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Long-term Effects of Glucosamine Sulphate on Osteoarthritis Progression

ABSTRACTS & COMMENTARY

Synopsis: *The results of this study are further evidence that glucosamine sulfate in a dose of 1500 mg per day is a safe neutraceutical that alleviates the symptoms of knee osteoarthritis.*

Sources: Reginster JY, et al. *Lancet.* 2001;357:251-256; McAlindon T. *Lancet.* 2001;357:247-248.

Glucosamine sulphate is the sulphate derivative of the natural amino-monosaccharide glucosamine and a normal constituent of glycosaminoglyucans in cartilage matrix and synovial fluid. Because several short- to medium-term clinical trials in osteoarthritis have shown that oral administration of glucosamine is safe and associated with reduction in symptoms, Reginster and associates carried out a 3-year, well controlled trial designed to examine the effects of glucosamine (compared to placebo) on both joint symptoms as well as joint structure.

The study subjects were patients older than 50 years of age who had primary knee osteoarthritis of the medial femorotibial compartment. Progression of disease was assessed by serial, standing (weightbearing) x-rays of the joint space. Symptoms were assessed using the WOMAC index, which combines pain, function, and stiffness assessment as reported by questionaire. The study enrolled 212 subjects, who were randomly assigned to receive either 1500 mg of prescription-grade glucosamine or placebo daily.

Reginster et al report that "there was no average loss of joint-space width in the patients receiving glucosamine sulphate. Conversely, patients on placebo had a significant mean and minimum joint-space narrowing after 3 years." Similarly, "There was an improvement in the primary symptom outcome measure represented by the total WOMAC index" in patients taking glucosamine, but "symptoms of patients in the placebo group worsened." For both joint-space changes and symptom differences, the

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results were assessed to be significant. Nevertheless, there was no correlation between preservation or progression of joint-space narrowing and improvement in symptoms. That is, "patients receiving glucosamine sulfate tended to improve their symptoms regardless of structure outcome."

COMMENT BY MICHAEL K. REES, MD, MPH

In an accompanying editorial, Dr. Tim McAlindon of the Arthritis Center, Boston University Medical Center, gives high marks to the methodology used by Reginster et al: "In fact, the results are impressive; patients assigned to glucosamine experienced significant improvement in pain and disability that were sustained for the 3 years of the study, whereas the scores among the palcebo group worsened." He further comments that the lack of correlation with joint-space preservation may reflect that the current (and perhaps incorrect) thinking that osteoarthritis is a disorder of progressive hyaline-cartilage loss, when—in fact—more recent evidence suggests the pan-articular nature of knee osteoarthritis and that joint-space loss reflects meniscal extrusion rather than hyaline-cartilage erosion.

The results of this study are further evidence that glucosamine sulfate in a dose of 1500 mg per day is a safe neutraceutical that alleviates the symptoms of knee osteoarthritis. Its mechanism of action is unknown. Because in the United States glucosamine sulfate is considered a food supplement and is not regulated as a medication, the problem faced by our patients is confidence in its supply and the cost thereof. The potential to commit fraud is significant. ❖

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Between a Rock and a Hard Place: How Much Do We Really Know About Anticoagulation in Atrial Fibrillation?

ABSTRACT & COMMENTARY

Synopsis: *Although we simply do not yet have enough data comparing antiplatelet treatment to anticoagulation in patients with nonrheumatic atrial fibrillation to draw firm conclusions, the evidence for long-term anticoagulation in this group of patients is weak.*

Source: Taylor FC, et al. *BMJ*. 2001;322:321-326.

This is a meta-analysis of all randomized, controlled trials comparing long-term anticoagulation with antiplatelet treatment in patients with nonrheumatic atrial fibrillation. Taylor and associates found 5 such studies.[1-5] In aggregate, they included 3298 patients with follow-up ranging from 12-42 months. There were no significant differences in mortality rates (odds ratio [OR] 0.74, confidence interval [CI] 0.39-1.4 for stroke death and OR 0.86, CI 0.63-1.17 for vascular death). There was a statistically significant difference in nonfatal stroke, favoring anticoagulation (OR 0.68, CI 0.46-0.99). Taylor et al reanalyzed this data, excluding 1 trial with weak methodological design and found a nonstatistical difference of nonfatal stroke (OR 0.75, CI 0.50-1.13). There were more major bleeding events among patients on chronic anticoagulation than those on

antiplatelet therapy (OR 1.45, CI 0.93-2.27). Taylor et al conclude that there is "considerable uncertainty about the value of long-term anticoagulation compared with antiplatelet treatment."

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

It is ironic that this paper was published at about the same time that Ariel Loewy, whose research helped to unravel the mechanism of the clotting cascade, died of a stroke.[6] This meta-analysis (whose first author, Taylor, is a "systematic review training fellow"), underscores how little we really know about the comparative benefits of an easy, relatively safe, inexpensive treatment and a difficult, risky, expensive treatment. Perhaps one of the most important findings of this paper is that the 5 studies currently available simply do not include enough patients to detect a significant superiority of anticoagulation over antiplatelet treatment (if it exists). Given that finding, the trends toward reduced deaths from strokes and vascular events, and the reduced risk of nonfatal stroke with anticoagulation compared with antiplatelet therapy, one might consider erring on the side of using long-term anticoagulation. Unfortunately, there is a considerable downside to chronic anticoagulant use, including a 45% increase in risk of major bleeds and an approximate 15-fold increase in cost with universal chronic anticoagulation compared with universal chronic use of aspirin.[7] Taylor et al state, "Given the uncertainty over the greater efficacy of anticoagulation, its undoubted hazards, and the consideration of cost effectiveness we would strongly favour antiplatelet drugs in preference to long-term anticoagulation." I am not so sure. Some might consider a nonfatal stroke worse than a fatal stroke. Ultimately, I think that chronic anticoagulation vs. aspirin in patients with nonrheumatic atrial fibrillation is yet another of those things that we simply need to sit down and talk with the patient about. He/she is assuming risk one way or another, and needs to be actively involved in the decision. ❖

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Screening Mammography in Older Women

ABSTRACT & COMMENTARY

Synopsis: *Regular screening mammography up to and even past 85 years of age was found to reduce mortality by detecting breast cancer at its earliest stages.*

Source: McCarthy EP, et al. *J Am Geriatr Soc.* 2000;48: 1226-1233.

Two sources of data were combined for a large sample of women 67 years of age and older to match their use of mammography with diagnosis of a first primary breast cancer and subsequent mortality. The National Cancer Institute and the Health Care Financing Administration have developed a linkage between Medicare physician claims which record mammography use, and the national breast cancer registry for Surveillance, Epidemiology and End Results (SEER). By analyzing a 7-year period from 1987-1993, McCarthy and associates were able to track a study sample of 11,399 women in 3 geographically separate areas who received a new diagnosis of first primary breast cancer. They were also able to obtain demographic and ethnic information from the Medicare beneficiary enrollment files.

Regular mammography use declined with advancing age at diagnosis: only 10% of women age 85 and older had regular mammograms, compared to 23% of women age 75-84 and 29% of women age 67-74. Regular use was defined as at least 2 mammograms in the 2 years preceding their breast cancer diagnosis, at least 10 or more months apart. Later stage breast cancer was generally detected in the oldest women: 53% of women age 85 and older had stage II or greater compared to 41% and 45% for the younger age groups.

When stage of diagnosis was matched with use of mammography, it was clear that regular users of mammography were significantly more likely to be diagnosed with early stage breast cancer compared to nonusers. Only 28% of regular mammography users of all ages presented with late-stage disease. If women did not use regular mammography, the late-stage disease increased with advancing age, from 49% for age 67-74 up to 69% for age 85 and older. Even after adjusting for

factors known to be associated with late-stage diagnosis, such as race, comorbid conditions, and income of zip code of residence, the lack of mammography remained a significant predictor of late-stage diagnosis within all age groups.

Survival also decreased with later stage of diagnosis, and decreased even further with advancing age within each cancer stage. After adjusting for comorbidity and sociodemographic factors, nonusers of mammography had a significantly greater risk of death from breast cancer within each age group.

COMMENT BY MARY ELINA FERRIS, MD

Breast cancer remains the second leading killer of women from cancer (lung cancer being the first), and accounts for the largest number of new cancer cases in women other than skin cancer. The risk of breast cancer for older women rises with age, but it's long been a quandry in geriatric medicine whether to continue annual screening mammography in women older than age 70 when many guidelines stop further recommendations. Although the American Cancer Society and the National Cancer Institute recommend indefinite annual or biennial screening, other organizations such as the American Academy of Family Physicians recommend stopping at age 69, and the NCQA HEDIS® quality indicators for managed care health plans measure regular mammography only up to age 69. The American College of Physicians recommends mammography screening until age 74 years, based on the oldest ages of clinical trial participants. The U.S. Preventive Services Task Force analysis of the scientific evidence behind these recommendations has stated that there is limited and conflicting evidence for use in ages 70-74, and little research for use in age 75 and older.[1]

This new article provides strong support for continuing screening mammography for older women of any age as long as they would benefit from the early detection of breast cancer. Both the breast cancer stage at diagnosis and mortality were better for women who were regular users of mammography, especially at advanced ages. Combined with another recent article that also confirmed increased life expectancy for women using mammography during ages 70-79,[2] this will probably be the best evidence we can hope for in lieu of randomized controlled trials.

New recommendations from the American Geriatrics Society urge us to continue annual or at least biennial mammography until age 75 and subsequently every 2-3 years thereafter with no upper age limit as long as women have an estimated life expectancy of at least 4 or more years.[3] While it will still remain an individual decision between the clinician and the older woman whether to continue screening mammography, there is now much better scientific support to continue mammography well into the oldest years. ❖

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Enoxaparin Proves Equivalent to Unfractionated Heparin for Treatment of DVT

ABSTRACT & COMMENTARY

Synopsis: *In a clinical trial of low molecular weight heparin (enoxaparin) administered either once or twice daily, comparable efficacy was demonstrated when compared to continuous, intravenous unfractionated heparin. Clinical outcomes, including the appearance of recurrent, symptomatic venous thrombosis or pulmonary emboli, were investigated. This trial provides further support for the use of LMWH in the initial management of DVT.*

Source: Merli G, et al. *Ann Intern Med*. 2001;134:191-202.

Deep vein thrombosis (dvt) remains a major cause of morbidity and mortality. Typically, patients with diagnosed DVT are treated with 5-10 days of unfractionated heparin intravenously, as initial treatment and warfarin is added within the first few days. Recently, low molecular-weight heparins (LMWH) have been introduced and have been used successfully for both prevention and treatment of DVT.[1,2] Randomized trials and meta-analyses have shown subcutaneously administered LMWH to have antithrombotic efficacy equal to[3-6] or greater than[7-9] that of continuously administered unfractionated heparin in the initial treatment of DVT, and equal to that of unfractionated heparin in the treatment of pulmonary embolism (PE).[10,11] However, many of these

trials were small, did not biochemically monitor LMWH activity, and used intermediate end points, such as venographic, plethysmographic, or scintigraphic end points rather than clinical end points such as recurrent DVT or PE.

The study conducted by the Enoxaparin Clinical Trial Group (and supported by Aventis) was designed to determine whether enoxaparin administered subcutaneously once or twice per day is as effective as continuously infused unfractionated heparin in the treatment of patients with acute, symptomatic venous thromboembolic disease. Patients with acute DVT (n = 900), including 287 (32%) with pulmonary embolus, from 74 hospitals in 16 countries were randomized to receive initial therapy with dose-adjusted intravenous unfractionated heparin compared with subcutaneous enoxaparin at fixed dosages of 1.0 mg/kg of body weight twice daily or 1.5 mg/kg once daily. Long-term oral anticoagulation (warfarin) was started in all patients within 72 hours of randomization.

Equivalent efficacy was seen in the heparin group and both enoxaparin groups. Recurrent DVTs occurred in 12 of 290 patients receiving unfractionated heparin (4.1%), 13 of 298 patients receiving once daily enoxaparin (4.4%), and nine of 312 patients receiving twice daily enoxaparin (2.9%). Compared with unfractionated heparin, the treatment difference was 0.2% (95% CI, 3.04-3.49%) for once-daily enoxaparin and -1.2% (95% CI, 14.2-1.7%) for twice-daily enoxaparin. Adverse events were comparable in the three groups. Major hemorrhage occurred in six of 290 patients (2.1%) in the unfractionated heparin group, five of 298 patients (1.7%) in the once-daily enoxaparin group, and four of 312 patients (1.3%) in the twice-daily enoxaparin group.

Subgroup analysis on the basis of age, sex, weight, medical history (prior PE, presence of cancer, etc.), and location of DVT did not reveal any significant differences in either efficacy or occurrence of adverse events in any particular subgroup.

Thus, Merli and colleagues concluded that subcutaneous enoxaparin once or twice daily is as effective and safe as dose-adjusted, continuously infused unfractionated heparin in the prevention of recurrent symptomatic venous thromboembolic disease.

COMMENT BY WILLIAM B. ERSHLER, MD

The introduction of LMWHs to hospital and community pharmacies has been a major advance in the past decade. Physicians have been quick to use these agents because they offer the advantage of ease of treatment and reduced length of hospital stay (and, thereby, costs). Furthermore, there has been a sense that adverse events were fewer, and the incidence of treatment-associated thrombocytopenia was reduced.[12] Yet, there is also a feeling of uncertainty because laboratory monitoring is not readily available.

Thus, the current study offers reassurance for those of us who have already adopted this approach for the management of acute DVT. Furthermore, it demonstrated that once-daily injection of a larger dose of enoxaparin was equivalent to the twice-daily dose. The rationale for trying the once-daily dose was based upon pharmacokinetic studies that were specific for this particular LMWH, and should not be applied to other LMWHs, some of which already were shown to be effective at once-daily dosing. With regard to enoxaparin, however, a careful review of the data presented in this paper suggest that for the particularly high-risk patients (eg, those with cancer, prior PE, or obesity), there was a trend, albeit, not significant, that would suggest that twice-daily dosing was more efficacious than the single dosing. Perhaps, in a larger study, these trends would reach a level of significance.

This was a carefully performed, multi-center clinical investigation with outstanding design, cautious interpretation, and a clear presentation of results. Clinical trials designed to establish comparable efficacy with an agent already known to be efficacious in a great majority of patients are complicated, require large sample sizes, and clearly stated, statistical objectives. This report is an excellent example of the way it should be done, and is recommended in that light for those developing skills in clinical trial methodology. (*Dr. Ershler is Director, Institute for Advanced Studies in Aging, Washington, DC.*) ❖

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Pharmacology Update

Esomeprazole Magnesium Capsules (Nexium—AstraZeneca)

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

Astrazeneca is launching its new proton pump inhibitor (PPI) esomeprazole (Nexium). The new drug is coming to market just as AstraZeneca is losing patent protection on its multibillion dollar PPI omeprazole (Prilosec). Esomeprazole, the S-isomer of omeprazole, is touted as being the most potent PPI available.

Indications

Esomeprazole is indicated for the healing of erosive esophagitis, treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD) and the maintenance of healing of erosive esophagitis. It is also indicated for the eradication of *Helicobacter pylori* in combination with amoxicillin and clarithromycin.[1]

Dosage

The recommended dose for the treatment of erosive esophagitis is 20 or 40 mg once daily for 4-8 weeks. For the treatment of heartburn and other symptoms associated with GERD, the recommended dose is 20 mg once daily for 4-8 weeks. The dose for maintenance of healing of erosive esophagitis is 20 mg once daily. For the eradication of *H pylori* the dose is esomeprazole 40 mg once daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily for 10 days. Esomeprazole should be taken at least 1 hour before a meal. If the patient has difficulty in swallowing the capsule, the contents may be mixed with a tablespoon of apple sauce. The pellets should not be chewed or crushed.[1]

Potential Advantages

At the recommended doses, esomeprazole appears to be the most potent PPI on the market. It has greater acid suppression than omeprazole, lansoprazole, or pantoprazole.[4] Esomeprazole has greater systemic bioavailability than omeprazole due to a lower first-pass metabolism and nonlinear pharmacokinetics.[3,4] The systemic bioavailability is about 80% higher for esomeprazole 20 mg compared to omeprazole 20 mg and about 5 times greater with esomeprazole 40 mg. This results in greater acid suppression throughout the day. The mean duration for maintaining gastric pH more than 4 for esomeprazole 40 mg, esomeprazole 20 mg, and omeprazole 20 mg is 16.8 hours (95% CI, 15.0-18.4), 12.7 hours (95% CI, 11.0-14.4), and 10.5 hours (95% CI, 8.8-12.2), respectively.

More than 55% of patients maintain intragastric pH more than 4 with esomeprazole 40 mg compared to 24% for esomeprazole 20 mg and 14% for omeprazole 20 mg.[3]

Potential Disadvantages

Food decreases the extent of absorption of esomeprazole by 33-53%. The drug should be taken at least 1 hour before a meal. Esomeprazole may inhibit the metabolism of drugs which are metabolized via cytochrome P450 2C19. A 45% decrease in the clearance of diazepam has been reported.[1] The side effects of esomeprazole appear to be similar to those reported for omeprazole with headache, diarrhea, and abdominal pain being the most common with a frequency of 4-6%.

Comments

Esomeprazole is the S-isomer of omeprazole which is a racemic mixture (S- and R-isomers). They both have the same mechanism of action but differ in their pharmacokinetic and pharmacodynamic properties. Greater acid suppression throughout the day has been reported with esomeprazole compared to other PPIs.[3] The improved potency has resulted in modest improvements in the healing of erosive esophagitis. Four large studies (from 572-1216 subjects/arm) were reported by the manufacturer, 2 reported statistical differences between esomprazole and omeprazole and 2 did not.[1,2] Generally, the efficacy of esomeprazole and omeprazole did not differ dramatically. Healing rates were 64.7-69.5% for omeprazole 20 mg, 68.7-70.5% for esomprazole 20 mg, and 71.5-81.7% for esomeprazole 40 mg at 4 weeks. Healing rates at 8 weeks were 84.2-89.8%, 89.9-90.6%, and 92.2-94.1% for esomeprazole. One published study reported faster time to sustained resolution of symptoms.[2] Median time to sustained resolution for esomeprazole 40 mg, 20 mg, and omeprazole 20 mg were 5, 8, and 9 days, respectively. No real differences were seen in the median time to first symptom resolution, 2 days for each regimen. Esomeprazole is effective for maintaining healed erosive esophagitis.

Healing after 6 months was maintained in about 93% of patients treated with esomeprazole 40 mg or 20 mg compared to 29% with placebo and 57% with esomeprazole 10 mg.[6] Esomeprazole is approved for once daily dosing as part of a triple *H pylori* eradication regimen

with amoxicillin and clarithromycin.[1,7] Eradication rates, 84-85%, are similar to the twice daily PPI-based regimens. AstraZeneca is pricing esomeprazole 40 mg and 20 mg similar to that of omeprazole 20 mg.

Clinical Implications

GERD is a common chronic condition affecting about one-third of the population.[5] PPIs are generally regarded as the treatment of choice for severe cases although antireflux surgery is also an option. Esomeprazole appears to be marginally more potent than the available PPIs and may offer some benefit to those who have not adequately responded to existing PPIs. ❖

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CME Questions

22. For older women with at least 5 years life expectancy, when should screening mammography be *stopped*?

a. age 69
b. age 74
c. age 80
d. no age limit

23. Which of the following statements about the use of low molecular weight heparins for the treatment of deep venous thrombosis is true?

a. Subcutaneously administered LMWH has been shown to have greater efficacy in the treatment of acute deep venous thrombosis than unfractionated heparin by continuous intravenous infusion.
b. Subcutaneously administered LMWH has been shown to have lesser efficacy in the treatment of acute deep venous thrombosis than unfractionated heparin by continuous intravenous infusion.
c. Subcutaneously administered LMWH has been shown to have comparable efficacy in the treatment of acute deep venous thrombosis than unfractionated heparin by continuous intravenous infusion.
d. Subcutaneously administered LMWH has been shown to be associated with more adverse events than intravenous infusion of unfractionated heparin.

By Louis Kuritzky, MD

Folate Levels in the Evalution of Macrocytosis or Anemia

Evaluation of red blood cell (RBC) macrocytosis typically includes measurement of serum folate. Serum folate, however, is an inconsistent reflection of actual body stores, since depleted plasma levels are rapidly replenished by minimal folate intake. Even though RBC folate levels better represent body stores, this measurement may remain unaltered early in deficiency states. Robinson and Mladenovic examined the clinical use of folate measurements by retrospectively reviewing all folate levels (n = 2998) ordered in 3 teaching hospitals over a 12-month period.

Only 2.3% of folate measurements were too low. Chart review indicated that only half of subnormal folate levels were so-indicated in the hospital progress notes (possibly indicating that some results returned to the record after patient discharge). Similarly, only half of those with low folate noted by clinicians actually received folic acid replacement therapy.

Almost $90,000 was spent to perform the 1247 folate tests. Only 9 patients had any clinical intervention as a result of the testing. Given that folic acid replacement is of minimal cost (< $5/3 months supply), Robinson and Mladenovic note that empiric folate treatment would have incurred a cost savings of almost $83,000 in this study group.

In the evaluation of macrocytosis, vitamin B-12 assessment is necessary, lest folate replacement mask progressive neurologic consequences of B-12 deficiency. Robinson and Mladenovic suggest that empiric folic acid replacement in this circumstance (0.4-1 mg/d folic acid) be tried, with folate measurement reserved for macrocytosis unresponsive to this intervention. ❖

Robinson AR, Mladenovic J. Am J Med. 2001;110:88-90.

Compounded Testosterone Gel in Hypogonadal Men

Testosterone replacement in hypogonadal men currently depends primarily on either intramuscular injection or transcutaneous patches; neither of these methods is fully satisfactory to all patients. Recently, a gel formulation of testosterone intended for transcutaneous use has been available to clinicians. Cutter used a personally compounded testosterone gel applied to 10 men who had been previously managed with either depot testosterone injections or transdermal testosterone (Androderm patch).

Testosterone gel was compounded by mixing micronized testosterone and lecithin in a Pluronic F-127 vehicle. Patients applied 1-3 mL of compounded testosterone gel (0.5-10% concentrations) daily. Doses were increased by monitoring testosterone levels weekly until a therapeutic level was achieved (attained in 9/10 patients by 4 weeks).

Treatment was associated with statistically significant improvements in erectile capacity, memory, depression, and energy levels. Respondents indicated satisfaction with treatment and desire to continue to use this method of treatment. Cutter reports that subsequent to this report, he has empirically arrived at a dose of 6% gel, 2.5 mL, applied daily to a nonhairy body area near the axilla, as efficacious for most subjects. A proprietary formulation of testosterone gel 1% (Androgel™) is currently available for clinicians wishing to consider this method of testosterone replacement. Caution must be observed that areas of cutaneous application not contact intimate partners, as transfer of hormone may thus unintendidly occur. Testosterone gel offers another therapeutic tool for androgen replacement. ❖

Cutter CB. J Am Board Fam Pract. 2001;14:22-32.

Effectiveness of Oseltamivir

The rapid spread of influenza to family contacts is a prominent source of community virus dissemination. There is some information that first-generation influenza antivirals (amantadine, rimantadine) reduce contact infection. Since the second-generation influenza agent oseltamivir (OSV) is efficacious for both influenza A and B, the therapeutic role of more selective therapies such as amantadine and rimantadine has greatly diminished. This study evaluated the efficacy of OSV in preventing spread of influenza virus from infected persons to household contacts.

Index case subjects were initially identified by clinical profile, consisting of fever, respiratory symptoms, and constitutional symptoms. Influenza virus infection was subsequently confirmed in almost half of clinically diagnosed cases. Within 48 hours of symptom onset in the index case, OSV 75 mg QD (or placebo) orally for 7 days was administered to all household contacts older than age 12.

Use of OSV reduced the incidence of laboratory-confirmed influenza by almost 90% in contacts of an index case. There were no serious adverse effects. When administered within 48 hours of contact with an index case, clinicians can anticipate a high protective success rate for OSV treatment of asymptomatic household contacts. ❖

Welliver R, et al. JAMA. 2001;285: 748-754.

In Future Issues: Does Pravastatin Prevent Stroke?