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It's the Fast Food, Stupid!

ABSTRACT & COMMENTARY

Synopsis: *The optimum body mass index (BMI) for adults is probably 18.5 to 21.9 kg/m^2.*

Source: Field AE, et al. *Arch Intern Med.* 2001;161:1581-1586.

This was a prospective 10-year follow-up of 77,690 women from the Nurses' Health Study and 46,060 men from the Health Professionals Follow-up Study. Both are ongoing studies. The women were enrolled starting in 1976, and were 30 to 50 years of age at the time of enrollment. They are sent questionnaires every other year; the questionnaires include queries about diet, physical activity, smoking, contraception, and medical diagnoses. Field and colleagues also obtain medical records (with permission) for diseases of particular interest, follow-up with relatives in the event of death, and send supplementary questionnaires to subjects who report diabetes. The men were enrolled starting in 1986, and were 40 to 75 years of age when the study began. Data collection in the Health Professionals study is similar to that of the Nurse's Health Study.

For the current analysis, Field et al used logistic regression to correlate body mass index (BMI) with high cholesterol levels, hypertension, gallstones, type 2 diabetes, heart disease, stroke, and colon cancer. They controlled for age, smoking, and ethnicity. Subjects who reported being diagnosed with cancer before 1986, those who smoked, were missing data, or who had BMIs of less than 18.5 were excluded from analysis.

For both men and women, the risk of developing diabetes, gallstones, hypertension, heart disease, and stroke increased with the severity of overweight. Being overweight was a particularly strong risk factor for diabetes (duh). When those with a BMI between 18.5 and 21.9 were used as a reference group, men and women with a BMI of 22-24.9 were found to be at increased risk of diabetes, hypertension, and high cholesterol level. Women were at increased risk for gallstones and heart disease, and men for colon cancer. Further, both men and women who had BMI's between 25 and 29 were at significantly increased risk of developing all conditions reported except for stroke.

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INSIDE

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

This study clearly demonstrates that obesity not only kills, but also maims. What is new about this paper (besides the excellent methods and large sample size) is the association of morbidity with BMI levels previously believed to be "safe." Field et al point out that in studies correlating weight with health, the higher the BMI is for the reference group, the lower the risks of obesity will appear to be. This is because some people who are actually at risk will be placed in the reference group. The US Department of Agriculture has recently suggested an overweight cutoff of a BMI of 25, instead of 27. Field et al support that proposal with this data.

This is by no means the first paper to point out the risks of moderate obesity. Among the health hazards reported here, overweight has previously been shown to be a risk factor for diabetes,[1,2] hypertension,[3,4] dyslipidemia,[5] coronary heart disease,[6] stroke,[7] and gallbladder disease.[8] In addition to the risks studied and reported here, obesity has been linked to osteoarthritis,[9] obstructive sleep apnea,[10] breast cancer,[11,12] endometrial cancer,[12] and prostate cancer.[13]

We are the most obese nation on the planet. We are also the home of McDonald's, Coca-Cola, and jumbo portions. All-cause mortality rises above a BMI of 25.[14] I think we have to add fast food to the (long) list preventable risk factors for premature mortality. ❖

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Update on Stroke Prevention: News from National Meetings—The WARSS and PROGRESS Trials

CONFERENCE COVERAGE

Source: Mohr JP for the warfarin-aspirin recurrent stroke study (WARSS) study group. Presented at the American Academy of Neurology, May 1999, Philadelphia, Pa.

The warss trial was designed to compare warfarin therapy with antiplatelet therapy (aspirin) in the prevention of recurrent stroke. The trial was a randomized, double-blind, multicenter trial of 2206 patients at 47 US centers. The trial had 4 substudies: PICSS, APASS, HAS, and GENESIS, examining issues such as the risk of stroke with patent foramen ovale (PFO) and antiphospholipid antibodies. Data

from the substudies have not yet been presented.

The inclusion criterion for WARSS was an ischemic stroke within the prior 30 days. Patients with a cardioembolic source of stroke, such as atrial fibrillation (AF) or a symptomatic, operable carotid stenosis, were excluded. Patients were randomized to receive either aspirin (325 mg/d) or warfarin (INR 1.4-2.8) for at least 2 years. Adjustments of warfarin were based on either real or computer-generated INR values.

Among warfarin-treated patients, a mean INR 2.0-2.1 was sustained over 2-year follow-up. There were no statistical differences in the risk of recurrent stroke or in major hemorrhage. No statistical differences were found in subgroups defined by sex, race, or stroke subtype.

COMMENT BY ALAN Z. SEGAL, MD

We eagerly await the upcoming formal publication of the WARSS data to provide further insight into this landmark study. These preliminary findings alone already portend a major decrease in the empiric use of warfarin post-stroke. The WARSS data, however, are open to at least 3 major criticisms that may still justify the use of coumadin by those who wish to use it.

1. The INR range chosen, 1.4-2.8, may have been too low. INRs in the range of 1.5-2.0 have been shown to be inadequate for stroke prevention in the setting of AF. It is possible that if all patients were maintained with INRs above 2.0, an advantage for warfarin may have been found.
2. The WARSS study was comprised of a large proportion of patients (> 50%), with lacunar disease. Since antiplatelet therapy rather than warfarin has traditionally been considered optimal for these small vessel lesions, inclusion of all these patients may have skewed the results toward aspirin. Data from the warfarin aspirin study of intracranial disease (WASID) comparing these therapies among patients with large vessel intracranial stenoses may yield different results.
3. Finally, while the WARSS study did not show an advantage for warfarin over aspirin, neither did it show a detriment. Under study conditions, with strict control of warfarin therapy, no increase in hemorrhage among warfarin patients was observed. If one is willing to accept the added inconvenience of warfarin therapy, its use remains justifiable based on the WARSS data.

J Chalmers for the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). Presented at the 11th European Meeting on Hypertension, June 2001, Milan, Italy.

Hypertension is a well-recognized stroke risk factor. The immediate reduction of blood pressure in the post-stroke setting is, however, a matter of some controversy as perfusion may be augmented by higher blood pressures. Blood pressure control beyond the acute setting is a uniform goal in stroke survivors.

In the PROGRESS study, 6105 patients with a history of a stroke within the previous 5 years were randomized to a regimen of perindopril 4 mg along with indapamide 2.5 mg compared with placebo. All patients were treated with other antihypertensives as deemed necessary by their physicians along with medications such as aspirin and statin drugs.

The overall stroke risk was reduced by 28% in treated patients compared with placebo. The risk of fatal or disabling stroke was reduced by 38%. This benefit applied to both ischemic and hemorrhagic stroke. While patients with either hypertension or diabetes showed the most striking reduction (approximately 33%), a benefit of 22% was observed in patients without high blood pressure.

COMMENT BY ALAN Z. SEGAL, MD

These data indicate that angiotensin converting enzyme (ACE) inhibitors have potent benefits in recurrent stroke prevention. This benefit applies irrespective of whether hypertension is actually present. These data parallel those of the heart outcomes prevention (HOPE) study (Yusuf S, et al. *N Engl J Med.* 2000;342:145-153) showing that the ACE inhibitor ramipril (Altace) provided marked reductions of both cardiac risk and stroke. The relative risk of stroke with ramipril treatment was 0.68 ($P < 0.001$) compared with placebo.

The accumulating data from studies such as PROGRESS and HOPE indicate that ACE inhibitors have vascular benefits extending far beyond blood pressure control. These effects may include antiatherogenesis, arteriolar remodeling, endothelial cell modulation, platelet inhibition, and alterations in atrial naturetic peptide and other hormones. Most likely, this is a class effect applying to all ACE inhibitors. Perindopril is marketed in the United States under the trade name Aceon. The PROGRESS investigators specifically chose this drug for study as this agent is thought to maintain cerebral autoregulation and blood flow even in the setting of blood pressure reduction.

It is likely that future stroke prevention guidelines will include ACE inhibitor therapy regardless of whether hypertension is present. ❖

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The Role of Acid and DGER in Symptomatic GERD

ABSTRACT & COMMENTARY

Synopsis: *Acid, not bile, is the determinant of most symptomatic gastroesophageal reflux. It remains clear that acid control is the mainstay of GERD therapy.*

Source: Koek GH, et al. *Am J Gastroenterol.* 2001;96: 2033-2040.

Mixed reflux of acid and duodenal contents frequently can be found in gastroesophageal disease (GERD), and many surgeons have strongly supported the view that so-called "bile reflux" is particularly important in GERD pathogenesis. More importantly, they have stated that such "bile reflux" cannot be eliminated by antisecretory therapy. This Dutch study used pH monitoring and simultaneous assessment of duodenogastric reflux in 72 symptomatic patients using the Bilitech® system. Five hundred forty-four symptom episodes were identified. Of these symptoms, 28% were temporarily associated with acid reflux, 9% with duodenal gastroesophageal reflux (DGER), and 12% with mixed reflux. A positive symptom-association probability for acid reflux was present in 22% of patients, for DGER in 7% of patients, and for mixed acid and "bile" reflux in 10% of patients. Koek and colleagues conclude that there is little likelihood that DGER ("bile reflux") will prove to be clinically important in symptom causation for many patients.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Controversy has raged about the importance of "bile reflux" in the pathogenesis of GERD, particularly severe GERD including Barrett's esophagus. This study seems to put this notion to rest once and for all. Only 7% of all reflux episodes involved DGER as measured by the Bilitech probe. In a number of previous studies, it has been pointed out that severity of GERD depends on the total duration of reflux, particularly prolonged in Barrett's esophagus. Barrett's patients do have more DGER than patients with lesser degrees of GERD but they also have more acid reflux. Indeed, Richter and his colleagues at the Cleveland Clinic have shown that PPI therapy decreases DGER as much as it does acid reflux (presumably by the profound effects of PPI administration on gastric volume).[1] It is clear from the present study, done by well-known European investigators, that symptoms of GERD are mostly acid related and not likely to represent any sort of "bile reflux." It would seem to be a rational corollary that aggressive antisecretory therapy remains the mainstay of GERD treatment. ❖

Reference

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Changes in Lifestyle Can Prevent Type 2 Diabetes!

ABSTRACT & COMMENTARY

Synopsis: *Reducing weight and moderate daily exercise prevented the development of type 2 diabetes in subjects with impaired glucose tolerance.*

Source: Tuomilehto J, et al. *N Engl J Med.* 2001;344: 1343-1350.

The incidence of diabetes is increasing worldwide at an alarming rate. This study was done to see whether type 2 diabetes can be delayed or prevented by interventions that affect lifestyles of subjects at high risk.

The study group assigned 522 middle-aged, overweight subjects (172 men and 350 women), mean age 55 years, mean body mass index 31, with impaired glucose tolerance, to either an intervention group or to a control group. The intervention group received individualized counseling aimed at reducing weight, total intake of fat and saturated fat, and increasing intake of fiber and physical activity. An oral glucose tolerance test was performed annually; the diagnosis of diabetes was confirmed by a second test. The mean duration of follow-up was 3.2 years. The study was stopped early because of the significant difference between the 2 groups.

The mean weight loss between baseline and the end of the first year was 9.24 lbs in the intervention group and 1.7 lbs in the control group; the net loss by the end of year 2 was 7.7 lbs in the intervention group and 1.7 lbs in the control group ($P < 0.001$ for both comparisons between groups). The cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group. During the trial, the risk of diabetes was reduced by 58% in the intervention group. The reduction in diabetes was directly associated with changes in lifestyle. Tuomilehto and colleagues concluded that type 2 diabetes can be pre-

vented by changes in lifestyles of high-risk subjects.

This was an "intention to treat" protocol and it is remarkable that none of the subjects who reached 4 or 5 of the goals developed diabetes (49 in the intervention group and 15 in the control group).

The subjects in the intervention group were given detailed advice about how to achieve a 5% reduction in weight loss, to reduce the total fat intake to less than 30% of the energy consumed, and an intake of saturated fat to less than 10% of the energy consumed, an increase in fiber to at least 15 g per 1000 calories, and to perform moderate exercise for 30 minutes daily. They were also advised to eat whole grain bread, vegetables, fruits, low fat milk, and meat and vegetable oils rich in monounsaturated fatty acids.

The individualized exercise prescriptions included walking, jogging, aerobic ball games, and swimming to increase cardiorespiratory fitness. Individualized circuit-type resistance training sessions were offered to improve functional capacity and strength. The rate of participation in these sessions varied from 50-85% at the various centers. This appears to be an exercise program that improves aerobic fitness and would reduce muscle cell fat content.

COMMENT BY RALPH R. HALL, MD, FACP

Two recent papers emphasize the importance of lifestyles and their relevance to the development of type 2 diabetes. The first paper by Salmeron and colleagues in analyzing the Nurses' Health Study found a strong correlation between the intake of trans fatty acids and the incidence of type 2 diabetes.[1] The diet prescribed in this study does lower the trans fatty acid intake. It is similar to the DASH diet,[2] (and, if you will, a diet similar to the Mediterranean diet). The Lyon Heart study using the Mediterranean diet resulted in a 70% reduction in "all cause" mortality due to a reduction in coronary heart disease without lowering the LDL cholesterol.[3]

In another paper, Toth and colleagues found a greater relationship between exercise endurance capacity (VO_2 Max) and glucose disposal rates than from either total or regional adiposity.[4] The more fit the individual the better the glucose disposal rate and the less the insulin resistance.

There has been a trend toward emphasizing that just a little exercise is better than none and ultimately influencing people to reduce the amount of exercise they do. There has been the fear that if we asked patients to do more intense exercise that they would be intimidated and do less. The results of these studies suggest that we must prescribe exercise so that it is intense enough to have a training effect (increasing VO_2 max).

Using diet and exercise we have the tools to drastically reduce the incidence of a disease that not only is costing billions of dollars but leads to suffering, early death and disability from heart disease, blindness, and renal failure. There is a great need and opportunity to use these tools more effectively than we have done in the past.

Imagine your patients' response to being prescribed a Mediterranean diet rather than a Step One National Cholesterol Education Program diet. ❖

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Prevention or Procrastination? The Effect of Coumadin on Long-Term Risk of Thrombosis

ABSTRACT & COMMENTARY

Synopsis: *The benefits of long-term anticoagulation for idiopathic DVT dissipate after stopping coumadin.*

Source: Agnelli G, et al. *N Engl J Med.* 2001;345:165-169.

The warfarin optimal duration italian trial was a multicenter, nonblinded, randomized, controlled trial of 268 patients with an indiopathic deep vein thrombosis (DVT).[1] All patients received 3 months of coumadin and were then randomized either to discontinue coumadin or to continue coumadin for an additional 9 months. All patients were then followed for a minimum of 2 years (mean follow-up 37 months) for the primary end points of recurrence of a thrombosis, pulmonary embolism, major bleeding, and death. Patients with a known history of cancer, hypercoagulopathy, venous stasis, or injury were excluded from the study.

At the 1-year mark, patients treated with 12 months of coumadin had less DVT recurrence than patients treated with 3 months of coumadin (RR = 0.36; 95% CI,

0.12-1.11). At the conclusion of 2 years of follow-up, however, there was no difference in the recurrence of DVT (RR = 0.99; 95% CI, 0.57-1.73). Twenty-eight patients (21%) in the control group and 31 patients in the treatment group had complications. There was no difference in mortality.

COMMENT BY JEFF WIESE, MD

The trial is consistent with previous studies that have established that 6 months of coumadin following an idiopathic DVT is superior to 3 months of therapy in reducing the recurrence of DVT.[2,3] This study asks the important question: what happens to those patients treated with 6 months of coumadin after the drug is stopped? Do they continue to enjoy protection from DVT, or has coumadin only delayed the inevitable rethrombosis?

Patients treated with 12 months of coumadin had a reduced risk of recurrence than those treated with only 3 months of therapy (RR = 0.36; 95% CI, 0.12-1.11). However, this difference had evaporated at 24 months of follow-up. Patients who had been protected from thrombosis while on coumadin experienced thrombosis when the drug was stopped. At the conclusion of 2 years of follow-up, 21 (16%) patients in both groups had experienced a recurrent DVT. Furthermore, there was no benefit in prevention of mortality or pulmonary embolism with the additional 9 months of coumadin. This suggests that coumadin had only delayed the inevitable thrombosis, and the delay offered no benefit to the patient.

Further study will be required to change the current standard of care that suggests that patients should receive 6 months of coumadin following an idiopathic DVT. This study may ultimately change that standard, however. Because coumadin carries a 4% per year bleeding risk, most patients are assigned a stop date for the coumadin.[3] If an additional 9 months of coumadin only delays the inevitable thrombosis, then it stands to offer only the complications of bleeding during those 9 months. A shorter dose of coumadin may be preferable.

This study may have been underpowered to detect a difference between the 2 groups at the 2-year point. The difference in gender between the 2 groups (55% men in the control group vs 61% in the treatment group) also raises questions about the success of the randomization. It is possible that the intervention group was assigned a disproportionate number of patients with Factor V Leiden or antithrombin, variables not assessed in this study population.

Physicians should be aware that a certain subgroup (15%) of patients is likely to have recurrent DVT even after coumadin is stopped. The duration of coumadin therapy does not seem to alter this risk. ❖

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Pharmacology Update

IV Pantoprazole—The First Parenteral PPI

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

The first parenteral proton pump inhibitor (PPI) is now available in this country. Wyeth Laboratories' pantoprazole, which has been marketed for more than a year under the trade name Protonix, will soon be available as an injectable for use in hospitals. Although this is the first PPI available in a parenteral form in this country, several others are currently available in Europe.

Indications

Pantoprazole sodium IV is indicated for short-term treatment (7-10 days) of gastroesophageal reflux disease (GERD) in patients in whom oral therapy is not appropriate.[1]

Dosage

The recommended dose of pantoprazole sodium is 40 mg daily for 7-10 days. It should be administered over a period of 15 minutes at a rate not faster than 3 mg/min. No dosage adjustment is required in patients with mild, moderate, or severe renal impairment, or mild or moderate hepatic impairment.[1] Pantoprazole sodium is supplied as a freeze dried powder containing 40 mg of pantoprazole.

Potential Advantages

Pantoprazole is the first PPI to be available in parenteral form. The oral and intravenous forms of pantoprazole appeared to be equipotent. No change in dosage is required when switching from one formula-

tion to the other.[2,3] Pantoprazole has low potential for drug-drug interactions involving the cytochrome P450 isoenzymes.[1]

Potential Disadvantages

Postmarket spontaneous reported adverse events involving intravenous or oral pantoprazole have included anaphylaxis, angioedema, anterior ischemic optic neuropathy, severe dematologic reactions (eg, erythemia multiforme, Steven-Johnson syndrome, toxic epidermal necrosis, and hepatocellular damage).[1]

Comments

Pantoprazole sodium is the first PPI to be available in an injectable form. For patients temporarily unable to take oral PPI initiating therapy with parenteral pantoprazole for 5-7 days followed by oral pantoprazole for 8 weeks has been shown to be effective in the healing of moderate or severe (stage II and stage III) GERD.[4] Complete healing was achieved in 77% of patients in 4 weeks and 85% in 8 weeks based on intent-to-treat analysis and 87% and 95%, respectively, per protocol. Parenteral pantoprazole (160-240 mg/d) has also been reported to be effective in controlling acid output in patients with Zollinger-Ellison syndrome.[5] Pantoprazole costs about $24 per 40 mg vial.

Clinical Implications

Pantoprazole sodium is the first parenteral PPI approved in the United States. Only histamine 2 receptor antagonists such as ranitidine, famotidine, and cimetidine are currently available in parenteral form. When a PPI has been needed in patients unable to swallow the oral dosage form, the drug has been administered by mixing it with a liquid and injecting it through the nasogastric tube. The parenteral form would facilitate administration in this setting. Although the drug is only approved for GERD, other potential uses of parenteral PPIs include Zollinger-Ellison syndrome, prevention of stress ulcer, acid-induced lung injury, and bleeding peptic ulcers.[6] ❖

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CME Questions

12. Which body mass index (BMI) is associated with the lowest risk of hypertension, diabetes, and high cholesterol level in both men and women?

a. 18.5-21.9
b. 22-24.9
c. 25-29.9
d. 30.0-34.9
e. > 35

13. Reducing weight and moderate daily exercise prevented the development of type 2 diabetes in subjects with impaired glucose tolerance.

a. True
b. False

14. Symptomatic GERD is most closely associated with:

a. reflux of duodenogastric contents ("bile reflux").
b. mixed acid and "bile" reflux.
c. reflux of acidic gastric contents.
d. motility abnormalities of the esophagus.
e. None of the above

15. In patients with an idiopathic deep vein thrombosis, what is the effect of coumadin on the recurrence of DVT?

a. Coumadin has no effect on preventing the recurrence of DVT.
b. A longer course of coumadin reduces the incidence of DVT recurrence, but this effect disappears after the drug is stopped.
c. Twelve months of coumadin reduces the long-term risk of DVT recurrence when compared to 3 months of coumadin.
d. Three months of coumadin is sufficient to prevent recurrence of idiopathic DVT.

16. Which statement is *false* about pantoprazole injection?

a. No dose adjustment is needed in renal failure.
b. It is given once a day.
c. Drug/drug interactions are common.
d. It is approved for the treatment of GERD.

By Louis Kuritzky, MD

Does the Antihypertensive Response to Angiotensin Converting Enzyme Inhibition Predict the Antihypertensive Response to Angiotensin Receptor Antagonism?

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) share the common effect of blockade of the renin-angiotensin-aldosterone system, albeit through different mechanisms. The preponderance of consensus advice currently recommends that the primary role of ARBs in cardiovascular drug therapy be as substitute medication for patients in whom ACEIs are efficacious, but side effects like cough prove problematic. Since, despite similarities, there are distinct pharmacodynamic effects of these 2 classes of agents, Stergiou and colleagues sought to discern whether responsiveness to ACEIs was predictive of responsiveness to ARBs.

Hypertensive patients (n = 33) were randomized to receive lisinopril (20 mg QD) or losartan (50 mg QD) for 5 weeks, and then crossed over. Blood pressure was monitored by 24-hour ambulatory monitoring. "Responders" were defined as having at least a 10/5 decline in BP.

More than one-third of subjects had "discordant" responses to the 2 drugs; ie, over 33% of persons who were responders to ACEIs did not respond to ARBs, and vice versa. Stergiou et al conclude that despite their mechanistic similarities, there is diversity of responsiveness to these 2 classes of agents. Clinicians might anticipate that failure to respond to one class of agent, then, need not preclude efficacy of the other within the same patient, nor does efficacy of one class ensure efficacy of the other, within the same patient. ❖

Stergiou GS, et al. Am J Hypertens. 2001;14:688-693.

Bone Mineral Density in Women with Essential Hypertension

There have been disturbances in calcium metabolism noted in hypertensive populations, including hypercalciuria associated with increased salt intake. Hypertensive animals have lower trabecular bone mineralization than normotensive controls. To investigate the association of hypertension (HTN) with bone mineral density (BMD) in humans, Tsuda and colleagues performed DEXA scans on Japanese women (n = 31) with untreated essential HTN.

Despite the fact that serum calcium, magnesium, ionized calcium, and vitamin D levels did not differ between hypertensive and normotensive women, there was a significant decrease in BMD in hypertensive women when compared with normotensives. Some of this difference was explained by a slight mean age difference in the 2 groups (hypertensive group mean age = 62, normotensive = 57). Additionally, BMD was inversely associated with systolic blood pressure. The mechanism for decreased BMD in hypertensive women is not fully understood, but in this population, hypertensive women exhibited greater urinary calcium excretion. ❖

Tsuda K, et al. Am J Hypertens. 2001; 13:704-707.

Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease

Even after appropriate treatment for Lyme disease, some patients have persistent symptoms such as fatigue, joint and muscle pain, neurologic symptoms, and cognitive disturbance. Some anecdotal reports have indicated that prolonged antibiotic treatment courses may cause such Lyme-related symptoms to remit. To examine the role of antibiotic treatment in persons who manifest protracted symptoms associated with Lyme disease, Klempner and colleagues report on 2 randomized trials comprising seropositive and seronegative Lyme disease patients with symptoms persisting at least 6 months after acute infection (combined n = 129).

Antibiotic treatment consisted of ceftriaxone IV 2 g/d × 30 days followed by doxycycline 200 mg PO QD × 60, or placebo. Outcomes included physical and mental health scores on the SF = 36 General Health Survey.

Though the original intention of Klempner et al had been to enroll 260 patients, the data as analyzed by the safety monitoring board suggested that the study be discontinued early, since no demonstrable improvement was discernible in patients receiving active antibiotic treatment, and continuing the study longer was highly unlikely to indicate a favorable response. ❖

Klempner MS, et al. N Engl J Med. 2001;345:85-92.

In Future Issues: Guidelines for Adults on Self-Medication of Acute Diarrhea

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End-of-Life Care Still Far From Satisfactory

IOM report calls for thorough reorganization

By Julie Crawshaw

Despite increasing publicity surrounding end-of-life care, a recent report says little has been done to alleviate serious end-of-life problems that will undoubtedly magnify as more Americans enter old age and approach death.

The panel that prepared the report, sponsored by the Institute of Medicine and the National Cancer Advisory Board, called for reorganizing virtually the entire US health care system to provide uninterrupted appropriate care for those dying from cancer.

The report recommends that the Centers for Medicare and Medicaid Services (CMS—formerly the Health Care Finance Administration) change reimbursement methods to expand payments for palliative care, including reimbursing physicians and caregivers for time spent meeting with pain experts, psychologists, and family members to organize pain relief.

Though this report focused on the plight of cancer patients, the situation isn't any better for those suffering from other terminal illnesses. Pain relief and other palliative care measures are too often elusive across the board, according to John G. Weg, MD, FCCP, professor of internal medicine, pulmonary and critical care medicine at University of Michigan Medical Center in Ann Arbor, Mich.

Weg, who has worked on end-of-life care issues for more than 30 years, says it simply isn't reasonable to put patients in intensive care when there's nothing left that can cure them unless there is a specific intercurrent problem that can be reversed. He says he feels strongly that it's critical to recognize when there is no longer a treatment that is likely to do any good.

"Telling patients 'I can't cure you' isn't the same as telling them you can't help them," Weg observes. "I think every physician has an obligation to make a patient as comfortable as possible. We can almost always control symptoms to a point acceptable to the patient."

Paul A. Selecky, MD, FCCP, director of the pulmonary department and head of the ethics committee at Hoag Memorial Hospital in Newport Beach, Calif, says there is a lack of physician understanding about how to deal with pain. "The vast majority of patients in the US die in a hospital," Selecky says, "yet the SUPPORT [Study to Understand Prognoses and Preferences, Outcomes and Risks of Treatment) study done a few years ago showed that even when using a nurse-clinician as an intervention, patients often die in significant pain."

Don't Wait for New Drugs; Change the System Now

Joanne Lynn, MD, president of Americans for Better Care of the Dying (ABCD) and director of RAND Center to Improve Care of the Dying, says a big part of the problem is that many physicians are reluctant to discuss end-of-life measures with their patients. Lynn, who served as consultant to the IOM panel, says physicians and caregivers aren't using the knowledge already available to manage patients' end-of-life care.

"It isn't that we have to wait until a new molecular biology determines a better drug," Lynn says. "We have pretty good drugs and decent ways of knowing how to support families and patients. The problem is implementation."

Lynn agrees that the rates of untreated pain are still substantial, as are the numbers of patients who are just a few months from death but don't realize they have a fatal illness and, thus, can't plan to bring life to a decent close. "Modern medicine has created the opportunity to live a long time with a bad disease," she says. "But we haven't built a system to deal with that."

In part, Lynn says, building an effective end-of-life care system means wholeheartedly engaging in quality improvement and reporting out those measures that really work because health care insurers and agencies demand visible proof.

She points out that some kinds of end-of-life care rearrangements are sufficiently substantial and visible to be tested in formal research—for example, she said, organizing 3 cancer centers one way and comparing them to 3 at which no changes were made.

"We could do that this year and know the results in 18 months," Lynn says. "We could put patients suffering from diseases that are eventually going to prove fatal into a comprehensive care system like hospice that covers drugs and in-home services and try to make it a lower per day cost. Two years from now we'd know what works, what kind of good comes at what kind of price," Lynn says. "In 3-5 years, we could build a reliable care system."

Advance Directives: Essential but Mostly Missing

"One wonderful thing about the fact that most of us get to die slowly now is that you can anticipate what's coming and make some reasonable plans," Lynn says. But although advance directives are a major piece in end-of-life planning, most patients don't use them. Those who do frequently use very vague, general phrases such as "when it's clear I'm dying, please don't put me on machines."

"What is 'clear'? What is 'dying'? Does 'on machines' include insulin pumps and oxygen tubes or is it just dialysis and ventilators?" Lynn asks. "Every piece of phrasing needs interpretation."

Even when patients know what they want to say, many don't know how to say it, and physicians must help them to communicate clearly, says David Beyda, MD, medical director of the Phoenix (Ariz) Children's Hospital pediatric critical care unit. "Simply taking time to sit and listen to a patient is what is needed," he says.

Beyda suggests using videos of physicians who deal with death and dying and talking to patients to educate medical students. "As we become more comfortable with death and the dying process, young physicians use us as role models to guide their behavior," he says.

Lynn observes that as terminal illness progresses, many patients can develop increasingly specific directives but may prefer to spend what time and energy they have with family instead of making end-of-life decisions. "We need to involve the patient preferences and the family's capabilities and the care system's capabilities and craft the best support," she says. "And that means a lot of communicating by everyone involved."

Most Errors Occur in Transitions

However, even the best possible advance directives are useless if no one knows what or where they are. Lynn points out that industrial engineers know what health care providers have been slow to learn—that most errors happen during transitions from one team to another.

"A hotshot team in the ICU and a hotshot team in the nursing home who don't communicate and standardize procedures means advance care and treatment plans will be lost, knowledge about how this particular patient responded to a particular drug will be lost," she says.

Lynn sees the increasingly large population of patients going back and forth between ICU and nursing homes as a set-up for disaster. "How many ICU personnel have even been in the local nursing home, or vice versa?" she asks. "Almost all the communication is between social workers and one-page discharge summaries. It's a recipe for disaster, and it happens every day."

What's needed is for someone to assume responsibility for the gap. Now, physicians are responsible only for performance within their own little setting. Lynn says they should be responsible for all the incoming and outgoing patients until the patient is safely ensconced in the next place and all the way from when they were safely ensconced at the last one. "For really

sick people, it isn't enough just to write a comprehensive discharge plan of care," she says.

Indeed, to fill the void, ABCD has developed a set of agendas—promises Lynn says the medical community ought to be able to make to a very sick patient.

They are:

1. Provision of evidence-based medical care.
2. No symptoms will be allowed to become overwhelming.
3. Patient ability to plan ahead to avoid emergencies.
4. Patient ability to shape care plan to preferences.
5. There will be no gaps in care from one provider type to another.
6. Family issues will be taken seriously and weighed in the decision making.
7. Care system will be arranged to help patient live fully despite the disease.

"These are all pretty obvious until you realize that the usual care system can't promise them that," Lynn says. "The average ICU doc can't make these promises for their care system, because they don't have any idea what happens when people go to the nursing home or home care."

Hospice: A Solution and a Problem

Selecky concurs that transitions can be perilous but points to the logistical problems involved. He observes that hospice growth, fueled by the fact that hospices are now for-profit enterprises, brings another set of problems: Physicians must use the typical Medicare evaluation and management codes, and there is essentially no physician reimbursement for in-home patient care.

"When the patient goes into hospice care, does the physician continue or turn the patient over to the hospice director?" Selecky asks. "Can you have more than one physician caring for the patient? That seems to be unclear."

Though it will take time to sort out the logistics, ABCD refers physicians to the following list of 20 improvements in end-of-life care that can be made right now. These were written by Don Berwick, MD, of the Institute for HealthCare Improvement in Boston.

- Ask yourself as you see patients, "Would I be surprised if this patient died in the next few months?" For those sick enough to die, prioritize the patient's concerns—often this is symptom relief, family support, continuity, advance planning, or spirituality.
- To eliminate anxiety and fear, chronically ill patients must understand what is likely to happen. When you see a patient who is sick enough to die, tell the patient, and start counseling and planning around that possibility.
- To understand your patients, ask 1) "What do you hope for, as you live with this condition?" 2) "What do you fear?" 3) "It is usually hard to know when death is close. If you were to die soon, what would be left undone in your life?" and 4) "How are things going for you and your family?" Document and arrange care to meet each patient's priorities.
- Comprehensive and coordinated care often breaks down when providers don't have all the facts and plans. The next time you transfer a patient or a colleague covers for you, ask for feedback on how patient information could be more useful or more readily available next time.
- Unsure how to ask a patient about advance directives? Try: "If sometime you can't speak for yourself, who should speak for you about health care matters?" Follow with: 1) "Does this person know about this responsibility?" 2) "Does he or she know what you want?" 3) "What would you want?" and 4) "Have you written this down?"
- To identify opportunities to share information with patients and caregivers, ask each patient who is sick enough to die: "Tell me what you know about (their disease)." Then: "Tell me what you know about what other people go through with this disease."
- Most internists' practices have educational handouts on heart failure, COPD, cancer, and other fatal chronic illnesses to give to patients. Read them—if your handouts do not mention prognosis, symptoms, and death, exchange them for ones that do. Considering making "The Handbook for Mortals" and other resources available to your patients.
- Some patients and their families are getting most of their information from the Internet. Log onto a patient-centered Internet site about an eventually fatal chronic illness to learn what is of interest to patients and families.
- Is coordinating the care of your chronically ill patients taking up too much of your time? Call a local advocacy group (American Heart Association, American Cancer Society, etc) for help, or consult with a care management service.
- Discussing and recording advance directives with all your patients may take a while. How many patients older than 85 years do you have? Start making plans with them. Expand to all who are sick enough to die.
- Use each episode in the ICU or emergency room as a "rehearsal." Ask the patient what should happen the next time. Be sure the patient has all necessary drugs at home and knows how to use them. Can you promise prompt relief from dyspnea near death? Tell

the patient and family what's possible and make plans together.

- Ask your next patient who is sick enough to die whether anything happened recently regarding their medical situation for which they were unprepared. Work to anticipate the expectable complications and to have plans in place.
- Since meperidine (Demerol) is almost the only opioid that has toxic metabolites and, thus, is contraindicated for chronic pain, banish meperidine from your prescribing and from the formularies where you work.
- Very sick people will often be most comfortable at home or in nursing homes. Identify programs that are good at home care, send patients to those quality services, and work with them to fill the gaps your patients encounter.
- Feedback on performance guides improvement. Find the routine surveys, administrative data, and electronic records that record symptoms, location of death, unplanned hospital or emergency room use, family satisfaction after the death, and other outcomes. Set up routines to get feedback on performance and improvement every month.
- Except in hospice, most families never hear from their internist after a death. Change that. Make a follow-up phone call or set a visit to console, answer questions, support family caregivers, and affirm the value of the life just recently ended. At least, send a card!
- Working with very sick patients who die is hard on caregivers. Next week—and every week—praise a professional or family caregiver who is doing a good job.
- We can't really change the routine care without changing Medicare. Contact your congressional representatives to ask for hearings, demonstration programs, research, and innovation to improve the Medicare program.
- Some of our language really does not serve us well. Never say "There's nothing more to be done," or "Do you want everything done?" Talk instead about the life yet to be lived and what can be done to make it better.
- Patients and families need to be able to rely on their care system. Consider what you can promise on behalf of your care system—pain relief, family support, honest prognosis, enduring commitment in all settings over time, planning for complications and death, and so on. Pick a promise that your patient needs to hear and start working with others to make it possible to make that promise. Quality improvement strategies work. ❖

Increase Staff Knowledge of Pain Management

By Julie Crawshaw

With new pain management standards from the Oakbrook Terrace, Ill-based Joint Commission on Accreditation of Healthcare Organizations, hospitals have been alerted to the need for increased education on this topic, says Roxie Foster, PhD, RN, FAAN, associate professor at University of Colorado Health Sciences Center School of Nursing in Denver.

"Thus, it is an excellent time for nurses to let administrators know exactly what education they need," Foster recommends.

The most effective education is evidence-based, ongoing, provides a variety of forums for learning, and establishes a base for expert judgments, she says. "Occasional consultation visits from pain management experts can validate local efforts and open a dialogue about practices in other areas," Foster adds. "Many of these experts have sponsors to offset consultation costs."

Look at Literature, Conferences

To locate experts, search current literature on pain management, Foster suggests. "The experts are usually well-published, and their contact information is listed with the article," she says. "Also ask co-workers about speakers they have heard at conferences who might make good consultants."

Stay abreast of the current literature in pain management, Foster urges. "Ask the hospital librarian to prepare a monthly update of pain-related articles available within the institution," she says. Selected articles might be collated in a notebook on the unit and the information used for evidence-based practice initiatives, she adds.

Journal clubs are a good way to start a dialogue with physicians and other professionals, suggests Foster. "These usually involve discussing one or more articles of interest that are made available to the group in advance." This provides an opportunity to review sophisticated literature and to discuss its relevance and application for the population of interest, says Foster.

"Interdisciplinary partnership is a prerequisite for optimal pain relief," she says. ❖

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