Providing Evidence-based Clinical Information for 28 Years

INTERNAL MEDICINE ALERT®

A twice-monthly update of developments in internal and family medicine

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Financial Disclosure:

Internal Medicine Alert's Editor, Stephen Brunton, MD, is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and AstraZeneca, and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

This Cup is Way Less than Half Full

ABSTRACTS & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Merck, ResMed, and GlaxoSmithKline, and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and ResMed.

Synopsis: *Three simultaneously published reports from the Women's Health Initiative demonstrate that a low-fat diet did not reduce the risk of breast cancer, colorectal cancer, or cardiovascular disease over 8 years of follow-up.*

Sources: Howard BV, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655-666; Prentice RL, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:629-642; Beresford SA, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:643-654.

THE WOMEN'S HEALTH INITIATIVE (WHI) IS AN ONGOING, LONGITUDINAL study of 48,835 women between the ages of 50 and 79 years enrolled at 40 US centers between 1993 and 1998. This group is extremely well-characterized and closely followed, with meticulous data about diet and lifestyle collected annually. Comprehensive reports of methods and baseline characteristics have been published.[1,2] For this trio of studies, the dietary intervention was designed to reduce fat intake to 20% of total calories and also to increase consumption of vegetables and fruits to at least 5 servings a day, and grains to at least 6 servings a day.

The intervention group received intensive behavioral modification which included 18 group sessions (led by a nutritionist) in the first year, then quarterly thereafter. There was personalized attention to each woman's total fat gram goal based on height. Dietary data were collected using the Frequency Food Questionnaire (FFQ), an instrument designed and validated for use in the WHI. The FFQ was administered at baseline, at one year following randomization, and then yearly to about a third of the participants in a

VOLUME 28 • NUMBER 5 • MARCH 15, 2006 • PAGES 33-40

NOW AVAILABLE ONLINE!
www.internalmedicinealert.com

rotating sample. Comprehensive 4-day food records were also collected from all women at baseline. All participants were contacted every 6 months, and a variety of measurements were made at these contacts, including height, weight, waist circumference, and blood pressure. A small subset of women provided additional intensive dietary monitoring, with additional 4-day food record at 1 year and 24 hour dietary recalls at 3 and 6 years. Fasting serum was collected at baseline and at 1 year for all women, and at 6 years in a subset (n = 2186) of women; this serum was analyzed for a variety of measures, including lipids, carotene and tocopherol levels. Serum hormone levels were also measured at baseline and at one year from 150 women in both the intervention and the control group.

To screen for incident cardiovascular, breast cancer, or colon cancer risk, medical update questionnaires were completed every 6 months. These questionnaires were extensive and included information about new diagnoses, procedures, and overnight hospitalizations.

Additionally, to screen for cardiovascular risk, electrocardiograms (ECGs) were digitally acquired every 3 years. Major coronary heart disease (CHD) was defined as acute myocardial infarction (MI) requiring hospitalization or silent MI determined from serial ECGs or death; composite. CHD was defined as MI, CHD death, and coronary revascularization procedures. To assess for breast cancer risk, women were expected to undergo mammography at baseline and every 2 years; tissue diagnosis was required to be included as a case in this study. Screening for colon cancer occurred based on decisions made by the participants and their physicians; there was no specific protocol for this.

End points in this study were incident breast or colon cancer, CHD or individual coronary heart disease events. The effects of the low-fat diet were based on time-to-event curves based on intention to treat. Hazard ratios for the end points for the control compared with dietary intervention group were stratified for age at entry, prevalent disease, and whether the participant was taking HRT. Women who had a given outcome variable at baseline were excluded from calculations for that particular outcome. In secondary analyses, the investigators compared event rates in the intervention and control group controlling for relevant known risk factors for the event; for example, for CHD, data were analyzed controlling for ethnicity, age, BMI and other health characteristics known to influence the risk of CHD.

By year 6, mean fat intake decreased by about 8.1 % (of total caloric intake) in the dietary intervention group, and there were small increases in vegetable and fruit intake. Of note, although the goal was to reduce fat intake to fewer than 20% of calories, the actual reduction (despite intensive intervention) was to 28.8% compared with the control group's 37.8%. The dietary intervention group did not have reduction in incident CHD, stroke, invasive colon cancer, or invasive breast cancer, although encouraging trends were seen. Secondary analyses suggested a lower HR of breast cancer risk for women who were more adherent to the low-fat diet, or who had higher fat intake at baseline. There was a trend toward lower CHD risk in those with lower intakes of saturated fat and trans fat or higher intakes of fruits and vegetables. Low density lipoprotein cholesterol, diastolic blood pressure, and factor VII c levels were statistically significantly reduced (though absolute reductions were quite small: 3.55 mg/dL, 0.31 mm Hg and 4.29%, respectively). High-density lipoproteins, triglycerides, glucose, and insulin levels did not change between the 2 groups.

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.
MARKETING PRODUCT MANAGER: Gerard Gernazian.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail: customerservice@ahcpub.com

Editorial E-Mail: robert.kimball@thomson.com

World-Wide Web: www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $125).

Multiple Copies
Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

Canada
Add 7% GST and $30 shipping

Elsewhere
Add $30 shipping

Accreditation

Thomson American Health Consultants (AHC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AHC designates this educational activity for a maximum of 45 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Internal Medicine Alert has been reviewed and is acceptable for up to 24 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/01/06.Term of approval is for one year from this date. Each semester (12 issues) is approved for 12 Prescribed credits. Credit may be claimed for 1 year from the date of this issue.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Robert Kimball**, Managing Editor, at (404) 262-5413 (e-mail: robert.kimball@thomson.com) between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

COMMENTARY

Remember the Woody Allen movie, *Sleeper* in which a health food store owner wakes up hundreds of years in the future? The baffled but hungry time traveler asks for a health food salad, and evokes mirth in his futuristic friends, one of whom comments incredulously, "Imagine! He believes that hot fudge sundaes are bad for you!" to which his companion responds, "Yes. Exactly the opposite of what we now know to be true!" Once again, the WHI study (which shot down routine use of hormone replacement for postmenopausal women)[3] has disproved, or at least seriously dampened enthusiasm for, a cherished clinical belief. The results of these studies challenge, in triplicate, the rationale for a low-fat diet.

This issue of *JAMA* includes 2 editorials[4,5] that address these papers. Buzdar notes the trend toward reduction in breast cancer, points out that there was a reduction in estrogen receptor positive (progesterone receptor negative) breast cancer and reviews the rationale for an association between high fat intake and breast cancer. He suggests that a low-fat diet may be of benefit for those who have survived early stage breast cancer to prevent recurrence. Anderson and Appel suggest that the WHI trial did not take into account the different kinds of fat (eg, trans fat, saturated, polyunsaturated and monounsaturated) and associated risks, and note that reduction in fat intake in the intervention group was modest. We all wonder if longer-term follow-up will ultimately demonstrate a difference; the trends noted in 8 years of follow-up certainly suggest that there might be, particularly for breast cancer.

Where does that leave us now? We can't honestly tell our patients that a low-fat diet will affect their risk of these common and deadly killers: breast cancer, colon cancer, and cardiovascular disease. There are so many things for which lifestyle change is conclusively known to cause immediate, unequivocal benefit (seat belts and smoking abstinence come to mind, not to mention exercise) that it's difficult to drum up much enthusiasm for harping on a low-fat diet based on present evidence. ■

References

1. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61-109.
2. Ritenbaugh C, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Ann Epidemiol.* 2003; 13(9 Suppl):S87-S97.
3. Anderson G, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701-1712.
4. Buzdar AU. Dietary modification and risk of breast cancer. *JAMA*. 2006;295:691-692.
5. Anderson CA, Appel LJ. Dietary modification and CVD prevention: a matter of fat. *JAMA*. 2006;295:693-695.

Under Pressure to Heal an Ulcer?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus

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

Synopsis: *Healing of Stage II-IV pressure ulcers is associated with use of moist dressings and adequate nutrition. An additional factor for Stage III and Stage IV ulcers is cleansing with soap and water or saline.*

Source: Bergstrom N, et al. The National Pressure Ulcer Long-Term Care Study: outcomes of pressure ulcer treatments in long-term care. *J Am Geriatr Soc*. 2005;53:1721-1729.

THE NATIONAL PRESSURE ULCER LONG-TERM CARE Study (NPULTC) was a retrospective cohort study with convenience sampling conducted between February 1, 1996, and October 31, 1997. Using data from medical records, Minimum Data Sets, physician orders, and medication logs, the researchers examined the resident, the ulcer, and the care to identify factors that are associated with prevention and healing. The patients were studied over 12 weeks. Each pressure ulcer (PrU) was measured and described (ie, presence of eschar, necrosis, granulation tissue, drainage, undermining, tunneling, or infection, and wound bed color, location, and stage). Stage I PrUs, PrUs smaller than 0.25 cm^2 and PrUs in unusual locations (navel, chin, penis, etc) were excluded. The primary outcome was change in PrU area. Treatment modalities were grouped into broad categories: cleansing, dressing, support surfaces, and nutritional supplements. No attempt was made to evaluate specific products.

After exclusion there were 882 subjects with 1,589 PrUs. Most common locations were coccyx, back, or buttocks (44%), foot or malleolus (36%), trochanter (2%), and ischial tuberosities (5%). Stage III and Stage IV ulcers had the greatest reduction in size

when patients were receiving sufficient enteral feedings (≥ 30 kcal/kg/day), when cleansing consisted of soap and water or saline, and when moist, rather than dry, dressings were used. Two patient characteristics were also associated with better healing: having no or uncomplicated dementia or having dementia with agitation or depression. Stage II PrUs followed the same pattern, except that cleansing with soap and water or saline healed more slowly. Not surprisingly, debridement was associated with an increase in ulcer size. Factors not associated with healing were diabetes, incontinence, age, cardiovascular disease, requiring assistance with activities of daily living, and type of bed (support surface).

COMMENTARY

Pressure ulcers are a common and costly problem in acute care, nursing home, and home care populations. In 1994 the cost of treatment in the United States was estimated to exceed $1.335 billion.[1] Liability related to PrUs is increasing.[2,3] Judgments were highest for PrUs caused by multiple factors. The highest awards for PrUs caused by a single factor were seen when that factor was inadequate nutrition.

This group has previously written about prevention of PrUs.[4,5] The factors that help prevent PrUs include adequate nutritional support, fluid orders, medications, and nursing staffing patterns. Most studies of PrUs have looked at single interventions. The NPULTC is unique in that it examined multiple factors that influenced each other. For instance, a treatment that failed to heal a PrU might be followed by debridement, which in turn, increased the size of the ulcer. The 12-week study period was too short to allow healing of all ulcers. The fact that a PrU is getting smaller does not necessarily mean it will eventually heal completely. Ross Products Division of Abbott Laboratories provided funding for this study.

The Agency for Health Care Policy and Research, now the Agency for Healthcare Research and Quality (AHRQ) published guidelines for the prevention and treatment of pressure ulcers in 1992 and 1994, respectively. These guidelines were reviewed in 2001 and were found to be valid still. Physicians caring for bed- or chair-bound patients would do well to review them now. ■

References

1. Miller H, Delozier J. Cost implications of the pressure ulcer treatment guideline. Center for Health Policy Studies. Columbia, MD: Contract No. 282-91-0070. 1994:17.
2. Bennett RG, et al. The increasing medical malpractice risk related to pressure ulcers in the United States. *J Am Geriatr Soc*. 2000;48:73-81.
3. Voss AC, et al. Long-term care liability for pressure ulcers. *J Am Geriatr Soc*. 2005;53:1587-1592.
4. Horn SD, et al. The National Pressure Ulcer Long-Term Care Study: pressure ulcer development in long-term care residents. *J Am Geriatr Soc*. 2004;52: 359-367.
5. Horn SD, et al. RN staffing time and outcomes of long-stay nursing home residents: pressure ulcers and other adverse outcomes are less likely as RNs spend more time on direct patient care. *Am J Nurs.* 2005;105: 58-70.

S. aureus: The Nose Knows

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *In 2001-2002, an estimated 89.4 million individuals in the United States were nasally colonized with* S. aureus *and 2.3 million with MRSA.*

Source: Kuehnert MJ, et al. Prevalence of *Staphylococcus aureus* Nasal Colonization in the United States, 2001-2002. *J Infect Dis*. 2006;193:172-179.

Samples obtained by swabbing both nares of almost 10,000 individuals > 1 year of age in the US National Health and Nutrition Survey in 2001-2002 were cultured on mannitol salt agar. *S. aureus* was identified in 32.4% of subjects and 0.8% were colonized with methicillin resistant *S. aureus* (MRSA). Extrapolated to the entire US population, it was estimated that approximately 89.4 million were nasally colonized with *S. aureus* and 2.3 million with MRSA.

The prevalence of *S. aureus* colonization was highest in individuals 6 to 11 years of age. MRSA colonization was associated with female gender and age > 60 years; health care exposure was not a significant risk factor. In unweighted analyses of a sample of isolates, one or more toxin genes (enterotoxins A-H, PVL, TSST-1 were sought) were identified in 52% of methicillin susceptible *S. aureus* (MSSA) and 76% of MRSA. TSST-1 was the most commonly identified virulence gene in MSSA, while enterotoxin D was most frequent in MRSA. Fifty-one percent of MRSA carried SCCmec type II and 49% carried SCCmec type IV. All MRSA isolates with the PVL gene carried SCCmec type IV. The PVL gene was detected in only 1% of MSSA.

COMMENTARY

This extensive study gives us a snapshot (albeit at slow shutter speed) of the prevalence of nasal colonization with MSSA and MRSA in the United States in 2001 and 2002. Its overall results are consistent with those of previous studies, with approximately one-third being colonized at this site with *S. aureus*, representing an astounding estimated 89.4 million individuals. The prevalence of MRSA nasal colonization was only 0.8%, but this extrapolates to approximately 2.3 million people.

It is quite likely that a repeat of this study now would find a significantly greater prevalence of nasal colonization with MRSA, as community-acquired strains carrying SCCmec type IV continue their spread. An increased prevalence of MRSA colonization has recently been documented in homeless youth in San Francisco, as well as children in Nashville and in Houston.

It should also be noted that only one site—the nares—was evaluated for colonization. Studies have shown that a greater yield is obtained when additional sites, such as the axillae and inguinal areas, are sampled.

Pharmacology Update

Rotavirus Vaccine, Live, Oral, Pentavalent (Rota Teq®)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationships to this field of study.

THE FDA HAS APPROVED A LIVE, ORAL, VACCINE FOR the prevention of rotavirus gastroenteritis in infants. An earlier vaccine approved for this indication (RotaShield®) was withdrawn in 1999 due to an increased risk of intussusception. In a large trial, of more than 70,000 children, risk of intussusception was not observed with the new vaccine. The new oral rotavirus vaccine will be marketed by Merck & Co., Inc. as Rota Teq®.

Indications

Rotavirus vaccine is indicated for the prevention of rotavirus gastroenteritis in infants and children (ages, 6-32 weeks) caused by serotypes G1, G2, and G4.[1]

Dosage

Rotavirus vaccine liquid is given orally, as 3 doses, starting at 6 to 12 weeks of age. The subsequent doses are given at 4 to 10 week intervals. The third dose should not be given after 32 weeks of age. There are no restrictions on food or liquid intake before or after the vaccine. Although the vaccine should not be mixed with other vaccines or solutions[1] it may be co-administered with other commonly used infant vaccines. Oral polio vaccine was not permitted in the clinical trials. There are insufficient data regarding potential interference with pertussis vaccine.[1]

Potential Advantages

Rotavirus vaccine has been shown to reduce all grades of severity of gastroenteritis, hospitalization, and emergency department visits occurring 14 or more days after the third dose through the first rotavirus season post vaccination as well as any time after the first dose through the first season.[1,2]

Potential Disadvantages

The vaccine strains do not grow well in the intestine and there is generally no shedding in the stool. Therefore 3 doses are required to achieve sufficient titers.[3] As with other vaccines, rotavirus vaccine does not provide complete protection in all recipients.

Comments

RotaTeq is an oral, live pentavalent (G1, G2, G3, G4 and P1[8]) WC3 human-bovine reassortant rotavirus vaccine. The parent strains were isolated from human and bovine hosts. Each reassortant virus contains a single gene encoding a major outer capsid protein from the most common human serotypes.[2] In 3 placebo-controlled trials (n = 72,324), study participants who received 3 doses of rotavirus vaccine had a reduction in any grade of severity of gastroenteritis by about 72.5%-74%, reduction in severe gastroenteritis by 98%-100%, and reduction in hospitalization by 95.8% in the first rotavirus season. For participants who received at least one dose, reduction of severe gastroenteritis and hospitalization was 96.4%-100% and 94.7%, respectively. Gastroenteritis of any severity was reduced by about 60%. Gastroenteritis was defined as 3 or more watery or looser-than-normal stools within a 24-hour period or forceful vomiting along with the detection of rotavirus antigen.[2] Severity was determined by a clinical scoring system taking into account the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral changes. The frequency of adverse events such as elevated temperature, vomiting, diarrhea, and irritability were

generally no different between the vaccine recipients and placebo recipients. Some adverse events had a higher incidence with the vaccine such as diarrhea (24.1% vs 21.3%), vomiting (15.2% vs 13.6%), otitis media (14.5% vs 13.0%), and nasopharyngitis (6.9% vs 5.8%). Seizure was reported in 33 of 36,150 vaccine recipients compared to 18 of 35,556 placebo recipients. The vaccine does not appear to increase the risk of intussusceptions based on clinical trials. This serious adverse event will be monitored in post-licensure studies.[4] The wholesale cost of Rota Teq is $66.50 per dose.

Clinical Implications

Rotavirus is the leading cause of childhood gastroenteritis and death. It accounts for about one-half million deaths and one third of hospitalizations worldwide.[5] The Center of Disease Control and Prevention estimated that approximately 55,000 hospitalizations annually in the United States were due to rotavirus. Rota Teq appears to be a safe and effective vaccine. ■

References

1. RotaTeq Product Information. Merck & Co., Inc. February 2006.
2. Vesikari T, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354:23-33.
3. Glass RI, Parashar UD. The promise of new rotavirus vaccines. *N Engl J Med*. 2006;354:75-77.
4. FDA News. www.fda.gov/bbs/topics/news/2006/NEW01307.html.
5. Parahar UD, et al. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis*. 2003;9: 565-572.

CME Questions

10. A 54 year-old woman with hypertension and a family history of breast cancer asks your advice about a low-fat diet to reduce her risk of cardiovascular events and breast cancer.

You tell her:

a. There is strong evidence that a low-fat diet will reduce her risk of both cardiovascular events and breast cancer.
b. There is no evidence that a low-fat diet will reduce her risk either cardiovascular events and breast cancer.
c. There is strong evidence that a low-fat diet will reduce her risk of cardiovascular events but not breast cancer.
d. There is strong evidence that a low-fat diet will reduce her risk of breast cancer but not cardiovascular events.
e. There is inconclusive evidence that a low-fat diet will reduce her risk of both cardiovascular events and breast cancer.

11. Factors associated with healing of Stage III and Stage IV pressure ulcers include all of the following, except:

a. having dementia with agitation or depression.
b. use of dry, rather than moist, dressings.
c. enteral feedings of at least 30 kcal/kg/day.
d. cleansing with soap and water or saline.

Answers: 10 (e); 11 (b)

For access to your 2006 online bonus report, visit: www.ahcpub.com.

Attention Readers

Thomson American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

Readers who have ideas or proposals for future single-topic monographs can contact Editorial Group Head Glen Harris at (404) 262-5461 or (800) 688-2421 or by e-mail at glen.harris@thomson.com. ■

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances; and
- to describe cost-effective treatment regimens.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Use of High-Dose Acyclovir in Pityriasis Rosea

Although it has been long suspected that pityriasis rosea (PTR) is of viral origin, proof of that remains lacking. Recent evidence suggests that herpes virus 6 (HSV 6) and herpes virus 7 (HSV7) are etiologic in PTR. Antiviral therapy such as acyclovir (ACV) has proven effective for management of other HSV infections, but it is not clear whether PTR is treatment-responsive. Indeed, PTR is often treated with watchful waiting or antipruritic medication, on the basis that it is usually self limited. Nonetheless, because HSV6 has been associated with increased risk for abortion, were antiviral treatment effective for PTR, treatment might be worth considering on this basis coupled with potential symptom reduction.

Consecutive patients (n = 82) with typical dermatologic findings of PTR underwent serologic evaluation for HSV6 and HSV7. Other bacterial and viral agents which might produce similar dermatologic findings were included in serologic analysis (eg, *Borellia*, toxoplasmosis). Patients were alternately assigned to either ACV treatment (800 mg five times daily for one week), or placebo in a single-blind fashion.

On day 7, regression of PTR skin lesions was seen in 90.5% of the ACV treatment group vs 26.7% in the placebo group. New lesions appearing beyond one week were seen in *none* of the treatment group, and 40.5% of the placebo group. By 2 weeks, complete lesion regression was seen in 78.6% in the ACV group, but only 4.4% in the placebo group.

PTR-associated symptoms, eg, fatigue, headache, sore throat, irritability, insomnia, and nausea, followed a similar course: by day 7, none of the placebo recipients were fully symptomatically resolved compared with 36.8% in the ACV group. These data suggest that ACV treatment may be helpful in PTR. ■

Drago F, et al. J Am Acad Dermatol. 2006;54:82-85.

Rimonabant in Overweight or Obese Patients

Despite a growing public and professional awareness of the health consequences of overweight, there is little in the way of pharmacologic management to provide a meaningful impact on excess body weight. Recently, interest has been expressed in capturing the influence of the endocannabinoid system, which has receptors in the CNS, adipose tissue, muscles, GI tract, and liver. Stimulation of the cannabinoid-1 receptor results in increased eating, decreased muscle mass, and lipogenesis. Rimonabant (RIM) is a cannabinoid-1 receptor blocker, and has shown favorable effects upon both body weight and some of the metabolic consequences of overweight. The RIO-North America study is a randomized, controlled trial of RIM in adult overweight or obese individuals.

Through 2002, subjects were enrolled and randomly assigned to either RIM 5 mg/d, RIM 20 mg/d, or placebo. After 1 year, subjects who had received RIM were rerandomized to drug or placebo; the original placebo group continued on placebo. All subjects were also placed on a diet.

RIM 20 mg/d produced favorable results at 1 year which were statistically significantly different from placebo: a reduction of body weight 6.3 kg, reduced waist circumference, increase in HDL, and reduction in triglycerides. Subjects who were switched from RIM to placebo in year 2 lost much of the favorable weight and metabolic changes attained in year 1, but those who remained on RIM 20 maintained these positive effects. Rimonabant is a promising method of modulating excess weight and attendant metabolic derangements. ■

Pi-Sunyer FX, et al. JAMA. 2006;295: 761-775.

Watchful Waiting vs Repair of Inguinal Hernia in Minimally Symptomatic Men

Inguinal hernia (ING) in men is rarely associated with serious adverse outcomes. Nonetheless, because ING can result in bowel incarceration and strangulation, there is some uncertainty about the propriety of watchful waiting (WW). Some men are motivated to intervene surgically because of pain or cosmetic effects; but the study by Fitzgibbons et al suggests that a conservative approach for men with minimal symptoms is appropriate.

The randomized trial included adults with ING (n = 720) who were randomized to surgical repair or WW. Subjects were followed for 2-4.5 years. Among those assigned to WW, 23% ultimately elected surgical repair during the study, most commonly due to increased pain; a similar percentage (17%) in the group originally randomized to surgery chose instead to use WW.

At 2 years, the primary end point (pain interfering with activity) was the same in the WW as the surgical group. Only 2 patients in the WW group who were followed for up to 4 years sustained incarceration.

The authors conclude that WW is a reasonable strategy for managing ING because serious adverse events are rare, and other clinical outcomes are similar with either approach. ■

Fitzgibbons RJ, et al. JAMA. 2006;295:285-292.

Those First 4 Beats

By Ken Grauer, MD

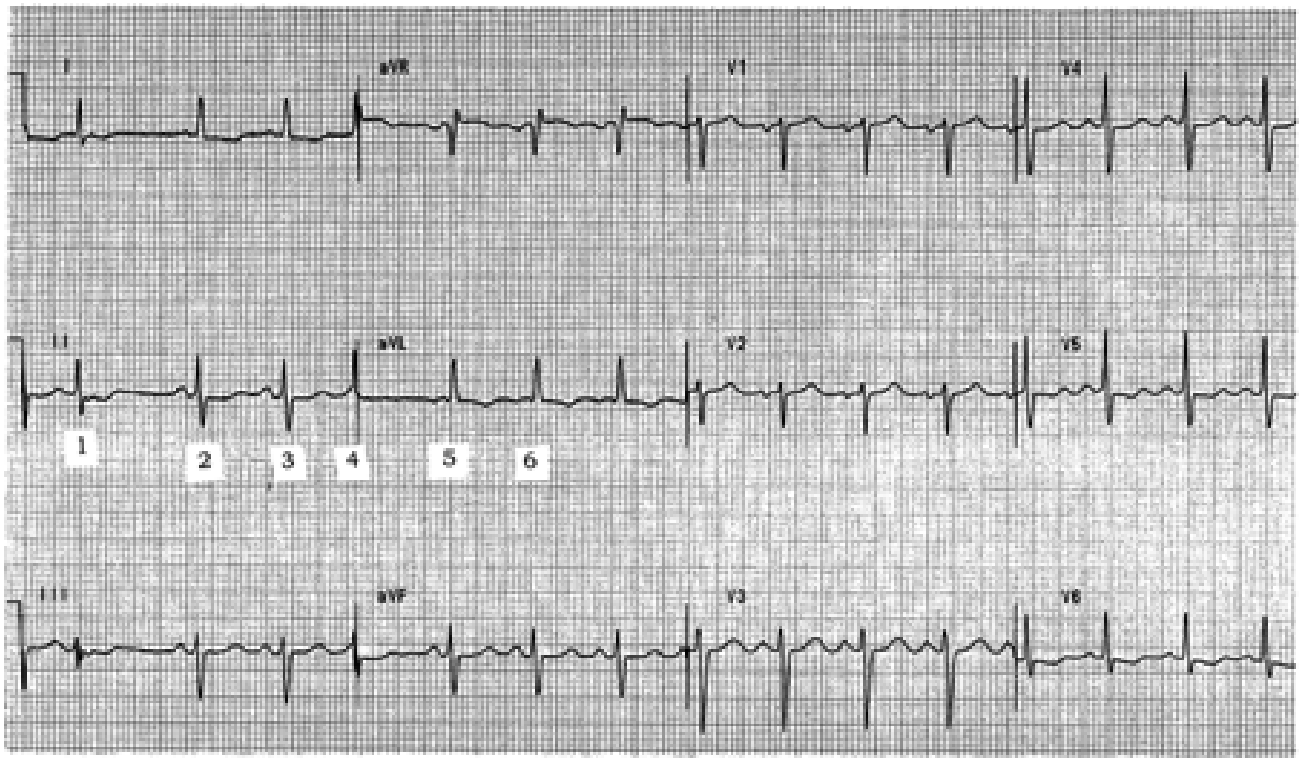

Figure. 12-lead ECG obtained from a 70-year-old woman with heart failure.

Clinical Scenario: The ECG in the Figure was obtained from a 70-year-old woman in heart failure. There are at least 6 findings that we feel are worthy of mention. Can you identify them? Clinically, what is your concern?

Interpretation/Answer: As suggested by the title of this ECG review, the tracing is most interesting in the way it begins. The underlying rhythm is sinus at a rate of about 100/minute [Finding #1 = sinus tachycardia]. There is initial irregularity in the rhythm, which is obvious from the longer R-R interval between beats #1 and 2, but not so obvious at the point of lead change between leads I, II, III and aVR, aVL, and aVF. Without seeing what occurred before, it is impossible to be sure about beat #1. However, we suspect this complex is supraventricular because the QRS is narrow and preceded by a P wave. The P wave preceding this beat looks to be different however, from the P wave preceding beats #2 and 3 in lead II. Slight variation in QRS morphology of beat #1 compared to the QRS morphology of beats #2 and 3 suggests that this first beat looks different because of aberrant conduction. Notching in the early part of the ST segment of beat #1 is probably the result of a blocked PAC (premature atrial contraction), which accounts for the relative pause between beats #1 and 2. Regular sinus P waves are seen for the rest of the tracing. Though partially hidden by the lead change, the PR interval preceding beat #4 is clearly short. We suspect that beat #4 is a fusion beat (near simultaneous occurrence of a PVC [premature ventricular contraction] with a sinus complex).

Additional findings on this 12-lead ECG are leftward axis (of about -20°), persistent S waves across the precordial leads, and nonspecific but fairly diffuse ST-T wave flattening/depression. These ST-T wave changes could be from the relatively rapid underlying rate, drug or electrolye effect, left ventricular "strain" (even though voltage for LVH [left ventricular hypertrophy] is lacking), ischemia - or any combination of the above. Given the patient's presentation in heart failure, clinical correlation is essential. ■

In Future Issues: **A Normal Temperature May Not Be What We've Been Taught**

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.

Treating Opioid-Dependent Patients with OAT

A Perspective article in the Jan. 17 *Annals of Internal Medicine* reviews pain management in patients with a history of opioid addiction who are receiving opioid agonist therapy (OAT) with maintenance methadone or buprenorphine. These patients present unique challenges that frequently result in suboptimal treatment of acute pain.

The authors provide an excellent review of these challenging patients and point our 4 common misconceptions: 1) Maintenance opioids provide analgesia—not only is this not the case, but OAT may reduce the effectiveness of standard pain relief measures; 2) Opioids for analgesia may result in addiction relapse—there is no evidence that treatment of acute pain triggers relapse; 3) The additive effects of opioid analgesics and OAT may cause respiratory and CNS depression—tolerance to the respiratory and CNS effects of opioids develops rapidly and is not exacerbated by acute therapy; 4) Reporting pain is drug-seeking behavior—as long as there is clinical evidence of pain, or an acute injury, pain may be safely treated. Drug seeking and manipulation is more likely characterized by vague reports of long-term pain than requests for short term pain relief. Plus, patients on OAT are less likely to experience euphoria associated with coadministered opioids, so there is less incentive to drug seek.

The authors provide specific pain treatment recommendations for patients on methadone and buprenorphine. They conclude, "Addiction elicits neurophysiologic, behavioral, and social responses that worsen the pain experience and complicate provision of adequate analgesia. These complexities are heightened for patients with opioid dependency who are receiving OAT, for whom the neural responses of tolerance or hyperalgesia may alter the pain experience. As a consequence, opioid analgesics are less effective; higher doses administered at shortened intervals are required. Opioid agonist therapy provides little, if any, analgesia for acute pain. Fears that opioid analgesia will cause addiction relapse or respiratory and CNS depression are unfounded. Furthermore, clinicians should not allow concerns about being manipulated to cloud good clinical assessment or judgment about the patient's need for pain medications. Reassurance regarding uninterrupted OAT and aggressive pain management will mitigate anxiety and facilitate successful treatment of pain in patients receiving OAT" (Alford DP, et al. *Ann Intern Med*. 2006;144:127-134).

Long-Term Effects of Warfarin Use

Warfarin use may be associated with osteoporosis and fractures in men, but not women, with atrial fibrillation, according to new study. In a retrospective cohort study of Medicare benefici-

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.

aries with atrial fibrillation in United States, 4461 patients on long-term warfarin therapy were compared to 7587 patients who were not prescribed warfarin. The adjusted odds ratio of fracture was 1.25 in patients who took warfarin (95% CI, 1.06-1.48). The odds ratio for men was 1.63, and a nonsignificant 1.05 for women. In patients who were prescribed warfarin for less than one year, the risk of osteoporotic fracture was not increased significantly. The authors speculate that since warfarin blocks vitamin K dependent clotting factors, it may also block vitamin K dependent osteocalcin and other bone matrix proteins. Interestingly, use of beta blockers reduced the risk of fracture in this population. The authors conclude that long-term use of warfarin was associated with osteoporotic fractures in men with atrial fibrillation, and that beta-blockers may be somewhat protective (Gage BF, et al. *Arch Intern Med*. 2006;166:241-246).

Statins' Multiple Benefits

Mounting evidence suggest that statins have benefits beyond their ability to lower LDL cholesterol. Multiple studies show that statins reduce inflammation in patients without heart failure. Now, 2 new studies suggest that they also reduce inflammation in patients with heart failure. In a study from Emory University, 108 patients with nonischemic heart failure were randomized to atorvastatin 20 mg per day or placebo. Inflammatory markers such as C reactive protein, interleukin-6, and TNF-alpha were all reduced in the atorvastatin group. Atorvastatin treated patients also showed an improvement in LVEF from 0.33-0.37 over one year (P = 0.01) (Sola S, et al. *J Am Coll Cardiol*. 2006;47:332-337).

A second study, from Harvard, in patients with heart failure showed that atorvastatin 10 mg/ day led to an 8% reduction in TNF receptor 1, a 37% reduction in C reactive protein, and a 17% reduction in endothelin-1 (Mozaffarian D, et al. *Am J Cardiol*. 2005;96:1699-1704). Atorvastatin may also have anti-thrombotic effects in patients with unstable angina according to a study from Greece. Forty-five patients with normal cholesterol levels and unstable angina were randomized to 10 mg of atorvastatin or placebo, starting right after hospital admission and continuing for 6 weeks. After one week of treatment circulating levels of anti-thrombin III, factor V, and von Willebrand factor were all significantly reduced in the atorvastatin group (Tousoulis D, et al. *Int J Cardiol*. 2006;106:333-337).

FDA Actions

The FDA has approved the first inhaled insulin for the treatment of adults with type I and type 2 diabetes. Inhaled insulin, a powder form of recombinant human insulin, has been in development for over 10 years, and has been the subject of intense scrutiny by the FDA. Concerns over long-term safety, particularly in people with underlying lung disease, has delayed approval, and safety in children and teenagers is still under investigation. Inhaled insulin is delivered through a device that is significantly larger than an asthma inhaler and, even folded, is the size of a flashlight. A blister pack of insulin powder is inserted into the device, which is then triggered. It is not to be used by smokers or people who quit smoking within last 6 months, and is not recommended for people with asthma, bronchitis, or emphysema. The FDA also recommends pulmonary function testing prior to starting inhalation therapy, and every 6 to 12 months thereafter. Although the product is approved for treatment of both type I and type 2 diabetes, fewer than 30% of type I diabetics achieve adequate control with inhaled insulin alone. Inhaled insulin is a joint effort by Pfizer, Sanofi-Aventis, and Nektar Therapeutics. It will be marketed under the trade name Exubera.

The FDA has approved an intravenous form of Ibandronate that can be administered every 3 months for the treatment of postmenopausal osteoporosis. The 3 mg dose is injected intravenously over 15 to 30 seconds by a healthcare professional. The drug is an option for women who cannot take pills or are unable to sit upright for 30 to 60 minutes after taking an oral bisphosphonate. Efficacy with the injectable form of ibandronate was better than once-a-day oral dosing of Ibandronate 2.5 mg in a study of over 1300 women with osteoporosis. Intravenous and oral forms of the drug were equally well tolerated. The FDA is recommending measurement of serum creatinines prior to administration each dose. Ibandronate is also approved is a 2.5 mg once a day oral dose and a 150 mg monthly oral dose. All 3 formulations are marketed as Boniva.

Berlex's combination estradiol-levonorgestrel patch (Climara Pro) has been approved for the indication for prevention of postmenopausal osteoporosis in women with an intact uterus. The patch was previously approved for the indication of moderate to severe vasomotor symptoms associated with menopause. The osteoporosis indication was based on a 2-year, double-blind, randomized trial that showed that the estradiol-levonorgestrel patch was associated with significant maintenance of bone density compared to placebo. ■