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INSIDE

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Perhaps You Already Suspected This…

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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

Dr. Phillips is a consultant to Cephalon and Ventus and serves on the speakers bureaus of Cephalon and Boehringer Ingelheim.

Synopsis: *A significant proportion of patients with difficult-to-control asthma are non-adherent to both inhaled and oral corticosteroid therapy.*

Source: Gamble J, et al. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009;180:817-822.

THIS REPORT IS THE RESULT OF A RETROSPECTIVE CROSS-SECTIONAL analysis of data in Northern Ireland Regional Difficult Asthma Service. The hypothesis was that medication non-adherence is a significant contributing factor in difficult-to-control asthma. For this report, data were obtained on 182 of 188 patients in the cohort. None of the patients included in this study had non-adherence suspected as a major clinical issue at the time of referral to the difficult asthma service, and all subjects denied non-adherence at the time of first clinical assessment at the clinic.

Difficult asthma was defined as persistent symptoms despite treatment at the Global Initiative for Asthma (GINA) at step 4/5.[1] (After a look a the GINA web site, I concluded that GINA 4/5 treatment would include a medium- or high-dose inhaled corticosteroid [ICS], plus a long-acting beta agonist, plus a leukotriene modifier, plus sustained release theophylline, and perhaps an oral glucocorticoid. This is a lot of medication.)

The investigators assessed adherence both to inhaled and to oral corticosteroid treatment in this cohort of individuals who met criteria for difficult asthma. Adherence is easier to measure in Northern Ireland than in the United States. In Northern Ireland, all prescribed medication is obtained via prescription from a single source, which

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allows use of prescription refill information as a measure of adherence. Combination inhaled steroids/long-acting beta agonist (ICT) is basically a universal part of the treatment for asthma in Northern Ireland and was prescribed in all subjects in this study. General practitioner prescription records were obtained for the previous 6 months for prescription refill rates and were compared with prescribed medication, taking into consideration the number of doses per inhaler and the daily doses prescribed. This was expressed as a percentage of prescribed medication. To assess adherence to oral corticosteroid treatment, plasma prednisolone and cortisol assay levels were used to identify non-adherence when patients were supposed to be taking prednisolone. Non-adherence to oral steroids was defined as undetectable blood plasma prednisolone with detectable plasma cortisol, and the investigators confirmed their assessment of oral corticosteroid non-adherence by discussing their suspicion of it with patients when it was suggested by testing.

Patient demographics, hospital admissions, lung function, outpatient steroid treatment, courses, and quality of life (QoL) data were obtained retrospectively from clinic notes. QoL scores were measured using a generic QoL instrument, the EuroQol EQ-5D,[2] and the disease-specific Asthma Quality of Life Questionnaire.[3] Anxiety and depression were measured using the Hospital Anxiety and Depression Scale.[4]

One hundred eighty-two consecutive referrals to the difficult asthma clinic were assessed. Of these, 63 patients (35%) filled 50% or fewer prescriptions for ICT (defined as the non-adherent group), 21% of patients filled more than 100%, and 45% of subjects filled between 51% and 100% of prescribed medication. Patients filling 50% or fewer of prescriptions for ICT were more likely to have been admitted to the hospital on three or more occasions in the previous year. Women were significantly more likely to be non-adherent to ICT than men (42% female; 23% male). There were no age differences between the groups. There was a tendency for the non-adherent group to have been prescribed higher and more frequent doses of daily inhaled steroid and higher total beta-agonist inhaler doses than the adherent group, although this failed to reach statistical significance. Non-adherent patients were more likely to have been prescribed a nebulizer and used significantly more nebulized beta agonist over the 6-month study period. There were no statistical differences between adherent and non-adherent groups for anxiety and depression scores. Subjects filling 50% or fewer of prescriptions for ICT scored significantly lower in asthma-specific QoL scores for symptoms, activity, and overall score, as well as scoring lower in the general QoL scale. Linear multivariate stepwise regression analysis with percent adherence to ICT as a continuous variable demonstrated three variables to be significantly related to low adherence: female sex (P = 0.001), EuroQoL score (P = 0.02), and hospital admission in the preceding 12 months (P = 0.02).

For the 51 patients in the group who were supposed to be on oral prednisolone (34 patients on maintenance steroids and 17 patients on a short rescue course), 23 patients (45%) were identified as non-adherent using the criteria defined above (undetectable plasma prednisolone with detectable cortisol levels). In two patients taking maintenance oral steroids, prednisolone was detectable with concomitant detectable cortisol. When adherence to prednisolone was discussed, both patients admitted intermittent use of maintenance oral steroids. Of the 26 subjects who were adherent to prednisolone, about one-third of them were filling fewer than half of their inhaled corticosteroid prescriptions. Of the 23 subjects who were non-adherent to prednisolone, only about one-third were adherent to ICS.

When ICT non-adherence findings were discussed with the patients who continued to be followed in the Difficult Asthma Service Clinic, 88% (45/51) admitted variability in taking ICT. Of the six patients who denied non-adherence to ICT despite having a low prescription filling rate, three had undetectable levels of pred-

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nisolone/detectable cortisol or theophylline despite also reporting taking these therapies.

When non-adherence to oral prednisolone was discussed with patients, 86% (22/25) admitted variability in taking this oral steroid. Of the three patients who denied non-adherence to this therapy, two were also non-adherent to ICT. The authors concluded, "These findings indicate that nonadherence is a significant problem in an unselected group of patients attending a Difficult Asthma Service, and one could speculate that if they took regular preventative therapy (as prescribed) their asthma would probably improve substantially."

■ COMMENTARY

First, a clarification of terms. Sometime in the last couple of years, "adherence" has replaced "compliance" as the politically correct term for patients using prescribed treatments as recommended. The implication is that adherence is patient-driven and self-motivated, whereas compliance is somehow imposed from above.

This is the first study to evaluate adherence in a group of adult difficult asthmatics with persistent symptoms, and the findings are discouraging. Even in a cohort referred to a specialty clinic because of difficult-to-control asthma, all of whom initially claimed to be adherent, about a third were non-adherent to inhaled steroids, and about half were non-adherent to oral steroid therapy. And this report comes from a country where cost is not a barrier to treatment.

Asthma is a prevalent condition, and accounts for 1 in every 250 deaths and 15 million disability-adjusted life-years lost annually.[5] Despite intensive treatment, about 5% of adult patients remain difficult to control, with persisting symptoms and frequent exacerbations.[6] Although non-adherence has been suspected as a cause of this phenomenon, it has not been demonstrated so starkly before. Indeed, the American Thoracic Society (ATS) definition of refractory asthma includes the statement "subjects are felt to be generally adherent with therapy,"[7] but assessing adherence to asthma therapy can be difficult.

There are some take home messages here. First, we need objective measures of adherence before undertaking expensive testing or escalating treatment to more costly or risky modalities. The authors put it this way, "Objective surrogate and direct measures of adherence should be performed as part of a difficult asthma assessment and are important before prescribing expensive novel biological therapies." This recommendation is applicable to many medical conditions, not just asthma. Those of us who routinely compare objective CPAP use downloads with patient reports have learned to focus on adherence before jumping to expensive testing or medications for persistent sleepiness on CPAP.

Who's most at risk for inadequate use of prescribed treatment? This study suggests that it is women, those with lower quality of life, and those who are more likely to be hospitalized. The gender difference has been previously reported,[8] and may relate to depression, which is also more common in women.

Most of us do not have the ability to objectively measure adherence as these investigators did. But perhaps a healthy skepticism when patients are not responding well to multidrug efforts to treat chronic conditions would serve us and our patients well. ■

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Dying from Dementia

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Assistant Professor,
University of Southern California

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

Synopsis: *Advanced dementia mortality rates rise after episodes of fever, pneumonia, and eating problems. Treatment decisions often lead to burdensome interven-*

tions and distressing symptoms that might be avoided if caregivers were better informed about the expected complications and prognosis of this condition.

Source: Mitchell SL, et.al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-1538.

NURSING HOME RESIDENTS IN 22 FACILITIES WERE tracked prospectively over 18 months to better describe their clinical prognosis, and to determine how health care decisions made by their proxies influenced medical outcomes. Of 1763 nursing home residents, 572 met the advanced dementia eligibility criteria and 323 were recruited for the study (mean age, 85 years; 85% female, and 90% white). Median nursing home stay was 3 years, and median interval since dementia diagnosis was 6 years. Dementia diagnosis was established using scores on standard data sets and clinical description. Eligibility required the highest score on the Global Deterioration Scale, which reflects profound cognitive deficits such as inability to recognize family members, minimal verbal communication, total functional dependence, incontinence of urine and stool, and inability to ambulate independently. The study also required the availability of an appointed health care proxy who could communicate in English; the proxies were interviewed quarterly.

Within 18 months, 55% had died, with a median survival of 478 days. The overall probability of death within 6 months was 25%; this increased to nearly 50% if an episode of fever, pneumonia, or eating problems had occurred within the prior 6 months. Of those who died, 90% had documented eating problems (weight loss, swallowing or chewing problems, refusal to eat or drink) in the last 3 months of life. Sentinel events such as strokes, hip fracture, seizures, and gastrointestinal bleeding occurred in 10% but rarely were the cause of death. Distressing symptoms such as dyspnea, pain, pressure ulcers, and agitation increased as the end of life approached, ranging from 39% to 54%.

Health care proxies overwhelmingly supported comfort as the primary goal, but only 26% of the proxies for those who died expected death within 6 months. For the residents who died, 12% had been hospitalized, 30% received intravenous therapy, and 7% had tube feeding in the last 3 months of their life. The most common reason for hospitalization was pneumonia and other infections. If their health care proxies believed that they had less than 6 months to live, those residents were less likely to undergo one of these interventions.

■ COMMENTARY

Understanding advanced dementia as a terminal illness requiring palliative care will help improve the suboptimal treatment that many currently receive. Burdensome interventions lead to little comfort for the demented elderly in their last days of life, yet medical progress has allowed us to extend those lives, often beyond any rational reason. Patients with dementia who receive hospice care, in the model used for terminal cancer, have fewer hospitalizations, better pain control, and their families report greater satisfaction than when hospice is not used.[1]

If families and health care proxies understand the limited prognosis, they are more likely to avoid interventions, as this study shows. It describes the "clinical trajectory of end-stage dementia" that can help both families and nursing home staff understand its terminal nature, and adapt care to provide comfort rather than cure. Although it does not provide information about the duration of dementia after an initial diagnosis, it does help us establish when the end of life is near. After the occurrence of pneumonia, fever, or eating problems, survival is often 6 months or less; this is an opportunity to initiate discussions about hospice care or other palliative care programs. ■

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Brief Report

Bacterial Co-infection in H1N1 Influenza

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper conducts research for GSK Pharmaceuticals, Abbott Laboratories, and Merck. This brief was originally published in the December issue of Infectious Disease Alert. *At that time it was reviewed by Connie Price, MD, Assistant Professor, University of Colorado School of Medicine. Dr. Price reports no financial relationship to this field of study.*

Source: CDC. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) — United States, May-August 2009. *MMWR* 2009;58:1071-1074.

DATA EARLY ON IN THE PANDEMIC INFLUENZA OUTbreak suggested that most severely ill patients with influenza A were not suffering from bacterial co-infection. An initial *MMWR* report found no evidence of bacterial super-infection in 30 patients hospitalized in April-May

2009 with confirmed H1N1 in California, although 15 of 25 (60%) with chest radiographs had pulmonary infiltrates. Two-thirds had multilobar infiltrates and four patients required mechanical ventilation. A second report in *MMWR* this summer described an additional 10 patients with H1N1 influenza requiring critical care in Michigan lacking evidence of bacterial pneumonia.

These reports may have been misleading, insomuch as causative agents of pneumonia are difficult to identify, even under optimal circumstances. Newer data, based on autopsy specimens, suggest that nearly one-third of patients with fatal H1N1 illness have evidence of super-infecting bacterial pneumonia. Respiratory specimens (lung, trachea, and large-airway specimens) collected at autopsy from 77 patients with laboratory-confirmed fatal H1N1 infection were evaluated for evidence of bacterial infection. This included tissues stains, immunohistochemical antibody testing for various bacterial pathogens (including antibodies to *S. pneumoniae*, *S. pyogenes*, *S. aureus*, *H. influenza*, but not *Legionella* spp.), and PCR-based assays to further characterize streptococcal and pneumococcal infection. H1N1 infection was confirmed in 41 of the patients before death and identified in 36 patients post-mortem.

Of the 77 fatal cases of H1N1 infection submitted for analysis, 22 (29%) had histopathological, immunohistochemical, and molecular evidence of bacterial pneumonia.

Streptococcus pneumoniae was the most frequently identified pathogen, occurring in 10 persons (13%), followed by *S. aureus* (9.1%), *S. pyogenes* (7.8%), *S. mitis* (2.6%), and *H. influenza* (1.3%). Multiple bacterial pathogens were found in four patients (5%). The mean age at death was 31 (range, 2 months to 56 years), and half were male. The median duration of illness, available for 17 of the patients, was 6 days (range, 1-25 days). Fourteen had received some kind of medical care, at least seven had received antibiotics, and eight had been hospitalized. In 21 patients for whom this kind of information was available, 16 had significant underlying medical conditions known to increase the risk for severe influenza infection (five were described as obese, two with diabetes, asthma, and Down syndrome, and one with HIV infection).

The presence of bacterial pneumonia in nearly one-third of patients with fatal H1N1 infection should be viewed as a minimum estimate of the risk of bacterial super-infection in such patients. Even with the best techniques, super-infecting bacterial pneumonia in patients with viral pneumonia or ARDS may be difficult to confirm. Based on these data, empirical antibacterial therapy should be considered for critically ill patients with influenza, at least until their respiratory status has stabilized or improved. An agent with activity against MRSA should be considered, especially in persons at risk. ■

Pharmacology Update

Ustekinumab Injection (Stelara™)

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

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

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

A MONOCLONAL ANTIBODY AGAINST INTERLEUKIN-12 and interleukin-23 has been approved by the FDA for the treatment of plaque psoriasis. Ustekinumab is marketed as a subcutaneous injection by Centocor Ortho Biotech as Stelara™.

Indications

Ustekinumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy.[1]

Dosage

The recommended dose (given subcutaneously) is 45 mg (patients 100 kg or less) or 90 mg (over 100 kg) initially and 4 weeks later, and followed by 45 mg or 90 mg every 12 weeks. Injection should be given by a health care provider.

Ustekinumab is available as 45 mg or 90 mg single-use vials.

Potential Advantages

Ustekinumab was more effective than etanercept in achieving a 75% reduction on the Psoriasis Area and Severity Index (PASI) and clearing psoriatic lesions.[2]

Potential Disadvantages

Ustekinumab carries warnings and precautions similar to other biological agents that affect the immune system (i.e., infections including tuberculosis, malignancies, and reversible posterior leukoencephalopathy syndrome).[1] Common adverse events (3%-8%) include nasopharyngitis, upper respiratory infection, headache, and fatigue. Monitoring is recommended for patients on concomitant therapy with narrow therapeutic index drugs that are substrates of the CYP450 isoenzymes (e.g., warfarin, cyclosporine).[1]

Comments

Ustekinumab is a human immunoglobulin G1k monoclonal antibody that binds the shared p40 subunit of human interleukin-12 and interleukin-23. These cytokines are believed to play an important role in the pathogenesis of psoriasis.[3] The efficacy and safety of ustekinumab was based on two randomized, double-blind, placebo-controlled, phase III studies in 1996. Subjects included adults with moderate-to-severe plaque psoriasis with a minimum body surface involvement of 10% and a PASI score of 12 or higher, who were candidates for phototherapy or systemic therapy.[1,4,5] In study 1 (Phoenix 1), subjects were randomized to ustekinumab 45 mg or 90 mg at weeks 0, 4, and every 12 weeks. The control group received placebo at week 0 and 4 and were crossed over to ustekinumab at week 12. Those initially randomized to ustekinumab and who achieved long-term response were subsequently randomized, at week 40, to maintenance therapy or withdrawal of treatment until loss of response. The primary endpoint was the proportion of subjects achieving 75% reduction in PASI (PASI 75) and treatment success on the 6-category scale on the Physician Global Assessment (PGA) at week 12.

Study 2 (Phoenix 2) was similar in design except that partial responders (> PASI 50 but < PASI 75) were randomized at week 28 to continue therapy every 12 weeks or increased to every 8 weeks. PASI 75 response rates were 67% in the two 45 mg groups, 66% and 76% in the 90 mg group, and 3% and 4% for placebo. PGA success rates were similar in magnitude. In Study 1, 89% of subjects that were responders at week 28 and week 40 were still responders at week 52 on maintenance therapy compared to 63% who were withdrawn from therapy.[1] In Study 2, increased dosing frequency improved treatment success in partial responders for those initiated on 90 mg but not 45 mg.[5]

In a three-arm comparative trial (ustekinumab 45 mg, 90 mg, and etanercept 50 mg twice weekly) ustekinumab showed better efficacy at 12 weeks.[2] Ustekinumab appears to be well tolerated; however, long-term safety resulting from blockade of IL-12/IL-23 has not been established.

Clinical Implications

Ustekinumab is a biological agent with a different mechanism of action from currently available drugs for psoriasis. Most drugs such as etanercept, infliximab, and adalimumab target tissue necrosis factor (TNF). Ustekinumab, in contrast, targets IL-12 and IL-23. One unpublished study showed that ustekinumab was more effective than etanercept. Comparative studies with other biological agents will better define the role of this agent in the management of moderate-to-severe psoriasis. ■

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CME Questions

62. Non-adherence to steroids in difficult-to-control asthma:
a. is more prevalent in women than in men.
b. is easily recognized by clinicians.
c. usually resolves with specialty care.
d. occurs with inhaled steroids but not with oral steroids.

63. Which of the following will double the risk of death within 6 months when they occur in elderly persons with advanced dementia?
a. Eating problems
b. Pneumonia
c. Fever
d. All of the above

Answers: 62. a, 63. d.

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;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for Sucampo Pharmaceuticals, Takeda, Boehringer Ingelheim; and is a consultant and on the speaker's bureau for Novo Nordisk, Lilly, Daiichi Sankyo, Forest Pharmaceuticals, Cephalon, Novartis, and Sanofi Aventis.

Getting the most bang for your buck: Predictive value of lipid measurements

Source: The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.

THE EMERGING RISK FACTORS COLLABORATION collected data from prospective observational studies of persons without CV disease at baseline (n = 69 studies, with 302,430 participants). Lipid fractions measured in these studies included LDL, HDL, apo B, and apo A1. Risk for incurring CV endpoints was stratified for each lipid fraction.

Triglycerides have always been the lipid fraction demonstrating the weakest association with CVD endpoints. In this data set, although the unadjusted hazard ratio for triglycerides demonstrated increased hazard, adjusted hazard ratios were not convincing. In contrast, subjects with the lowest HDL levels showed an almost 3-fold greater hazard ratio for CV events than those in the highest third. The ratio of apo B:apo A1 was also an important CV risk predictor.

Interestingly, measurement of total cholesterol, HDL, apo B, and apo A1 in the non-fasting state did not appear to appreciably alter their predictive value. Sufficient information for risk prediction, according to these data, is obtained by simply measuring cholesterol levels (total and HDL). Additionally, the authors were not able to identify any significant additional CV risk prediction by adding triglyceride levels to their calculations.

The simplicity of focusing upon total and HDL cholesterol, and being able to use non-fasting results, may enable clinicians to more readily gather predictive information on a wider population of patients. ■

Nortriptyline, gabapentin, or both for neuropathic pain

Source: Gilron I, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 2009;374:1252-1261.

NEUROPATHIC PAIN (NPN), SUCH AS post-herpetic neuralgia or diabetic peripheral neuropathic pain, often requires what has been described as rational polypharmacy: the combination of multiple agents in an attempt to gain maximum therapeutic advantage while minimizing adverse effects. Both nortriptyline and gabapentin have achieved some success in modulation of NPN as monotherapy. Since the mechanism of action of these agents is complementary, a trial of their combination has intellectual appeal. When choosing among antidepressants for analgesic effects, norepinephrine reuptake inhibition appears to be a critical component. Hence, SSRIs have minimal effect, but tricyclics (e.g., amitriptyline, nortriptyline), SNRIs (e.g., duloxetine, venlafaxine), and highly selective norepinephrine reuptake inhibitors (e.g., milnacipran) effectively reduce pain.

Combination nortriptyline and gabapentin provided significantly greater pain reduction than either agent alone. No serious adverse effects were seen in either mono- or combination therapy. Clinicians are already commonly applying combination therapies to neuropathic pain syndromes; it is gratifying to encounter sound evidence supporting this practice. ■

The relationship of fasting plasma glucose and A1c to diabetic retinopathy

Source: Cheng YJ, et al. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population. *Diabetes Care* 2009;32:2027-2032.

THE IDEA THAT A1c MIGHT BE A REASONABLE metric to make the diagnosis of diabetes has been kicking around for more than a decade. Only very recently has there been advocacy from the American Diabetes Association that hemoglobin A1c (A1c) may be an acceptable method for diagnosis of diabetes (A1c ≥ 6.2%); a primary reason for this shift in perception is the widespread adoption of a nationally standardized A1c testing method. Ultimately, diagnosis is intended to go beyond simply categorizing an individual as diabetic or non-diabetic; rather, it is intended to predict risk for important complications of diabetes like retinopathy.

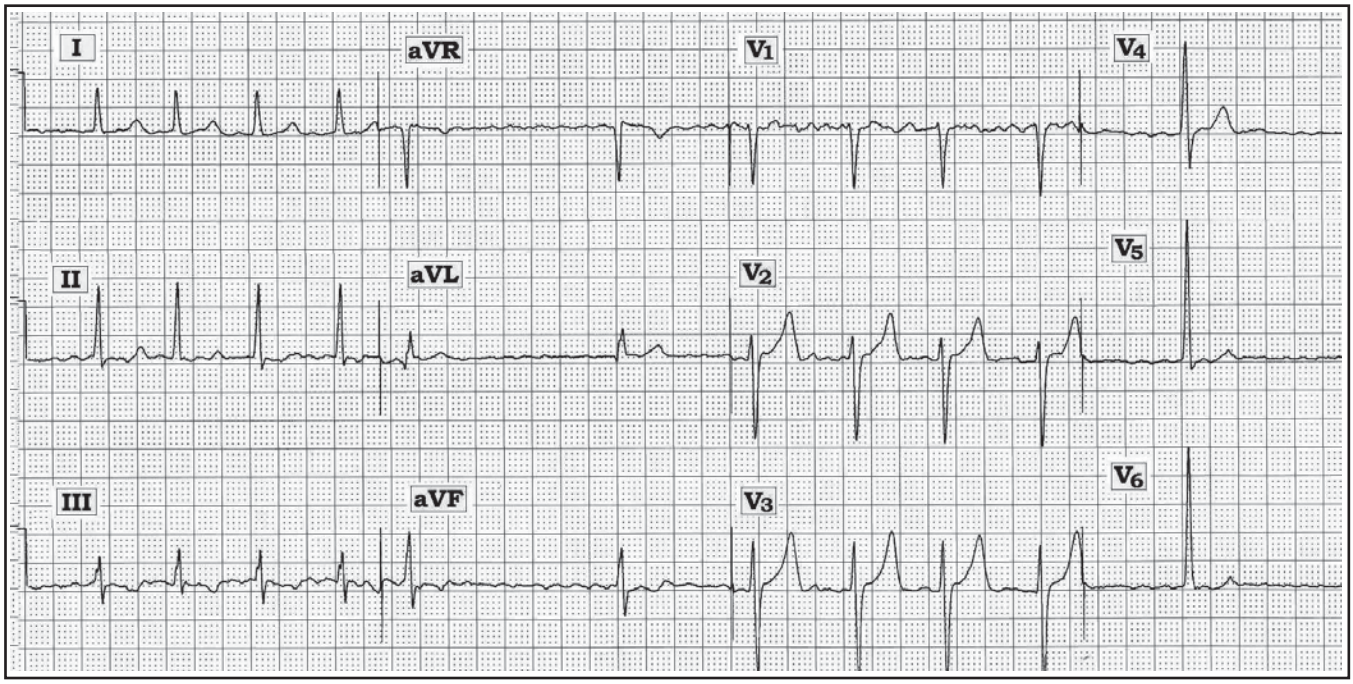
The NHANES (National Health and Nutrition Examination Survey) is a cross-sectional sampling of non-institutionalized civilian adults. From the NHANES 2005-2006 study population, a group of adults age ≥ 40 years had assessment of retinopathy, A1c, and fasting plasma glucose (FPG).

There was a steep increase in frequency of retinopathy at an A1c ≥ 5.5%. Although a similar increased risk was seen at a FPG of 126 mg/dL, overall, the A1c was a better predictor than FPG. Since A1c may be obtained whether or not the subject has fasted, it may become a more convenient (as well as more sensitive) method than FPG for identifying risk of retinopathy. ■

The Likely Diagnosis?

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.



Scenario

The ECG shown above was obtained from a 60-year-old man with a history of a dilated cardiomyopathy. Given this information, what clinical concerns might you have if this patient presented to the emergency department in heart failure with the tracing above?

Interpretation

The rhythm in the tracing is atrial fibrillation. Lack of a lead II rhythm strip makes it difficult to assess the ventricular response. The initial part of the tracing shows a heart rate just over 100 beats/minute. There follows two periods of extreme slowing in the ventricular response (in leads aVL and V_5). This should raise concern for the "tachy-brady" component of sick sinus syndrome vs excessive rate slowing from medication effect. If the marked bradycardia does not resolve after holding any potential rate-slowing medications — and both hypothyroidism and acute infarction are ruled out — then permanent cardiac pacing may be needed in view of the patient's symptoms.

Other findings of note on this ECG tracing include left ventricular hypertrophy (LVH), evidenced by the marked increase in R wave amplitude in leads V_5,V_6 in association with "strain-equivalent" relative ST-T wave flattening in these lateral precordial leads; a small q wave with a hint of ST elevation isolated to lead aVL; a suggestion of shallow T wave inversion in leads III and aVF; and T wave peaking (albeit with a broader base to the T wave than is usually seen with hyperkalemia) in leads V_2 through V_4. The LVH is consistent with this patient's underlying diagnoses of cardiomyopathy and heart failure. We'd guess that the findings described in the infero-lateral leads are not indicative of acute infarction, but serum troponins and serial tracings would be needed for confirmation. Whether the anterior T wave peaking was the result of hyperkalemia, posterior ischemia, or repolarization variant in this patient with probable sick sinus syndrome would be answered by results of serum electrolytes and the ensuing course of events. ■

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1. If you are claiming physician credits, please indicate the appropriate credential: ○ MD ○ DO ○ Other _____

After participating in this program, I am able to:	**Strongly Disagree**	**Disagree**	**Slightly Disagree**	**Slightly Agree**	**Agree**	**Strongly Agree**
2. describe new findings in differential diagnosis and treatment of various diseases.	○	○	○	○	○	○
3. describe controversies, advantages, and disadvantages of those advances.	○	○	○	○	○	○
4. describe cost-effective treatment regimens.	○	○	○	○	○	○
5. describe the pros and cons of new screening procedures.	○	○	○	○	○	○
6. The test questions were clear and appropriate.	○	○	○	○	○	○
7. I am satisfied with customer service for the CME program.	○	○	○	○	○	○
8. I detected no commercial bias in this activity.	○	○	○	○	○	○
9. This activity reaffirmed my clinical practice.	○	○	○	○	○	○
10. This activity has changed my clinical practice.	○	○	○	○	○	○

If so, how? _____

11. How many minutes do you estimate it took you to complete this entire semester (12 issues) activity? Please include time for reading, reviewing, answering the questions, and comparing your answers to the correct ones listed. _____ minutes.
12. Do you have any general comments about the effectiveness of this CME program?

_____

I have completed the requirements for this activity.

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OSHA enforcing N95 respirators for HCWs treating H1N1 flu patients

OSHA: 'We're looking for a good-faith effort.'

By **Gary Evans** and **Michelle Marill**
Editors
Hospital Infection Control & Prevention
Hospital Employee Health

Particulate respirators — a controversial step beyond common surgical masks — are now mandated by the Occupational Safety and Health Administration (OSHA) to protect health care workers from acquiring H1N1 pandemic influenza A from patients. With respirator shortages feared, "good-faith efforts" by health care employers will be recognized by OSHA, which nevertheless is warning that citations and fines may result from inspections that will be primarily prompted by employee complaints.

"Employers should do everything possible to protect their employees," said **Jordan Barab**, acting assistant secretary of labor. He emphasized, however, that where respirators are not commercially available, an employer will be considered to be in compliance if the employer made every effort to acquire respirators. Health care employers will need to be able to show documentation of orders that have been placed or statements from a manufacturer that the respirators are on back order. N95 respirators — already used by many hospitals for the treatment of tuberculosis patients — are the minimum level acceptable for H1N1.

"We're looking for some evidence that the employer has attempted to purchase N95 respirators," Barab said. "We're looking for a good-faith effort."

OSHA is issuing a compliance directive to enforce the Centers for Disease Control and Prevention's recently issued "Interim Guidance on Infection Control Measures for 2009 H1N1 Influenza in Healthcare Settings, Including Protection of Healthcare Personnel." (Available at http://www.cdc.gov/h1n1flu/guidelines_infection_control.htm.)

The CDC disappointed infection preventionists in the guidance by reaffirming its stance that surgical masks are not sufficient to protect workers from H1N1 patients. The CDC recommends the use of respiratory protection that is at least as protective as a fit-tested disposable N95 respirator for health care personnel who are in close contact (within 6 feet) with patients with suspected or confirmed 2009 H1N1 influenza. The president-elect of the Society for Healthcare Epidemiology of America said the CDC decision appeared to be made for reasons other than science, which has not shown burdensome, scarce N95s to be more effective in clinical studies.

"They are recommending a respirator that is not readily available, for transmission that has never been shown to be clinically relevant," said **Neil Fishman**, MD. "It presents a hardship to health care workers and health care providers that is unnecessary and offers nothing in [additional] degree of protection."

On the other hand, the CDC is under considerable pressure from health care unions and worker safety advocates since at least four nurses nationally have reportedly died of complications related to H1N1. Noting that H1N1 surveillance systems do not provide occupational data, the National Institute for Occupational Safety and Health (NIOSH) is asking for information from the public on health care worker H1N1 illnesses and deaths. (Information can be e-mailed to nioshh1n1data@cdc.gov.) NIOSH is asking for contact information so the agency can follow up on cases that have primarily been reported through the media.

"Once we get that information, we can make decisions about whether we want to do a more thorough investigation, whether it is a Health Hazard Evaluation or another kind of study," says **Christina Spring**, health communications specialist with NIOSH in Washington, DC.

Meanwhile, OSHA inspectors will ensure that health care employers implement a hierarchy of

Supplement to *AIDS Alert, Critical Care Alert, Clinical Trials Administrator, Contraceptive Technology Update, Case Management Advisor, Discharge Planning Advisor, Drug Formulary Review, ED Nursing, ED Management, ED Legal Letter, Emergency Medicine Reports, Hospital Case Management, Hospital Peer Review, Hospital Medicine Alert, Hospital Home Health, Healthcare Risk Management, Infectious Disease Alert, IRB Advisor, Medical Ethics Advisor, Occupational Health Management, Patient Education Management, Primary Care Reports, Pediatric Emergency Medicine Reports, Same-Day Surgery, State Health Watch,* and *Travel Medicine Advisor.*

controls, including source control, engineering, and administrative measures, and to encourage vaccination and other work practices recommended by the CDC. Where respirators are required to be used, the OSHA Respiratory Protection standard must be followed, including worker training and fit testing. While the ruling clearly applies to hospitals, as this report was filed OSHA had not responded to a written request for clarification regarding other medical settings. Employee complaints from clinics and physician offices could potentially result in an inspection because OSHA's respiratory protection standards also apply to small businesses.

CDC casts wide net

The CDC clarified that the scope of its guidance includes a wide range of medical settings: "This guidance provides general recommendations for health care personnel in all health care facilities," the CDC stated. "For the purposes of this guidance, health care personnel are defined as all persons whose occupational activities involve contact with patients or contaminated material in a health care, home health care, or clinical laboratory setting."

Since a shortage of disposable N95 respirators is possible, employers are advised to monitor their supply, prioritize their use of disposable N95 respirators according to guidance provided by CDC, and to consider the use of reusable elastomeric respirators and facemasks if severe shortages occur, OSHA advised. Health care workers performing high-hazard, aerosol-generating procedures (e.g., bronchoscopy, open suctioning of airways, etc.) on a suspected or confirmed H1N1 patient must always use respirators at least as protective as a fit-tested N95, even where a respirator shortage exists. In addition, an employer must prioritize use of respirators to ensure that sufficient respirators are available for providing close-contact care for patients with aerosol-transmitted diseases such as tuberculosis.

Where OSHA inspectors determine that a facility has not violated any OSHA requirements but that additional measures could enhance the protection of employees, OSHA may provide the employer with a Hazard Alert Letter. OSHA will inspect health care facilities under the Respiratory Protection Standard "to ensure that health care workers are protected and that protection is in line with CDC [guidance]," Barab said.

The CDC guidance to use respirators has been controversial and hotly debated almost since the onset of H1N1 last spring. Many infection preventionists argue that H1N1 is comparable to seasonal influenza in its virulence and transmission routes, and that droplet precautions (e.g., surgical masks) are sufficient. In fact, some state health departments diverged from CDC and called for surgical masks unless health care workers were performing aerosol-generating procedures.

The Healthcare Infection Control Practices Committee, a CDC advisory panel, endorsed the use of surgical masks rather than respirators. But an Institute of Medicine (IOM) panel charged with reviewing the available science concluded that surgical masks would not protect workers from airborne influenza particles. "[T]here is evidence that work-related exposures to patients infected with H1N1 virus result in health care workers becoming infected," the IOM report stated.

The answer, decided CDC director **Thomas Frieden**, MD, is to use respirators but to limit their use through other measures. "Use a scarce resource carefully," he said in a briefing on the guidance. "Follow a hierarchy of controls and limit the number of people who are potentially exposed and would need a higher level of protection."

The CDC is no longer recommending contact precautions — the use of gowns and gloves — but Frieden noted that influenza is spread through droplet, fomite, and aerosol transmission. "It is an unfortunate fact that we do not have definitive evidence on the portion of transmission that occurs from each of those three routes," said Frieden, noting that "the preponderance of belief" was that droplets were the most common route. "With that lack of knowledge and with the newness of H1N1 . . . we are recommending that N95s . . . would be clearly superior to surgical masks."

Still, CDC is providing some flexibility to hospitals. That means in some circumstances, health care workers may reuse respirators, continue to wear them while caring for more than one patient, or may even wear surgical masks as a last resort option. CDC states that extended use (in which the respirator is not removed while the health care worker cares for more than one patient) is preferred over reuse.

"We recognize that there may be shortage situations," said Frieden. "The need is for us not just to provide respiratory protection now, but the flu season lasts through May. We need to ensure we have a reliable supply."

The CDC guidance states that "when in prioritized respirator use mode, respirator use may be temporarily discontinued for employees at lower risk of exposure to 2009 H1N1 influenza or lower risk of complicated infection." ■

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*.

Insulin Regimens in Type 2 Diabetes

In this issue: Efficacy of once-daily insulin, aldosterone use in heart failure, erectile dysfunction Clinical Practice Guidelines, and FDA Actions.

Efficacy of once-daily insulin

Most type 2 diabetics, even those on oral medications, will eventually require insulin for glycemic control. A new study suggests that simple once-a-day insulin may be as effective as more complex regimens. Researchers from England evaluated 708 patients who had suboptimal hemoglobin A1c (HbA1c) levels while taking metformin and a sulfonylurea.

Patients were randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily with an increase to twice daily if needed. Sulfonylurea therapy was replaced by a second type of insulin if hyperglycemia became unacceptable during the first year of this study or if HbA1c levels were > 6.5%. Outcomes measures were HbA1c levels, the proportion of patients with HbA1c ≤ 6.5%, the rate of hypoglycemia, and weight gain. After 3 years, median HbA1c levels were similar in all 3 groups. More patients had HbA1c levels < 6.5% in the prandial and basal groups, although more than 80% of patients in the basal group required a second type of insulin. The median number of hypoglycemic events per patient per year during the trial was lowest in the basal group (1.7) compared to the the biphasic (3.0) and prandial (5.7) groups ($P < 0.001$). Weight gain was highest in the prandial group. The authors conclude that the basal or prandial insulin-based regimens added to oral therapy resulted in better HbA1c levels compared to a biphasic insulin regimen. In addition, the basal group also had fewer hypoglycemic episodes and less weight gain. The authors state that the "results support the initial addition of a basal insulin to oral therapy, with subsequent intensification to a basal-prandial regimen..." (published at www.nejm.org Oct. 22, 2009).

In an accompanying editorial, Michael Roden, MD, points out that regardless of group, most subjects were accelerated to multiple doses of insulin per day. The study was sponsored by a manufacturer of insulin analogues, and only their analogue products were used in the study, whereas current consensus statements recommend regular human insulin. The editorial also points out that blood sugar control is only part of the equation with diabetics. Aggressive blood pressure control and use of statins and aspirin are equally important. Still, more studies are suggesting an early intensification of treatment with insulin may effectively reduce complications in type 2 diabetes (published at www.nejm.org Oct. 22, 2009).

For updated guidelines on the treatment of type 2 diabetes, see the recently released one-page algorithm from the American Association of Clinical Endocrinologists: www.aace.com/pub/pdf/GlycemicControlAlgorithm.pdf. ■

Aldosterone use in heart failure

Aldosterone antagonists are underused in

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. Dr. Elliott reports no financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

patients with moderate-to-severe heart failure (HF) and systolic dysfunction according to a new study in the *Journal of the American Medical Association*. Aldosterone antagonists (spironolactone and eplerenone) have been shown to be very effective in the treatment of HF such that they were designated class I (useful and recommended) in the recent American College of Cardiology/American Heart Association Chronic HF Guidelines. Despite this, the drugs are underused in eligible patients.

The current study was an observational analysis of more than 43,000 patients admitted to the hospital with HF and discharged home from 241 hospitals participating in the Get With The Guidelines — HF quality improvement registry between 2005 and 2007. Among 12,565 patients eligible for aldosterone antagonist therapy, only 4087 (32.5%) received one of the drugs at discharge. There was wide variation in aldosterone antagonist usage among hospitals (0%-90.6%) and was more likely to be used in younger patients, African Americans, those with lower blood pressure, history of implantable cardioverter-defibrillator, depression, alcohol use, pacemaker implantation, and those having no history of renal insufficiency. Inappropriate use of aldosterone antagonist therapy was low. The authors conclude that use of aldosterone antagonist therapy is underutilized in HF patients, occurring in only one-third of eligible patients, although the rate of use increased gradually throughout the course of the study. They also state that use of evidence-based guidelines in hospitals may be warranted to improve treatment of HF patients (*JAMA* 2009;302:1658-1665).

Many clinicians shy away from use of aldosterone antagonists because of concerns regarding hyperkalemia, especially since many of these patients are also on ACE inhibitors or ARBs. Aldosterone inhibitor use in HF is not part of the Joint Commission/Centers for Medicare and Medicaid Services core performance measures. Regardless, aldosterone antagonists have been shown to benefit patients with HF and they are clearly underutilized. ■

Erectile dysfunction guidelines

The American College of Physicians has published a Clinical Practice Guidelines regarding hormonal testing and pharmacologic treatment of erectile dysfunction (ED) in men. The guideline recommends that clinicians initiate therapy with a PDE-5 inhibitor (sildenafil, vardenafil, or tadalafil) in men who seek treatment for ED and do not have a contraindication such as concomitant nitrate use. They rate this a strong recommendation with high-quality evidence. The choice of a PDE-5 should be based on preference, including ease of use, cost, and adverse effects profile. The guideline does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction due to insufficient evidence to determine benefits and harm. The guideline reviewed more than 100 randomized controlled trials that showed that PDE-5 inhibitors improved successful sexual intercourse and improved erections in men with ED (*Ann Intern Med* 2009 Oct 19;). ■

FDA Actions

The FDA has authorized emergency use of IV antiviral peramivir for treatment of 2009 H1N1 influenza in hospitalized patients. The drug is not yet approved for use in this country, but was authorized in response to a request from the CDC. IV peramivir is approved only for hospitalized adult and pediatric patients for whom an IV drug is clinically appropriate because the patient is not responding to either oral or inhaled antiviral therapy, because enteral or respiratory therapy is not feasible, or in adults when a clinician judges that IV therapy is appropriate due to other circumstances. This is the first available IV antiviral available for 2009 H1N1 infections. For more information see www.cdc.gov/h1n1flu/eua/.

The FDA has approved the quadrivalent human papilloma virus (HPV) vaccine (Gardasil®) for use in boys and young men. The vaccine is approved for males ages 9-26 as 3 injections given over a 3-month period. HPV is the most common sexually transmitted disease in the United States with 1 of 500 men infected every year. Previously, the vaccine had only been approved for use in females ages 9-26 years. In related news, a recent study from the National Cancer Institute, CDC, and American Cancer Society has suggested that the vaccine is not cost-effective for women older than age 30 who undergo annual or biennial screening for cervical cancer (*Ann Intern Med* 2009;151:538-545). Similarly, a study from Harvard found that HPV vaccination for 12-year-old girls was cost-effective, but the same vaccination for 12-year-old boys was not (*BMJ* 2009 Oct. 8).

The FDA has also approved a bivalent HPV vaccine for use in females, which protects against HPV types 16 and 18. The vaccine is being marketed as a "cervical cancer vaccine" by GlaxoSmithKline under the trade name Cevarix®. ■