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One-Year Outcomes in Survivors of Acute Respiratory Distress Syndrome

ABSTRACT & COMMENTARY

Synopsis: *In this prospective, longitudinal study of 195 patients, it was found that patients who survived acute respiratory distress syndrome (ARDS) have persistent functional limitation 1 year post-ICU discharge secondary to extrapulmonary limitation.*

Source: Herridge M, et al. *N Engl J Med*. 2003;348:683-692.

UNTIL RECENTLY, SURVIVAL-TO-HOSPITAL DISCHARGE WAS THE primary outcome for critical care studies, but recently clinicians have become increasingly aware of the importance of measuring the quality of life in survivors of critical care illnesses. As survival rates improve among patients with acute respiratory distress syndrome (ARDS), there is a growing need to understand the long-term effects of this condition and its treatment. In the past, few studies have prospectively evaluated ARDS patients postdischarge in terms of their physiological, functional, and quality-of-life outcomes.

This was a prospective, longitudinal study in Canada evaluating 195 patients postdischarge from the hospital who had been diagnosed and treated for ARDS. The goal of this study was to characterize long-term pulmonary and extrapulmonary function in a prospectively identified cohort of patients with ARDS.

The inclusion criteria were age older than 16 years, PaO_2:FiO_2 ratio less than 200, PEEP of 5 cm H_2O, chest roentgenograms (CXR) consistent with ARDS, and an identifiable risk factor for ARDS. The exclusion criteria were immobility prior to admission, pulmonary resection, or a previously documented neurological/psychiatric disease.

The severity of illness was determined using the APACHE II scores, the multiple organ dysfunction score (MODS), and the modified lung injury score. Outpatient follow-up was done at 3, 6, and 12 months postdischarge from the ICU.

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The primary outcome measure of the study was the distance walked in 6 minutes 3, 6, and 12 months after discharge from ICU, and secondary outcome measures were evaluation of pulmonary function tests (PFTs) and quality of life. The rate of follow-up at 12 months was 86%.

The 1-year mortality rate of those patients who survived to hospital discharge was 11%.

On discharge from the ICU, these patients were noted to have severe weight loss, mean of 18% of their baseline weight.

At 3 months, PFTs were consistent with a mild restrictive pattern and with a mild-moderate gas exchange abnormality as determined by DLCO. At 6 months, the spirometric and median lung volume measures had returned to within normal values. The DLCO, although improved by 9 percentage points over 1 year, was still mildly reduced. The 6-minute walk distance also improved over 1 year, but was still lower than predicted, with 6% of patients remaining hypoxic during the test (SaO2 < 88%). However, no patients required home oxygen at 1 year. A year postdischarge from the ICU, 49% of the patients were working and quality of life, as measured by the SF-36 score, improved as well.

Chest radiographs were normal in 80% of the patients at 1 year.

The results of univariate analysis demonstrated that a low Lung Injury Score (< 3) ($P = 0.009$), the use of systemic steroids in the ICU, the presence of illness acquired in the ICU, and the rate of resolution of MODS and Lung Injury were the most important determinants of the 6-minute walk score at 1 year. In the multivariate analysis, the most important determinants of 6-minute walk at 1 year were the slopes of the Lung Injury Score and MODS, the APACHE II on admission in ICU, and the presence of any illness acquired in the ICU. The only factor associated with a longer distance walked in 6 minutes at 1 year was rapid resolution of lung injury.

COMMENT BY DAVID OST, MD, AND ANDREAS KYPRIANOU, MD

Previous authors have retrospectively evaluated morbidity of ARDS survivors with PFTs[1] and quality-of-life measures[2] and most have found persistent morbidity on follow-up. This was the first prospective study to assess ARDS survivors and the long-term physiologic, functional, and quality-of-life outcomes. The conclusion of this study is that patients who survive ARDS have persistent functional limitation 1 year postdischarge from the hospital, primarily attributable to extrapulmonary disease, and to a much lesser extent due to intrinsic pulmonary morbidity as demonstrated by PFTs. Muscle fatigue and weakness was reported among the survivors of ARDS, as well as a 20% weight loss, so the possibility of an association between these may exist. In view of the above, critical-illness polyneuropathy or myopathy may also be an important contributing factor in determining the amount of functional recovery. ■

Dr. Kyprianou is Resident, New York Hospital Medical Center of Queens/Cornell Medical Program, New York, NY.

References

1 Ghio AJ, Jensen RL, et al. *Am Rev Respir Dis*. 1989; 139:1158-1162.

2 Angus DC, Clermont G, et al. *Am J Respir Crit Care Med*. 2001;163:818-829.

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Early Predictors of Severity in Acute Lower Intestinal Tract Bleeding

ABSTRACT & COMMENTARY

Synopsis: *Initial clinical data can help predict high-risk patients with lower GI bleeding, including tachycardia, hypotension, syncope, and absence of abdominal tenderness.*

Source: Strate L, et al. *Arch Intern Med*. 2003;163:838-843.

CLINICIANS OFTEN SEE PATIENTS WITH ACUTE LOWER gastrointestinal (GI) hemorrhage. This presentation may be trivial or life threatening. Also, 20-30 per 100,000 persons are hospitalized with lower intestinal tract bleeding (LIB). Mortality may be high, particularly with sustained or recurrent hemorrhage. There are now data to suggest that colonoscopic intervention within 12 hours of admission may improve outcomes. It would be useful if appropriate high-risk patients could be selected for such intervention.

This study from the Brigham and Women's Hospital in Boston reviewed all admissions for approximately 3 years up to July 1999. Exclusions included evidence of upper gastrointestinal (UGI) bleeding or a history of low-grade lower GI bleeding. Out of 2323 candidate admissions, 373 patients were ultimately identified as suitable for study. Fifty-seven percent of patients were female, mean age was 66, and mean initial hematocrit was 35%. Forty-one percent required transfusions, and 4% underwent surgery for bleeding control. The most common diagnoses were diverticular hemorrhage, ischemic colitis, post-polypectomy, and malignancy.

The risk factors identified were: blood pressure ≤ 115 mm Hg, tachycardia, syncope, lack of abdominal tenderness on exam, gross blood on rectal exam or active bleeding within 4 hours of observation, aspirin use, and significant co-morbidities. Eighty-four percent of patients with more than 3 risk factors had severe LIB. Only 9% of patients with no risk factors experienced severe LIB.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Simple clinical observation should allow stratification of risk in patients who present with LIB. It was interesting that lack of abdominal tenderness proved to be one of the risk factors, presumably because of the unlikelihood of tenderness in diverticular bleeding or bleeding from mucosal angiomas. Since colonoscopy may provide therapeutic options like epinephrine injection and thermal applications along with specific diagnosis in a great many patients with LIB, clinical stratification is clearly worthwhile. ■

Adefovir Dipivoxil Treatment of Chronic Hepatitis Due to HBV Infection

ABSTRACTS & COMMENTARY

Synopsis: *Adefovir dipivoxil, 10 mg p.o. daily, is safe and effective in the treatment of chronic hepatitis due to HBV, regardless of the presence or absence of HBeAg, and it did not select resistant mutants after 48 weeks of administration.*

Sources: Marcellin P, et al. *N Engl J Med*. 2003;348:808-816; Hadziyannis SJ, et al. *N Engl J Med*. 2003;348:800-807.

MARCELLIN AND COLLEAGUES RANDOMIZED 595 patients from 78 centers in North America, Europe, Australia, and Southeast Asia with HBeAg-positive chronic hepatitis to receive adefovir dipivoxil in 1 of 2 doses (10 mg or 30 mg daily) or placebo in a double-blind trial. Histologic improvement at 48 weeks was found in 53%, 59%, and 25%, respectively, and log-transformed HBV DNA concentration per mL of plasma decreased by 3.52, 4.76, and 0.55, respectively ($P < .001$ for both comparisons with placebo). No HBV polymerase mutations associated with adefovir resistance were identified. While the 10-mg dose of adefovir was associated with a safety profile similar to that of placebo, the higher dose was associated with an increased risk of adverse events. Of note was a mean increase in serum creatinine of 0.2 mg/dL in the recipients of 30-mg adefovir daily.

Hadziyannis and colleagues at 32 sites in Canada, Europe, Asia, and the Middle East randomized 185 patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis in a 2:1 ratio to receive either adefovir dipivoxil (10 mg q.d.) or placebo in a double-blind study. Among those with liver biopsies, improvement in hepatic histology at 48 weeks was observed in 64% of adefovir recipients and 33% of placebo recipients ($P < .001$). The log-transformed median decreases in plasma HBV DNA level were 3.91 and 1.35 ($P < .001$), respectively, while the ALT levels normalized in 72% and 29% ($P < 0.001$). Mutations in HBV polymerase associated with adefovir

resistance were not detected. Adefovir was well tolerated.

COMMENT BY STAN DERESINSKI, MD, FACP

There are now 3 FDA-approved medications for the treatment of chronic hepatitis due to HBV infection: interferon alpha, lamivudine, and adefovir. Tenofovir, approved for the treatment of HIV infection, also has significant activity against HBV. Adefovir dipivoxil is a prodrug of adefovir, a nucleotide analog of adenosine monophosphate that acts as an inhibitor of HBV DNA polymerase.

Interferon alpha is poorly tolerated and has been increasingly supplanted by lamivudine in the treatment of this infection. While lamivudine therapy has a favorable safety profile, its use is associated with selection of resistant mutants in approximately one-third of patients after a year of therapy. Adefovir was very well tolerated at the 10-mg daily dose in both these trials, but the 30-mg dose was associated with modest increases in serum creatinine and at least 1 case of a Fanconi-like syndrome, toxicities that were anticipated as the consequence of the experience with higher-dose adefovir in HIV infection. At the same time, no mutations associated with tenofovir resistance were detected in either of these studies after 48 weeks of therapy.

In these studies, adefovir therapy was associated with improvement in liver histology and an approximately 4 $\log_{10}$ decrease in HBV DNA in both HBeAg-positive and negative chronic hepatitis. The efficacy, safety, and lack of emergence of resistance make adefovir an excellent choice in the treatment of chronic hepatitis due to HBV infection. The next logical step, the use of tenofovir and lamivudine in combination, is being currently evaluated. ■

Dr. Deresinski is Clinical Professor of Medicine, Stanford University, Palo Alto, Calif.

Oral Contraceptives and Hypertension

ABSTRACT & COMMENTARY

Synopsis: *The use of oral contraceptives in women with hypertension produced higher blood pressures and poor control of blood pressure.*

Source: Lubianca JN, et al. *Contraception*. 2003;67: 19-24.

Lubianca and associates from Porto Alegre, Brazil, reviewed the experience of 171 women attending a clinic for the treatment of hypertension. Users of oral contraceptives had higher diastolic blood pressures (an average of 7 mm higher), and a greater prevalence of significant hypertension reflected inadequate control. There were a higher number of women with moderate-to-severe hypertension among the oral contraceptive users.

COMMENT BY LEON SPEROFF, MD

The standard of treatment for many years has been to support the use of oral contraceptives in women younger than 35 years of age with hypertension well controlled by medication, as long as they are otherwise healthy and do not smoke. Of course, the lowest dose estrogen formulations are recommended. This has been a judgment based upon the argument that careful monitoring and treatment of the blood pressure would maintain pressures below 140/90 and allow continuation of oral contraceptive usage. The problem is a lack of data in such patients.

There are important unanswered questions. How does the use of oral contraceptives influence of the efficacy and stability of antihypertensive treatment? Do women with controlled hypertension who use oral contraceptives have a greater risk of cardiovascular events?

This study is limited by its cross-sectional nature, but it does suggest that oral contraceptive use has a negative effect on blood pressure control in hypertensive patients. I have heard of a case-control study, not yet published, indicting a higher risk of myocardial infarction and stroke in women with controlled hypertension who use oral contraceptives. Therefore, there is reason for increasing concern with these patients.

Certainly, a woman with controlled hypertension who has additional medical problems or who smokes should not use oral contraceptives. At this point in time, the data are insufficient to categorically ban the use of oral contraceptives in young women with controlled hypertension who are otherwise healthy. However, very frequent and close monitoring of the blood pressure is essential. An adverse effect on the medical control, the hypertension is an urgent message to use another contraceptive method. Myocardial infarction and stroke rarely occur before the age of 35, and for this reason 35 is an accepted cutoff age limit for oral contraceptive use in women with risk factors for cardiovascular disease. ■

Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health Sciences University, Portland, Ore.

Pharmacology Update

Estradiol Acetate Vaginal Ring (Femring—Warner Chilcott)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

THE FDA HAS RECENTLY APPROVED A VAGINAL ESTROgen ring for the treatment of symptoms associated with menopause. The self-inserted ring releases 50 µg or 100 µg of estradiol daily for 3 months. It is manufactured by Galen Ltd of Northern Ireland and will be marketed by Warner Chilcott, Inc as "Femring." This will be the second vaginal estrogen ring available along with Estring.

Indications

Estradiol acetate vaginal ring is indicated for the treatment of moderate to severe vasomotor symptoms as well as moderate-to-severe symptoms of vulvar and vaginal atrophy associated with menopause.[1]

Dosage

The vaginal ring is inserted into the vagina and left in place for 3 months at which time it should be replaced with a new ring. The starting dose is 50 µg/d.

If the ring is expelled from the vagina, it can be reinserted after rinsing in lukewarm water.[1]

Femring is available as 50 µg/d and 100 µg/d.

Potential Advantages

The flexible ring can be self-inserted by women every 3 months and releases estradiol acetate in the vagina for a 3-month period. This may be more convenient than daily pills or weekly patches for some women. The absorbed estrogen relieves local symptoms of vaginal and vulvar atrophy, as well as vasomotor symptoms of menopause. In patients with recurrent symptomatic, bacteriological confirmed urinary tract infections, a vaginal ring (Estring) was more effective in reducing recurrent infections. In a 36-week study, 45% of patients remain infection-free compared to 20% for no treatment ($P = .008$).[2]

Potential Disadvantages

Estrogen is associated with increased risks of endometrial hyperplasia and cancer. The release from the vaginal ring is unopposed. The Women's Health Initiative (WHI) study also reported that it could increase the risks of myocardial infarction stroke, invasive breast cancer, pulmonary emboli, and deep-vein thrombosis in postmenopausal women.[3]

Comments

Femring is a flexible ring that releases estradiol acetate for a 3-month period. In a 13-week double-blind, placebo-controlled trial (n = 325), it was found to relieve both the frequency and symptoms of moderate-to-severe vasomotor symptoms. The 50 µg/d dose decreased the mean weekly number of moderate-to-severe vasomotor symptoms from 73.8 to 21.6 and 75 to 11.4 with the 100 µg dose.[1] The severity of symptoms was reduced by 31% and 54%, respectively. Estradiol acetate ring also increased vaginal superficial cells (16-19%) and increased vaginal pH (0.60-0.73). Estring, another vaginal ring, has also been reported to reduce urinary tract infections in patients with recurrent infections. The wholesale cost for Femring is $76.50 for 50 µg and $81.50 for the 100 µg dose. The cost for Estring is $86.88.

Clinical Implications

The WHI study significantly changed the use of estrogen with or without progestins in postmenopausal women. The new boxed warning introduced by the FDA highlights the increased risk for heart disease, heart attacks, strokes, and breast cancer.[4] Consideration for use includes treatment of moderate-to-severe vasomotor symptoms and treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy associated with menopause. Vaginal rings such as Estring or Femring are options for treating these indications. The American College of Obstetricians and Gynecologists suggest that vaginal cream, vaginal tablets, or vaginal rings may be considered for genitourinary symptoms. Estrogens in any form should be used at the lowest dose and for the shortest duration possible. ■

References

1. Femring Product Information. Warner Chilcott Inc., March 2003.
2. Eriksen BC. *Am J Obstet Gynecol*. 1999;180(5): 1072-1079.
3. WHI Investigators. *JAMA*. 2002;288:321-333.
4. FDA Press Release. January 8, 2003.

CME Questions

21. Which of the following statements is correct for ARDS survivors 1 year postdischarge from ICU as determined in the study by Herridge et al?

a. Spirometric measures and lung volumes deteriorate.
b. DLCO improves and returns to normal.
c. The distance walked in the 6-minute walk test improves and returns to normal.

d. Rapid resolution of lung injury is not associated with longer distance walked in 6 minutes.
e. Persistent functional limitation is largely due to extrapulmonary etiology and to a lesser degree due to intrinsic pulmonary morbidity.

22. Findings suggesting high risk of lower intestinal tract bleeding include all but which one of the following findings:
a. Syncope
b. BP < 115 mm Hg
c. Moderate-to-severe abdominal tenderness
d. Gross blood on rectal exam
e. History of recent aspirin ingestion

23. Which of the following is correct?
a. Adefovir is a nucleotide analog.
b. Adefovir is a nucleoside analog.
c. Adefovir is ineffective in patients with chronic hepatitis due to HBeAg-negative HBV infection.
d. Adefovir administration in patients with chronic hepatitis due to HBV infection is associated with the frequent emergence of resistance-associated mutations in the first 48 weeks of therapy.

24. The following statements are true regarding oral contraceptives and hypertension *except*:
a. The two major factors that increase the risk of cardiovascular events in women who use oral contraceptives are smoking and hypertension.
b. Oral contraceptives can increase blood pressure.
c. Women with controlled hypertension can use oral contraceptive if they do not smoke and are otherwise healthy.
d. Women with controlled hypertension can use low dose oral contraceptives until menopause.

Answers: 21 (e); 22 (c); 23 (a); 24 (d)

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By Louis Kuritzky, MD

Oral Vitamin D3 Supplementation on Fractures and Mortality

Despite recent enhanced clinician and public awareness, prevention and treatment goals for osteoporosis (OSPS) remain inadequately fulfilled. A variety of lifestyle and pharmacologic tools have been applied to OSPS management, including Vitamin D (VitD) supplementation, with some, albeit inconclusive, success.

This trial was a pilot study using VitD (cholecalciferol) supplementation in a British senior citizen population (age range, 65-85) solicited by mail (n = 2686) to participate in a placebo-controlled trial lasting 5 years. Unusual in this trial was the dosing metho-ology, which administered a single 100,000 IU VitD capsule once every 4 months for 5 years—not once daily, but once (total capsules administered in 5 years = 15). Participants were instructed to take the capsule they received in the mail immediately upon receipt, and respond by mail on a form indicating that they had indeed taken the medication.

Compared to placebo, the treatment group had a 22% lower rate for first fracture (any site) and a 33% lower hip, wrist, forearm, or vertebrae fracture rate. The parathyroid hormone concentrations did not differ significantly between active VitD and placebo, despite a 40% higher VitD level in the former.

Ultimately, the 100,000 IU dose of VitD is approximately equivalent to 800 IU per day, which has been used in other trials. However, the convenience, lack of toxicity, and monetary savings (in the United Kingdom, 3 capsules of 100,000 IU vitD costs less than 1 pound) provide intriguing stimuli for a larger trial. ■

Trivedi DP, et al. BMJ. 2003;326: 469-472.

Oral Opioid Therapy for Chronic Peripheral and Central Neuropathic Pain

Neuropathic pain (NPP) is often described as "opioid resistant," based upon some limited human and animal studies. On the other hand, parenteral opioid analgesia has produced success in NPP. Although data on postherpetic neuralgia indicate a degree of efficacy with opioid analgesia, other NPP syndromes are not well studied in prospective, blinded studies.

Because of the ethical boundary of administering placebo to patients suffering chronic pain, a study was performed comparing 2 different dosing levels of levorphanol, a potent mu-opioid agonist, for patients (n = 100) suffering chronic NPP, in a double-blind fashion. Patients were administered either 0.15 mg or 0.75 mg capsules, and allowed to titrate up to as many as 7 capsules 3 times daily (levorphanol has a 6-8 hour duration of analgesia). The primary outcome of the study was degree of pain reduction; secondary outcome was time to pain relief. The study period was 8 weeks duration.

As perhaps might be intuitive, high-strength levorphanol reduced pain to a significantly greater degree than in the lower-strength group, despite the option available to patients of up-titrating their medication dose. Encouragingly, both groups did report levorphanol efficacy (pain reductions, 21% and 36%). Contrary to popular wisdom, tolerance to opioid analgesia was not evidenced. Additionally, the magnitude of pain reduction in the high-strength group was similar to that achieved with other more traditionally used NPP tools like tricyclic antidepressants and gabapentin.

Clinicians who have excluded opioid analgesia as an effective tool in NPP may need to consider these data in their decision process. ■

Rowbotham M, et al. N Engl J Med. 2003;348:1223-1232.

Tacrolimus Ointment vs Topical Corticosteroids in Atopic Dermatitis

For several decades the mainstay of management of atopic dermatitis (AD) has been corticosteroids (CSD), usually administered topically. When AD is mild-moderate, low, and mid-potency, CSD often suffices, but more severe disease may require high-potency agents, or even systemic therapy. Since CSD can produce both local effects like skin atrophy and systemic effects such as hypothalamic-pituitary suppression, chronic administration requires a degree of caution. Recently, a class of topical immunomodulator agents (IMA), exemplified by tacrolimus (Protopic) and pimecrolimus (Elidel), has been offered for clinical use as an alternative to CSD and appears to be equally efficacious. There are no serious side effects of IMA, and they have been demonstrated to be both safe and effective in children as young as 2 years, with minimal side effects.

For patients with moderate-to-severe AD, the cost of treatment was similar for either high-potency CSD and IMA for a 4-week treatment regimen. For short-term treatment (2 weeks), IMA is more cost effective than CSD because there is less requirement for secondary interventions. If lower potency and less costly CSD are used efficaciously, the cost efficacy of IMA becomes less favorable. The combination of safety, efficacy, and cost has important therapeutic implications for the role of IMA in AD. ■

Ellis C, et al. J Am Acad Dermatol. 2003;48:553-563.

A Fib with PVCs?

By Ken Grauer, MD

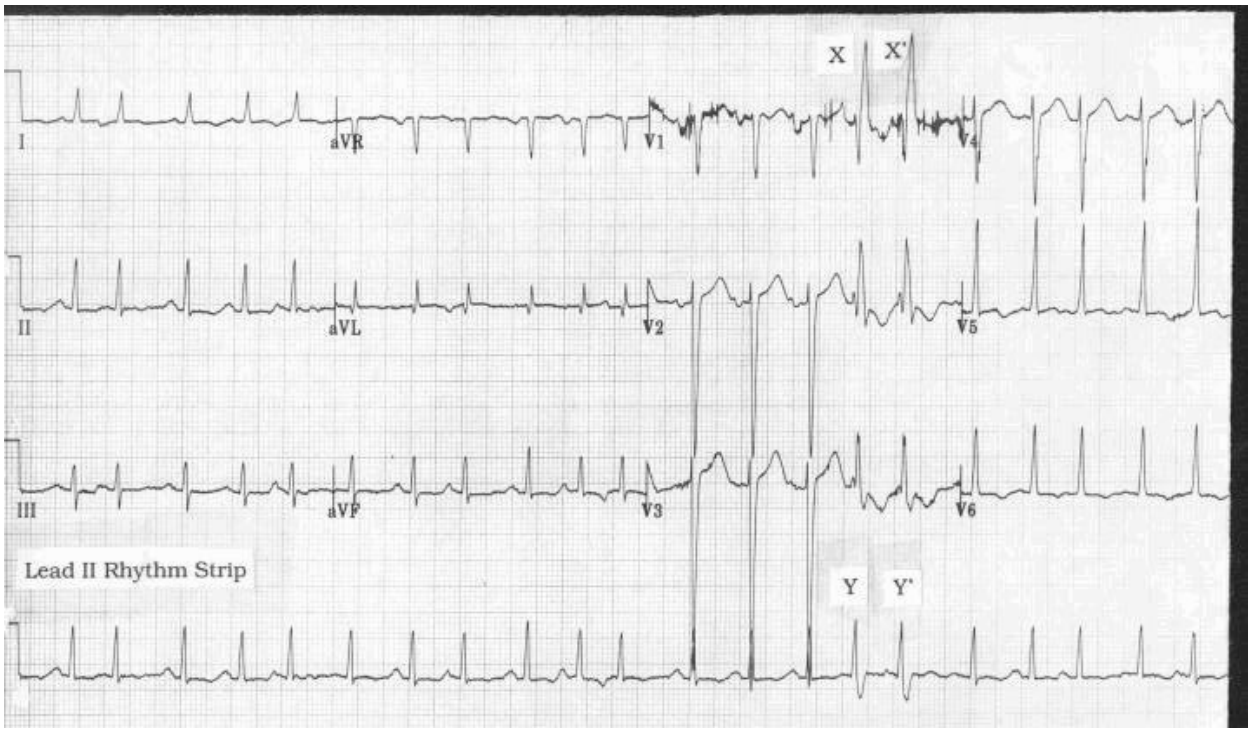

Figure. ECG obtained from a 55-year-old man with heart failure and emphysema. Do you agree with the computerized interpretation (above)?

Clinical Scenario: The computerized interpretation for the ECG in the Figure read, "Atrial fibrillation with PVCs (premature ventricular contractions)." Do you agree?

Interpretation/Answer: The rhythm is rapid and irregularly irregular. However, it is not atrial fibrillation. Although not readily apparent in many leads, P waves *are* indeed present. The rhythm strip at the bottom of this tracing emphasizes the importance of assessing an adequate number of beats before deciding on the true nature of the rhythm. Even in a lead II monitoring lead (as shown here), P waves are not always apparent in all parts of the tracing. Instead, overview of the entire rhythm strip is needed to confirm the presence of multiple P wave shapes throughout the tracing. The rhythm is therefore MAT (multifocal atrial tachycardia), supported by the information that this patient has emphysema. The two widened complexes in lead V_1 (beats X, X'-corresponding to beats Y, Y' in the rhythm strip) are almost certainly not PVCs. Instead, these beats appear to be early occurring supraventricular impulses that are conducted with aberration. The rSR' pattern with taller right "rabbit ear" in lead V_1 is consistent with a RBBB (right bundle branch block) morphology that is the most common form of aberrant conduction. In further support of our impression that these beats are aberrantly conducted supraventricular impulses rather than PVCs is the apparent finding of a premature P wave preceding beat X in lead V_1 (despite the artifact present in this lead, the preceding T wave looks especially peaked and pointed), and the underlying rhythm itself (the rapid ventricular response of the MAT rhythm seen here predisposes to the occurrence of multiple early beats, some of which are likely to occur during the relative refractory period). ■

In Future Issues:

Reducing Mortality in Sickle Cell Disease with Hydroxyurea

PHARMACOLOGY WATCH

Counterfeit Procrit Uncovered by FDA Surveillance

In one of the more bizarre stories of the year, the FDA has uncovered files of counterfeit Procrit (epoetin alfa—Johnson & Johnson) in routine surveillance. To make matters worse, the fake vials have been contaminated with bacteria and many contain no active ingredient. Johnson & Johnson is sending out a "Dear Doctor" letter to warn health care professionals about the counterfeit vials including the lot numbers of the suspected counterfeits. Fake Procrit was also discovered last summer in United States. At that time, counterfeiters apparently purchased 2000 U/mL vials and labeled them as the higher priced 40,000 U/mL vials. More information is available at the Johnson & Johnson/Ortho Biotech web site including pictures of the counterfeit vials.

Pharmaceutical Marketing Campaigns in Full Swing

Love 'em or hate 'em, direct-to-consumer (DTC) advertisements of pharmaceuticals are big business. The Kaiser Family foundation reports that spending on DTC ads increased nearly 10-fold in 10 years, from $260 million to $2.5 billion in 2000. More than 80% of respondents report seeing or hearing a drug ad in the last 3 months according to an FDA survey, and the Kaiser study reports that one third of patients have asked their doctor about an ad they saw on TV or in print. Unfortunately, drug ads are increasingly unregulated. The FDA is tasked with reviewing DTC ads for false or misleading statements, but according to a recent review in *Consumer Reports*, the agency has only 30 reviewers to handle 30,000 submissions each year. By the time false or misleading ads are pulled from the airways, they have often run their lifespan, with new ads appearing in their place. But are the pharmaceutical companies getting $2.5 billion of value from these ads? Apparently. A recent FDA survey of physicians revealed that when patients initiate a discussion about a prescription drug they've seen advertised, they asked for a prescription more than 50% of the time. Some 66% of physicians said they were not pressured to prescribe a drug in that situation. However, when a specific brand name drug was requested, physicians felt pressured to prescribe it more than 50% of the time. Despite this, physicians are split on the effect of DTC ads on their patients and practice, with 32% feeling negative about the ads, 40% feeling positive, and 28% feeling that DTC advertising has no effect on the practice (www.fda.gov/cder/ddmac/presentations.htm).

Ambulatory Antibiotic Reduction: Take the Good with the Bad

The national campaign to reduce antibiotic use in ambulatory practice seems to be working, but there is good news and bad news. Researchers from UCSF and Harvard reviewed the rates of overall antibiotic use in the National Ambulatory Medical Care Survey between 1991-1992, and compared those rates to usage between 1998-1999. The use of antibiotics decreased in the latter time period especially for the treatment of respiratory tract infections such as the common cold and pharyngitis (visits with a

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prescription decreased from 13% to 10% in adults, and from 33% to 22% among children). The use of broad-spectrum antibiotics increased over the same time span; however, including the macrolides azithromycin and clarithromycin, quinolones, amoxicillin-clavulanate, and second- and third-generation cephalosporins. The use of these antibiotics increased from 24% to 48% of all antibiotic prescriptions among adults and from 23% to 40% among children. An accompanying editorial reiterates the CDC's Campaign for Appropriate Antibiotic Use in the Community, which encourages prescribing antimicrobials only when they are likely to be beneficial to the patient, selecting agents that will target the likely pathogen, and using these agents in the correct dose and for the proper duration. The editorial suggests that we have been effective at decreasing the overall use of antibiotics, but less successful at promoting targeted therapy, ie, using narrow spectrum antibiotics whenever appropriate to reduce the likelihood of resistance in a population (*Ann Intern Med*. 2003;138:525-533,605-606).

Nefazodone Under Attack Once Again

Public Citizen, the national nonprofit watchdog organization, has petitioned the FDA to remove the antidepressant nefazodone (Serzone—Bristol-Myers Squibb) from the US market. The petition is based on evidence of liver toxicity associated with the drug including liver failure and death. Nefazodone was recently pulled from the European market after reports of a worldwide total of 28 cases of liver failure of which 18 patients died. The move in Europe was voluntary on the part of Bristol-Myers Squibb because of the call for increased liver enzyme monitoring requirements in several European countries. In this country, the FDA has required a black box warning on nefazodone since January 2002. Despite these concerns, nefazodone, which is a SSRI antidepressant, continues to be relatively popular, with more than 4 million prescriptions written last year. Bristol-Myers Squibb has no plans to withdraw the drug in this country at present.

Lindane Receives Black Box Warning

The FDA has issued a Public Health Advisory concerning the use of lindane for the treatment of scabies and lice. The boxed warning is the result of concern of potential neurotoxicity especially in children. The new advisory states that lindane is a second-line treatment and updates information about its potential risk in children and adults who weigh less than 110 pounds. The advisory also states that reapplication of lindane lotion or shampoo is not appropriate even if itching continues after the single treatment. The FDA is also requiring package sizes to be limited to 1 and 2 oz in order to minimize the potential for product access in a single treatment. Lindane, also known as gamma benzene hexachloride, is an industrial pesticide, has been in use for decades, and has been banned in several countries. Neurologic side effects include dizziness, seizures, and even death. The drug is currently approved for the treatment of lice and scabies in patients who have failed or are intolerant of other therapies. First-line agents for scabies include permethrin cream (Nix, Elimite, Acticin) and malathion lotion (Ovide) and for lice pyrethrum with piperonyl butoxide shampoo and cream rinse permethrin cream rinse (Nix and Rid).

Aspirin Could Help Reduce Colorectal Adenomas

Two different studies in the same issue of the *New England Journal of Medicine* suggest that daily doses of aspirin reduce the risk of colorectal adenomas. In the first study, 635 patients with previous colorectal cancer were randomized to receive either 325 mg of aspirin per day or placebo. The study was terminated early when a significant reduction in colorectal adenomas was shown during the planned interim analysis. After an average of 12.8 months of follow-up, 1 or more adenomas were found in 17% of patients in the aspirin group and 27% patients in the placebo group ($P = 0.004$). The mean number of adenomas was lower in the aspirin group ($P = 0.003$) and the time to detection of the first adenoma was longer in the aspirin group than in the placebo group ($P = 0.022$). In the second study, 1121 patients with a recent history of adenomas were randomized to placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients). Follow-up colonoscopy was done approximately 3 years after randomization. The incidence of 1 or more adenomas was 47% placebo group, 38% in the 81 mg aspirin group, and 45% in the 325 mg aspirin group (global $P = 0.04$). The risk of larger polyps including adenomas measuring > 1 cm or with tubulovillous or villous, or severe dysplasia was also lowest in the 81 mg aspirin group. An accompanying editorial suggests that inhibition of COX-2 may prevent inflammation, increased cell proliferation and angiogenesis. The author also cautions that prophylactic aspirin is not a substitute for colorectal cancer screening (*N Engl J Med*. 2003; 348:883-890, 891-899,879-880). ■