients with optimally cytoreduced ovarian cancer.

Given the context in which the current report falls, one could conclude, "third times a charm." On the surface, it is difficult to argue with results. Indeed the NCI has issued a statement outlining the merits of this therapy. (ctep.cancer.gov/highlights/ovarian.html) It is clear, we will need to look at this issue in further detail largely not to question the merits of the route of administration but rather how to get patients through it with acceptable toxicity. In an accompanying article from the Group, catheter-related problems were the primary reason patients were not able to complete their intended program of IP therapy. Patient selection, standardization of infusion ports and increased experience with care and symptom management will help. Alternative agents and schedules will likely also be investigated to make the treatment more user-friendly. When these goals are accomplished, we will certainly embrace this advance into our armamentarium against this lethal disease. ■

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Systemic Lupus Erythematosus and Contraception

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Estrogen-progestin oral contraceptives do not increase disease activity in women with mild to moderate, stable systemic lupus erythematosus.*

Source: Sanchez-Guerrero J, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med*. 2005;353:2539-2549.

In a clinical trial conducted in Mexico City, 162 women with systemic lupus erythematosus were randomized to treatment with 1 of 3 contraceptive methods: estrogen-progestin oral contraceptives, oral progestin-only, or a copper IUD. Disease activity remained equally mild and stable over 1 year in all

3 groups. There were no differences in the use of anti-inflammatory drugs. There were 4 cases of lower-limb thromboses, 2 in the group receiving oral contraceptives and 2 with progestin-only pills. All 4 had low titers of antiphospholipid antibodies. The authors concluded that estrogen-containing contraceptives do not exacerbate systemic lupus erythematosus.

The NIH-supported OC-SELENA (Safety of Estrogens in Lupus Erythematosus National Assessment) trial was a double-blind, randomized trial of 183 women with stable systemic lupus erythematosus treated either with a 35 µg ethinyl estradiol oral contraceptive or placebo and followed for 1 year.[1] Patients were excluded if they had elevated levels of anticardiolipin antibodies, lupus anticoagulant, or a history of thrombosis. Lupus flares, the primary end point, occurred equally in the 2 groups. Venous thrombosis did not occur more frequently in the oral contraceptive group. The authors concluded that low-dose, estrogen-progestin oral contraceptives can be used by patients with inactive or stable, moderate systemic lupus erythematosus who are at low risk for thrombosis.

COMMENTARY

These studies are important for at least 2 good reasons. First, there has been a general clinical impression that exogenously administered estrogens would increase lupus disease activity. Second, there are important effects of oral contraceptives that would be beneficial for patients with lupus. These beneficial effects include: 1) Contraception is a chief component of care for lupus patients because pregnancy outcome is adversely affected by unstable, active disease; 2) Patients with lupus experience major bone loss and an increase in fractures as an unwanted side effect of their medical treatment; and 3) Estrogen-progestin contraceptives may moderate the intensity of lupus.

The SELENA trial had another arm, one with estrogen-progestin therapy in postmenopausal women. The trial was ended prematurely in August 2002 by the NIH in response to the publications of the Women's Health Initiative. The results in postmenopausal women were reported for 1 year of treatment in 351 women with lupus.[2] Severe flares were not increased by the treatment, and there was a slight increase in mild to moderate flares. In actual numbers, 59% of treated patients had an increase compared with an increase noted in 50% of placebo patients, a small difference. There was no evidence of worsening of SLE in the treated group. The investigators emphasized that the most meaningful finding clinically was the lack of an increase in the rate of severe flares.

The results of these studies are reassuring. Postmenopausal hormone therapy and oral contraceptives can be considered in patients with stable or inactive disease, without renal involvement and high antiphospholipid antibodies. Patients with high-titer anticardiolipin antibodies, lupus anticoagulant, or previous thrombosis were excluded from the SELENA study. If hormone therapy is to be provided to these patients, some form of chronic anticoagulation should be considered (such as statins or low-dose aspirin). ■

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CME Questions

2. The following statements are true regarding exogenous estrogen and systemic lupus erythematosus except:

a. The administration of estrogens to women with unstable, active lupus has not been studied.
b. Estrogen-progestin contraception cannot prevent bone loss associated with glucocorticoid treatment.
c. It is best to avoid exogenous estrogen in patients at high risk for venous thrombosis.
d. Oral contraceptives should be avoided by women with lupus who smoke or have hypertension.

3. The following statements are true regarding medical abortion *except*:

a. The standard protocol for medical abortion in the U.S. is FDA-approved.
b. *Clostridium sordellii* can be found as part of the normal vaginal flora in some women.
c. The pathological findings associated with fulminant infection with *Clostridium sordelli* are the result of exotoxins produced by the bacteria.
d. An estimate of the mortality rate associated with *Clostridium sordelli* infection indicates a slightly higher rate compared to early surgical abortions.

Answers: 2 (b); 3 (a)

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Letrozole for Postmenopausal Women with Breast Cancer

Letrozole (Femara) is a potent aromatase inhibitor that is used to treat women with metastatic breast cancer and, in a neoadjuvant role, for women who have failed tamoxifen. Aromatase inhibitors exert their effect by blocking the conversion of androgens to estrogens and reducing estrogen levels in tissue and plasma. Recently, letrozole was compared with tamoxifen for adjuvant therapy in postmenopausal women with steroid-hormone-receptor-positive breast cancer.

A total of 8010 women were randomized to 5 years of letrozole (4003) or tamoxifen (4007). After a median follow-up of 25.8 months, there were 351 events (local or distant recurrence) in the letrozole group and 428 events in the tamoxifen group, with 5-year disease-free survival estimates of 84% and 81.4%, respectively. Adverse effects of the drugs were different with tamoxifen, resulting in a higher rate of thromboembolism, endometrial cancer, and vaginal bleeding, while letrozole was associated with a higher incidence of skeletal and cardiac events and hypercholesterolemia.

The authors suggest that in women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease (Thurlimann B, et al. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer. *N Engl J Med*. 2005;353:2747-2757). In an accompanying editorial Sandra Swain, MD, from the National Cancer Institute, states that "all the evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes and who are at a substantial risk for recurrent disease." (Swain SM, et al. Aromatase Inhibitors—A Triumph of Translational Oncology. *N Engl J Med*. 2005;353:2807-2809). Based on this study, the FDA has recently approved letrozole for adjuvant treatment (immediately after surgery) in postmenopausal women with hormone sense of breast cancer.

Do Antidepressants Increase Risk of Suicide?

An article in the January issue of the *American Journal of Psychiatry* asks "Is the FDA Warning About Antidepressants Wrong?" Researchers from Group Health Cooperative in the Pacific Northwest used population-based data to evaluate the risk of suicide death and serious suicide attempt in relation to the initiation of antidepressant treatment.

Computerized health plan records for over 65,000 patients with over 82,000 episodes of antidepressant treatment between 1992 and 2003 were reviewed. In the 6 months after initiation of antidepressant treatment, the risk of suicide was found be no higher than at any other time during treatment. The risk of suicide attempt was highest in the month before starting treatment, and declined progressively after starting medication. When newer drugs were compared to older drugs, an increase in suicidality was

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

only seen with the older drugs.

The authors conclude that the risk of suicide during acute-phase antidepressant treatment is approximately 1 in 3000 treatment episodes, and the risk of serious suicide attempt is approximately one in 1000. Available data do not indicate significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs (Simon GE, et al. Suicide Risk During Antidepressant Treatment. *Am J Psychiatry*. 2006;163:41-47, available free at ajp.psychiatryonline.org). The study calls into question the March 2004 FDA public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with 10 newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine).

Can Viagra Improve Heart Function?

Concern still lingers regarding the safety of erectile dysfunction drugs in patients with heart failure. A new study from Australia suggests that sildenafil (Viagra) actually improves heart function in patients with systolic dysfunction. In a randomized, placebo-controlled, double-blind, 2-way crossover study, 20 patients with controlled left ventricular failure and ejection fractions < 35% received sildenafil 50 mg or matching placebo. Cardiac output was determined by Doppler echocardiography, aortic pressure waveform, and aortic and femoral arterial stiffness was also evaluated. With a peak effect at 60 minutes after administration, sildenafil resulted in an increase in cardiac index of 0.37 L/min, decrease in total systemic resistance, decreased aortic and lower limb pulse-wave velocity, and decreased wave reflection (all significant at $P < .0001$). The authors conclude that sildenafil improved cardiac performance by decreasing LV load, resulting in increased cardiac output and increase in exercise capacity in heart failure patients (Hirata K, et al. Effect of Sildenafil on Cardiac Performance in Patients with Heart Failure. *Am J Cardiol*. 2005;96:1436-1440).

Can Tamoxifen Increase Your Height?

Tamoxifen may increase height potential in short pubertal periods, according to new study in the journal *Pediatrics*. The study was a retrospective chart review of 7 boys with a mean age of 15 who took tamoxifen 10-20 mg twice a day for a mean of 26 months. Six of the boys were also receiving growth hormone. Tamoxifen significantly decreased the rate of skeletal maturation and improved predicted adult height without negative effects on sexual maturation. Skeletal maturation was determined by review of bone radiographs by independent endocrinologists. The authors state that "additional evaluation of this therapy is now required to determine if the increase in predicted adult height results in a clinically significant increase in final adult height." (Kreher NC, et al. The Use of Tamoxifen to Improve Height Potential in Short Pubertal Boys. *Pediatrics*. 2005;116:1513-1515).

A Dramatic Increase of Clostridium difficile

Clostridium difficile is increasing in frequency and severity in both hospital and community settings. Widespread use of acid suppressing proton pump inhibitors (PPIs) and H2 receptor agonists (H2RAs) may be a contributing factor, according to new study. Two population-based, case-control studies from England reviewed all 1672 cases of *C. difficile* reported between 1994 and 2004, while a second study looked at cases defined as community acquired. All cases were matched 10 controls. The incidence of *C. difficile* increased dramatically between 1994 and 2004. The adjusted rate ratio of *C. difficile* associated disease with current use of PPIs was 2.9 (95% CI, 2.4-3.4) and, with H2RAs, the rate ratio was 2.0 (95% CI, 1.6-2.7). The authors conclude that the use of acid-suppressive therapy is associated with an increase risk of community-acquired *C. difficile*. Parenthetically, they also found an increased risk associated with use of nonsteroidal anti-inflammatory drugs (*JAMA*. 2005;294:2943-3048).

FDA Actions

The FDA has approved Bristol-Myers Squibb's abatacept (Orencia) for the treatment of rheumatoid arthritis. The drug, which is produced by recombinant DNA technology, is a T cell costimulation modulator. It is approved for patients with moderately-to-severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs, including TNF antagonists. It may be used as monotherapy or with other non-TNF inhibitor DMARD. Abatacept is administered as a 30-minute IV infusion at 0, 2, and 4 weeks, then every 4 weeks thereafter.

The FDA and GlaxoSmithKline have issued a "Dear Doctor" letter regarding rare reports of macular edema in patients receiving rosiglitazone (Avandia). The majority of the cases involved concurrent peripheral edema and, in the majority of cases, macular edema improved with discontinuation of the drug. Macular edema presents as blurred or distorted vision, decrease color sensitivity, and decreased dark adaptation. ■