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A monthly survey of developments in neurologic medicine

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Carotid Stenting vs. Endarterectomy for Symptomatic Stenosis: Endarterectomy Remains the Gold Standard

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Interim Chair and Neurologist-in-Chief, Department of Neurology and Neuroscience, Weill Cornell Medical College, New York Presbyterian Hospital

Dr. Fink reports no financial relationships relevant to this field of study.

Synopsis: *At the present time, carotid endarterectomy remains the treatment of choice for severe carotid artery stenosis, until additional evidence emerges from ongoing randomized clinical trials.*

Sources: Ederle J, et al. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): Long-term follow-up of a randomized trial. *Lancet Neurology* 2009;8:898-907. Bonati LH, et al. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS): Long-term follow-up of a randomized trial. *Lancet Neurology* 2009;8:908-917.

CAROTID ARTERY ANGIOPLASTY AND STENTING (CAS) BURST UPON the scene about 15 years ago and quickly became popular with endovascular specialists in cardiology, vascular surgery, neurosurgery, interventional radiology, interventional neuroradiology, and neurology. As so often happens with a new technique, CAS became a widespread treatment for carotid stenosis, both symptomatic and asymptomatic, even without appropriate randomized, clinical trials to demonstrate its safety and efficacy. And because of widespread publicity, many patients with carotid artery stenosis arrived at their neurologists' offices saying, "I want to be treated with a stent." To the credit of the investigators in the U.K. and Europe, The Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was started with

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the randomization of the first patients in 1992, and that allowed the investigators to report on the long-term results of CAS, compared to carotid endarterectomy (CEA), a tested and proven treatment for both symptomatic and asymptomatic carotid artery stenosis.

In 2001, the CAVATAS investigators reported on the peri-operative safety outcomes at 30 days, and revealed that there were similar rates of major complications compared to carotid endarterectomy (CEA), stroke lasting more than seven days or death, but the rates in both arms were unacceptably high (around 10%) and mandated additional comparative trials. Two other completed trials, EVA-3S and SPACE, did not establish the equivalence of CAS with CEA in terms of early safety (*Lancet Neurology* 2008;7:893-902,885-892) at 30 days, and the Cochrane Database meta-analysis (2007:4:CD000515) did not support a change in clinical practice away from CEA.

In the current reports, the CAVATAS investigators evaluated 504 patients (90% symptomatic) who were randomly assigned to CAS or CEA and followed for a median length of five years (R=2-6). Comparing endovascular treatment to CEA after the 30 day peri-operative period, the eight-year incidence and hazard ratio (HR) for ipsilateral stroke was 11.3% vs. 8.6% (HR = 1.22, 95% CI 0.59-2.54), for ipsilateral stroke or TIA was 19.3% vs. 17.2% (HR=1.29, CI 0.78-2.14), and any stroke after 30 days was 21.1% vs. 15.4% (HR=1.66, CI 0.99-2.80). Although there were more long-term strokes and TIAs in the endovascular group compared with CEA, these differences did not reach statistical significance. In addition, CAVATAS has a major limitation, in that most of the patients who underwent endovascular therapy had angioplasty alone, not angioplasty with stenting. Modern therapy includes stenting with use of an embolism protection device, making the CAVATAS data interesting but not definitive regarding endovascular therapies.

In a companion article, the CAVATAS investigators reported on the long-term risk of carotid restenosis in patients who were treated with CAS compared to those treated with CEA. Four-hundred thirteen (413) patients were randomized and followed for a median of five years, with carotid duplex ultrasound performed at a median of four years. Severe carotid restenosis (≥ 70%) or occlusion occurred more often in patients with endovascular therapy than in patients with CEA, and the differences were significant (HR=3.17, 95% CI 1.89-5.32: p<0.0001). The estimated five-year incidence of restenosis was 30.7% in the CAS arm and 10.5% in the CEA arm. It is very important to note in CAVATAS that of the 200 patients followed after endovascular therapy, 150 had angioplasty alone, and 50 were treated with a stent. Patients treated with a stent had a lower risk of developing restenosis than those with angioplasty alone. Smoking, currently or in the past, was a powerful risk factor in predicting restenosis of 70% or more (HR=2.32, CI 1.79-4.54, p=0.01). The risk of long-term stroke and TIA was higher in those patients who developed restenosis of 70% or more within the first year after treatment.

■ COMMENTARY

CAVATAS is an important study, because it is one of the few randomized clinical trials of endovascular therapy for carotid artery stenosis that was a comparison to CEA, early in the use of angioplasty and stenting. For that reason, it is one of the few studies that has long-term data (at least five years). Even though CAVATAS used a "primitive" form of endovascular therapy, it is clear from the results that endovascular therapy was not proven "non-inferior" to CEA and CEA remains the "gold standard" to which other therapies must be compared.

At the present time, there is no statistically valid data to support the use of CAS in symptomatic carotid artery stenosis except in patients who are poor or high-risk surgical candidates. That category includes restenosis after CEA, radiation-induced carotid stenosis, anatomically high lesions, and high risk from multiple medical comorbidities. One could make the point that high medical risk would argue against any surgical intervention, and would favor aggressive medical therapy. During the course of the CAVATAS study, aggressive use of statins and newer antiplatelet therapies were not available. One could argue that current medical therapy would have a better long-term result.

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So where to we go from here? There are two clinical trials that we await with great excitement and anticipation—the International Carotid Stenting Study (ICSS) from Europe, and the Carotid Revascularization Endarterectomy versus Stent Trial (CREST)—both which expect to report their results in early 2010. The CREST trial, in particular, has been designed with scrupulous credentialing of both endovascular and surgical specialists to ensure high-quality outcomes. Stenting was performed with the use of embolism prevention devices. CREST has been powered to detect clinically significant differences between the two procedures, and includes both symptomatic and asymptomatic patients. So, until the long-term results of ICSS and CREST are released, we do not have any evidence to support the use of endovascular therapies for severe carotid stenosis, unless the patient is not able to safely undergo endarterectomy. ■

Progressive Multifocal Leukoencephalopathy in MS Patients Treated with Natalizumab – Are We Closer to Understanding the Risk?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

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Dr. Gauthier reports no financial relationships relevant to this field of study.

Synopsis: *Two recent cases of progressive multifocal leukoencephalopathy in patients with multiple sclerosis that had received natalizumab monotherapy are presented. They survived after discontinuation of the drug and the initiation of plasma exchange.*

Sources: Chen Y, et al Asymptomatic reactivation of JC virus in patients treated with natalizumab. *N Engl J Med* 2009;361:1067-1074. Wenning W, et al. Treatment of progressive multifocal leukoencephalopathy associated with natalizumab. *N Engl J Med* 2009;361:1075-1080. Lindå H, et al. Progressive multifocal leukoencephalopathy after natalizumab monotherapy. *N Engl J Med* 2009;361:1081-1087.

NATALIZUMAB EFFECTIVELY REDUCES THE INFLAMMATORY burden in patients with multiple sclerosis (MS) as measured by a reduction in relapse rate and MRI activity; however, treatment with natalizumab carries a risk of progressive multifocal leukoencephalopathy (PML). The mechanism by which natalizumab increases the risk of PML, and which patients are at risk to develop the disease, remains unknown.

PML is caused by reactivation of the JC virus which remains latent in the kidney and lymphoid organs in healthy individuals, and under normal conditions can be detected in the urine, and less often, in the serum. Chen and colleagues studied 19 asymptomatic MS patients who were treated with natalizumab for up to 18 months and found that by 12 months, the presence of JC virus in the urine increased to 63% of the patients from a baseline level of 19%. Interestingly, in three patients the JC virus disappeared after 12 months of exposure to natalizumab. In the serum, the virus was initially undetectable but was present in 20% (3/15 patients) at 18 months. The level of virus in the peripheral-blood mononuclear cells (PBMCs) increased and was present in 60% (9/15 patients) over the same time period. Sequence analysis of the viral clones isolated from urine and PBMCs revealed similar regulatory sequences as those found in the central nervous system isolate MAD-1, although with differing point mutations. Finally, T-cell-mediated immune responses to JC virus decreased over time in patients with JC viremia as compared to those without a viremia.

The original reported risk of PML in natalizumab-treated patients was 1 in 1,000 patients who had 18 months of exposure, and combination therapy appeared to put patients at a higher risk.[1] Two recently published cases of PML associated with natalizumab provide further insight into the risk and ultimate prognosis for patients on this treatment. Wenning and colleagues reported a patient with MS, treated with long-term low-dose azathioprine, who developed PML after 12 infusions of natalizumab monotherapy. The patient was treated initially with two courses of intravenous methylprednisolone for the presumed diagnosis of a MS relapse. After worsening neurological status and MRI findings atypical for a MS lesion, plasma exchange was initiated. The patient improved immediately after the exchange, then quickly worsened, and contrast-enhancement on the MRI was appreciated; the patient was then diagnosed with immune reconstitution inflammatory syndrome (IRIS). Stabilization was achieved with pulse-steroid therapy and the patient continued to slowly improve on mefloquine and mirtazapine. Lindå and colleagues reported on a treatment-naïve patient who developed PML after receiving 14 doses of natalizumab monotherapy. Plasma exchange was initiated and within

a few weeks IRIS developed. The diagnosis of PML in this patient was based upon an atypical MRI lesion and worsening of symptoms on steroid treatment. The JC virus was undetectable in the CSF at a local laboratory on two occasions, but was eventually detected by quantitative PCR at a reference laboratory. Stabilization was reported after the patient received pulse-steroids for IRIS.

■ COMMENTARY

Natalizumab is an effective drug for the treatment of relapsing forms of MS, although cases of PML continue to be reported. Since its reintroduction, 13 cases of PML have been confirmed worldwide in patients treated with natalizumab monotherapy for multiple sclerosis. As described in the cases above, with early detection and treatment, patients can survive with varying degrees of disability. PML associated with natalizumab can occur in the following situations: 1) in treatment-naïve patients, 2) during monotherapy, and 3) with as few as 12 doses of natalizumab. The diagnosis of PML should be suspected in MS patients with atypical MRI lesions and symptoms atypical for a relapse. Plasma exchange has been demonstrated to quickly and effectively lower serum levels of natalizumab;[2] however, as demonstrated in these cases, IRIS can occur within only a few weeks after the plasmas exchange, as compared to three months with drug discontinuation only.[3]

Is it possible to identify patients at risk? Detection of JC virus in the urine is not uncommon in healthy individuals, but in this MS cohort, an increase in urine detection occurred before the observed viremia, and urinary monitoring may be a good screen. The viremia in this study was primarily cell-associated as opposed to free-floating. Given that the mechanism of natalizumab action is to act as an inhibitor of the α4-integrin adhesion molecule, the PBMCs containing virus would also be blocked, but detection of virus in these blood cells would place a patient at increased risk for developing PML. At the present time, there is no clear method to screen for patients at risk for PML while being treated with natalizumab, and clinical surveillance remains our only method for early detection.

References

1. Yousry TA, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006;354:924-933.
2. Khatri BO, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology* 2009;72:402-409.
3. Langer-Gould A, et.al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005;353:375-381. ■

Is Surgery Necessary for Carpal Tunnel Syndrome?

By Bridget T. Carey, MD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Carey reports no financial relationships relevant to this field of study.

Synopsis: *Surgery is useful for patients with carpal tunnel syndrome who have not yet manifested denervation on electrodiagnostic testing.*

Source: Jarvik JG, et al. Surgery versus non-surgical therapy for carpal tunnel syndrome: A randomized parallel-group trial. *Lancet* 2009;374:1074-1081.

COMPRESSION OF THE MEDIAN NERVE AT THE WRIST IS the most common peripheral nerve entrapment syndrome. Carpal tunnel syndrome (CTS) manifests as numbness, paresthesias, pain, and weakness in the median nerve distribution. As such, CTS is one of the most frequent causes of disabling hand disorders. The treatment for CTS splits into two arms: surgical decompression versus non-surgical management. The latter category consists of varying combinations of "conservative" measures, including splinting the wrist into a neutral position nightly or for a significant portion of each day. Additional measures include eliminating occupational causes, non-steroidal anti-inflammatory (NSAID) medications, hand therapy, ultrasound therapy, and steroid injections.

The aim of the Jarvik study was to compare functional and symptomatic outcomes following surgical or non-surgical treatment for patients with CTS. One-hundred sixteen (116) patients with a diagnosis of CTS were randomized into either surgical or non-surgical treatment groups. Diagnosis was made primarily on clinical criteria. Electrodiagnostic inclusion criteria were defined; however, the presence of electrodiagnostic abnormalities was not necessary to establish a diagnosis of CTS if sufficient clinical criteria were met. Patients with severe CTS were excluded from the study. Severe CTS was determined by the presence of thenar muscle wasting, abnormal two-point discrimination > 6 mm, and / or electrodiagnostic evidence of denervation.

The surgical group underwent either endoscopic or open carpal tunnel decompression within the first three months after randomization. This was followed by hand therapy, per the surgeon's usual post-operative protocol. The non-surgical group was provided with customized hand therapy sessions, NSAIDs, and encouraged to continue splinting. If subjects in the non-surgical group failed to improve after six weeks, ultrasound therapy was added to the regimen. If subjects failed to improve after three months, individuals allocated to this group had the option to proceed to surgical decompression. Subjects in both groups were evaluated at six weeks, three months, six months, nine months, and 12 months after randomization. The Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) for functional status was used as the primary outcome measure. Secondary outcome measures, including the CTSAQ for symptom severity, were also assessed. The CTSAQ consists of 9–11 questions, from which a "function" or "symptom" score of 1 through 5 is calculated, with 5 being most severe.

Both groups experienced symptomatic improvement throughout the experimental protocol. The surgically-treated group experienced slightly more improvement than the non-surgical group based on CTSAQ function scores, a difference of 0.4 points on the CTSAQ function scale. The authors concluded, however, that even though the differences were statistically significant, the differences were of questionable clinical significance. The investigators concluded that surgery is useful for patients with CTS, before denervation develops.

■ **COMMENTARY**

CTS is not a complex disease. The work of Seddon and Sunderland has long established the pathophysiology of peripheral nerve injury, and the prognosis associated with varying degrees of injury.[1] When a nerve is subjected to excessive pressure from an external force, myelin at the site of compression will degrade. If the rate of myelin degradation is slow, the surrounding Schwann cells are generally able to keep up with repair. If the external pressure is severe or prolonged, demyelination will progress faster than the rate of remyelination. If allowed to continue, the myelin sheath is essentially destroyed, and subsequent axonal injury ensues. In CTS, the median nerve is compressed by osseous and / or ligamentous structures in the carpal tunnel. This is a purely structural problem. If you decompress the tunnel, you stop the progression of injury.

A more important question than whether surgical intervention is helpful in CTS, is whether, and under what conditions, it is necessary. Assuming that the goal of treatment is to ensure a good functional and symptomatic outcome for patients, the purpose of treatment is to preserve nerve function. Whether surgery is needed to do this depends on the status of the median nerve. This study did not adequately address the extent of nerve injury in the enrolled patients, other than to exclude those with axonal injury (denervation). The extent of demyelination, however, can be ascertained through electrodiagnostic criteria. This was not done in this study. In many cases, CTS does not progress beyond the nerve's ability to repair itself, and we would not be helping these patients by subjecting them to surgery, even with a minimally invasive procedure with a low complication rate.

Reference

1. Seddon H, et. al. Three types of nerve injury. *Brain* 1943;66:237-288. ■

What Is the Best Technique for Removing a Chronic Subdural Hematoma?

By Roger Härtl, MD

Leonard and Fleur Harlan Clinical Scholar in Neurological Surgery, Associate Professor of Neurological Surgery, Department of Neurological Surgery, Weill Cornell Medical College

Dr. Härtl reports no financial relationships relevant to this field of study.

Synopsis: *In a prospective randomized trial, use of a post-operative drain was associated with lower mortality and less recurrence in the treatment of chronic subdural hematoma (SDH)*

Source: Santarius T, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: A randomised controlled trial. *Lancet* 2009;374:1067-1073.

CHRONIC SUBDURAL HEMATOMA (SDH) IS ONE OF THE most frequently encountered lesions that neurosurgeons treat. It consists of liquefied blood and blood-breakdown products that accumulate in the potential space between the pia-arachnoid membrane and the dura mater. Only in a minority of cases can a previous significant traumatic event be clearly identified. Pathogenesis most likely involves the combination of a coagulation defect with some type of inflammatory process, both of which initiate and propagate the development of blood

accumulation. Importantly, the inflammatory reaction frequently results in the development of a web of surrounding membranes with adhesions and septations. The presence of these adhesions can complicate surgical evacuation. Technically, the surgical treatment of SDH is straightforward and one of the most rewarding operations for neurosurgeons and their patients. The challenges result from the tendency of these lesions to recur.

Surgical options for treatment include twist drill trephination, burr holes, and open craniotomy with or without intraoperative irrigation and with or without a closed postoperative drainage system. More recently, a variation of the twist drill evacuation with a subdural evacuating port system has been described that can be placed at the bedside and permits drainage of fluid during a period of hours to days. The choice of operative technique is frequently dependent upon surgeon preference, training, and experience. A meta-analysis performed by Weigel and colleagues summarized 48 articles published between 1981 and 2001 and concluded that twist drill and burr hole evacuation were the safest procedures and that craniotomy was associated with the lowest recurrence rate but had a higher rate of perioperative complications.[1] Intraoperative irrigation and postoperative drainage systems were not associated with an increased infection rate. The authors recommended twist drill and burr hole craniostomy with a drainage system, as first tier treatment, while craniotomy should be considered as second tier treatment and primarily for recurrent SDH evacuation.

In their well-performed, randomized, single-institution study, Santarius and colleagues from Addenbrooke's Hospital, Cambridge, UK, report a recurrence rate of 9% using a drain (n=108) and a 24% recurrence without a drain (n=107). The drains were not associated with an increased rate of complications. The mortality at six months was 9% with a drain compared to 18% mortality without a drain.

■ COMMENTARY

In our experience, the success of surgery for SDH depends largely on the imaging characteristics of the SDH on preoperative CT or MRI scans. Chronic, homogenous fluid collections will usually be evacuated via twist drill or burr hole trephination, while the presence of substantial loculated pockets of subdural fluid will lead us to perform a craniotomy. The advantage of a craniotomy is that it allows fenestration with coagulation and / or removal of membranes. We always use intraoperative irrigation and postoperative drainage systems. One concern with the present study is the poor definition of chronic SDH and treatment assignment. The authors state that patients with "symptomatic chronic subdural haematoma proven by CT scan for burr-hole drainage were eligible for inclusion" and that those "in whom surgery other than burr-hole evacuation was indicated" were excluded. In our experience this would exclude the large number of patients with mixed density hematomas with septations, who likely would benefit more from a formal craniotomy. However, this remains unclear in the present study.

The authors certainly have to be applauded for performing a rare and needed prospective, randomized clinical trial comparing different neurosurgical operative techniques. Their results provide solid class I evidence and support what was expected based on previous studies. The significance of this trial can be best gauged when one takes into consideration the almost complete absence of prospective, randomized clinical trials within neurosurgery. For example, the "Guidelines for the Surgical Management of Traumatic Brain Injury" published in 2006 reviewed > 700 articles but found no controlled clinical trials to support one form of surgical management over another, or surgical vs. conservative treatment.[2] It is understandable that such trials cannot be easily performed in patients who are actively deteriorating. However, there is no reason why it should not be attempted to have evidence-based medicine guide us in situations where patients are relatively stable and the best surgical technique is unknown.

References

1. Weigel R, et al. Outcome of contemporary surgery for chronic subdural haematoma: Evidence-based review. *J Neurol Neurosurg Psychiatry* 2003;74:937-943.
2. Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2007; 24:Suppl 1. ■

Combination Therapy for Painful Neuropathy

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

Synopsis: *Combination therapies may be better than single agents for neuropathic pain relief, but side effects are a limiting factor.*

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

NUMEROUS DRUGS ARE AVAILABLE FOR THE LONG-TERM control of neuropathic pain. Regrettably, this is not entirely good news. If one choice is poorly tolerated or ineffective, another may be offered. However, the sheer number of drugs advertised underscores the fact that none works superbly in most patients. Hence the pursuit for alternatives, and combination therapy is one such avenue. In this double-blind, controlled, crossover trial undertaken through the Department of Anesthesiology at Queen's University, Kingston, Ontario, between November 2004 and December 2007, 56 patients with diabetic neuropathy or post-herpetic neuralgia were randomized to receive one of three sequences consisting of six weeks each of oral gabapentin, nortriptyline, and both. Each drug was titrated up to a maximum tolerated dose. Diagnostic criteria for diabetic neuropathy included a stocking sensory deficit on examination with decreased or absent ankle reflexes in a confirmed diabetic. Patients with post-herpetic neuralgia had a history of a zoster rash six months prior to trial enrolment. Inclusion criteria for both diagnoses required six months or more of a daily pain score measuring at least 4/10, serum liver function tests within 120% of normal, serum creatinine within 150% of normal, and HgbA1C < 13 %. Exclusion criteria comprised significant major organ system disease, psychiatric illness, substance abuse, hypersensitivity to study drug, a co-existing painful condition, and neuropathy due to other causes including hereditary conditions, thyroid disease, vitamin deficiency, collagen vascular disease, toxins, or amyloid. Outcome measures included measures of global pain relief, mood, quality of life, functional ability, and, the primary outcome measure, daily pain rated thrice daily for seven days on maximum tolerated dose of study drug. Secondary outcome measures included maximum study drug dosage and serum concentration, brief pain inventory, nocturnal pain as reported by patient, short McGill pain questionnaire, Beck depression inventory, global pain relief, and SF-36 general health survey. Analysis was by intention to treat, and data was analyzed by Fisher's exact method.

Of 73 patients screened, 56 were eligible and enrolled but, due to patient withdrawal, only 47 (84%) completed two treatment periods, with 45 (80%) completing all three. Compared to either drug alone, combination therapy resulted in significantly improved mean daily pain intensity, brief pain inventory score, and sleep interference. Dry mouth was the most common side effect, more so with nortriptyline (56%) than gabapentin (20%). Other adverse events included somnolence, fatigue, dizziness, headache, and inability to concentrate. No patient experienced any serious adverse event. Either gabapentin or nortriptyline alone may be used to control pain in diabetic neuropathy or post-herpetic neuralgia but, when necessary, their combination is safe and will provide even further significant pain relief.

■ **COMMENTARY**

Along with transcutaneous electrical nerve stimulation (TENS), acupuncture, and spinal cord stimulation, peripheral nerve fields stimulation (PNFS) is emerging as an alternative treatment for pain refractory to pharmacologic management. A 55-year-old man with post-herpetic neuralgia was unresponsive to combined pregabalin, amitriptyline, and fentanyl patches (*American Journal of Hospice & Palliative Medicine* doi:10.1177/1049909109342089). Following an excellent response to a diagnostic left supraorbital nerve block given on three consecutive days, he underwent a PNFS trial with a subcutaneous electrode placed under the left temporal region into the left supraorbital region. Complete relief was obtained and a permanent stimulator was implanted with continued pain relief. PNFS likely has a mechanism of action similar to TENS and should be considered in post-herpetic neuralgia when other options have run out. ■

CME Questions

17. Which of the following statements about carotid endarterectomy is *false?*

a. Carotid endarterectomy prevents stroke in high-grade stenosis better than medical therapy.
b. Carotid endarterectomy is a proven therapy that is safe and effective.
c. CEA and CAS are equivalent in safety and efficacy.
d. Carotid endarterectomy should be avoided in stenosis secondary to radiation therapy.

18. What finding on MRI helps to distinguish worsening PML versus IRIS?

a. An enlarging T2 hyperintense lesion
b. Contrast enhancement present within the hyperintense region on T2
c. T1 hypointensity corresponding to the hyperintense region on T2

d. There is no way to detect a difference by MRI.
e. Focal atrophy within the hyperintense region on T2

19. Carpal tunnel syndrome must be treated by surgical decompression.

a. True
b. False

20. Remyelination of an injured nerve may result in complete functional recovery.

a. True
b. False

21. Which of the following statements about chronic subdural hematoma (SDH) is *true*?

a. Chronic SDH is a surgical emergency.
b. Chronic SDH is always caused by known trauma.
c. Chronic SDH rarely recurs.
d. Type of treatment depends on the imaging characteristics on CT or MRI.

22. Treatment options for pain relief in post-herpetic neuralgia may include:

a. Peripheral nerve fields stimulation
b. Oral gabapentin
c. Oral nortriptyline
d. Combined oral gabapentin and nortriptyline
e. All the above are options for pain relief in post herpetic neuralgia.

Answers: 17. c; 18. b; 19. b; 20. a; 21. d; 22. e

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CME Objectives

Upon completion of this educational activity, participants should be able to:

1. discuss current scientific data regarding the diagnosis and treatment of neurological disease;
2. discuss the pathogenesis and treatment of pain;
3. describe the basic science of brain function;
4. discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
5. identify nonclinical issues of importance for the neurologist. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

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In Future Issues:

Current treatment for primary malignant brain tumors

NEUROLOGY ALERT®
A monthly survey of developments in neurologic medicine

CUMULATIVE INDEX
Volume 27, Numbers 5-12, Pages 1-96
Volume 28, Numbers 1-4, Pages 1-32
January 2009-December 2009

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NEUROLOGY ALERT®
A monthly survey of developments in neurologic medicine

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yes ○ no ○ 3. Are you able to present basic science lessons in brain function?

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Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 14, NUMBER 12 PAGES 23-24 DECEMBER 2009

PPIs and Clopidogrel: Do We Have to Worry?

Source: O'Donoghue ML, et al. *Lancet* 2009;374:989-997.

THE ANTIPLATELET EFFECT OF CLOPIDOgrel is dependent upon its conversion and activation through the 2C19 pathway of the P450 system. Blockade of this pathway occurs because of genetics, in persons who do not have sufficiently active 2C19, and pharmacotherapies that specifically block 2C19. Proton pump inhibitors (PPIs), particularly omeprazole, are recognized to be 2C19 inhibitors. Is there reason for concern?

Although the in vitro aspects of PPI-antiplatelet interactions are of interest, it is probably more important to see whether such interactions affect the bottom line: CV events. Fortunately, there is a large — and largely reassuring — database from which to glean the impact of the PPI-antiplatelet interaction.

The PRINCIPLE-TIMI and TRITON-TIMI are acute coronary syndrome trials in which clopidogrel and/or prasugrel were used. In both of these trials, some participants were also using PPIs, providing an opportunity to see if concomitant utilization of a platelet inhibitor and PPI affected outcomes.

Subjects who were on clopidogrel who also were receiving PPIs showed less effective platelet inhibition compared to clopidogrel alone (in vitro testing). This effect was less pronounced among prasugrel recipients, consistent with its lesser dependence upon the P450 system for full activity.

Although platelet aggregometry demonstrated diminished antiplatelet effect, in these 2 trials (total n > 15,000), there was no signal of increased adverse outcomes in subjects concomitantly receiving a PPI and clopidogrel or prasugrel. PPIs provide important GI protection for persons on NSAIDs, as well as excellent symptomatic relief for GERD patients. These data suggest that PPIs need not be avoided when treating acute coronary syndromes with clopidogrel or prasugrel. ■

Surgery vs Medical Treatment for CTS

Source: Jarvik JG, et al. *Lancet* 2009; 374:1074-1081.

SEVERAL TRIALS COMPARING SURGICAL with medical therapy for carpal tunnel syndrome (CTS) have been insufficient to clarify the optimum approach. Similarly, it is largely unknown which CTS characteristics predict a favorable response to either type of treatment. Jarvik et al conducted a controlled trial of CTS patients (n = 116) randomized to medical or surgical treatment. Additionally, wrist MRI and nerve conduction studies were performed to identify the predictive capacity of these metrics.

Surgical intervention consisted of either open or endoscopic carpal tunnel decompression (per surgeon preference). Medical treatment included ibuprofen 200 mg tid, physical therapy provided by a hand therapist, other analgesics, corticosteroid injections, and ultrasound (all as per clinician preference). The primary outcome was function as measured by the Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) at 12 months.

There were no serious adverse events in either treatment group. At 12 months, although both groups showed substantial improvement, the CTSAQ score was significantly better in the surgical group. Study subjects with baseline nerve conduction deficits responded less well to surgical intervention. On MRI, patients with signs of nerve edema (indicative of more advanced disease severity) had successful outcomes (30% improvement on the CTSAQ) only half as often as those without edema. In patients with more severe baseline disease, difference in outcome between surgery and medical management diminished. Overall, surgical intervention provides outcomes that are superior to medical therapy. MRI and nerve conduction data may assist patient selection. ■

Influenza Vaccine: Flu Shot vs Nasal Mist

Source: Monto AS, et al. *N Engl J Med* 2009;361:1260-1267.

IS INFLUENZA MANAGEMENT GETTING more complicated, or is it just me? Dealing with vagaries of virus antigenic shift and drift, the moving target of antiviral resistance, insufficiently sensitive point-of-care testing for influenza, and the ever-evolving designation of appropriate risk groups for "seasonal" (regular) vs "novel" (pandemic) influenza prevention is a daunting challenge.

Two major categories of trivalent influenza vaccine are available to prevent seasonal flu: inactivated (SHOT) and live attenuated (NASAL). A randomized double-blind placebo-controlled trial compared the efficacy of SHOT and NASAL vaccine to prevent influenza. Adults 18-49 years (excluding persons with contraindications to

live vaccine) received one vaccine or placebo, and recorded respiratory symptoms through the 2007-2008 flu season; throat swabs were obtained for confirmation of influenza during periods of respiratory symptoms.

Among the 1963 subjects, 6.1% experienced laboratory-confirmed influenza. SHOT efficacy vs placebo was 68% compared to NASAL efficacy of 36%. In the 2007-2008 influenza season, risk reduction of influenza was almost twice as great with SHOT. ■

Beleaguered Primary Care Clinicians

Source: Krasner MS, et al. *JAMA* 2009; 302:1284-1293.

IF DATA OBTAINED WITHIN THE LAST 5 years are correct, the majority of primary care physicians (PCPs) report emotional exhaustion, depersonalization, and/or low sense of accomplishment — collectively called burnout. The favorable results of an intervention to alleviate burnout deserves our focus.

Primary care physicians (n = 70) in Rochester, NY, participated in a year-long intervention: 8 weeks of intensive intervention, followed by once-monthly maintenance for 10 months. Although the complexity of intervention was too great to be captured in this communication, didactic materials (including presentations on dealing with conflict, reflecting on meaningful experiences, etc.), meditation (including yoga-type exercises), and narrative exercises (for instance, writing and sharing brief stories about challenging experiences in practice) were included. Sessions occupied 2.5 hours/week for 8 weeks, followed by monthly maintenance 2.5-hour sessions for 10 months. A single all-day session of mindfulness meditation was included during week 6-7.

Following the intervention, scores on the Maslach Burnout Inventory showed meaningful improvements. Although this is a time-intensive investment, it is encouraging to see tools through which clinicians might better enjoy, be better fulfilled by, and probably perform more effectively in their practice. ■

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Beyond Diabetes Prevention

Source: Perreault L, et al. *Diabetes Care* 2009;32:1583-1588.

MOST INDIVIDUALS WITH PREDIABETES, defined as either impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both, will go on to develop diabetes unless an intervention is instituted. To date, diet, exercise, and pharmacotherapy have all been shown to reduce progression to diabetes by as much as 60%, with diet + exercise being the clearest winner. Although prevention (or delay) of diabetes is important, many persons who do not progress to overt diabetes during a diabetes prevention trial remain prediabetic, which is still a high-risk category. The report by Perreault et al describes factors which were associated, during intervention for diabetes prevention, with restoration to normal glucose regulation.

The Diabetes Prevention Program was the largest diabetes prevention trial to date (n = 3234). Prediabetes subjects were randomized to intensive lifestyle intervention (diet + exercise), metformin (850 mg bid), or placebo, with a mean follow-up of 3 years.

Within the categories of impaired fasting glucose (glucose = 100-125 mg/dL) and impaired glucose tolerance (glucose = 140-199 mg/dL on oral glucose tolerance testing), persons with lesser baseline impairments were more likely to enjoy restoration to normal glucose regulation. Similarly, younger subjects and those who successfully lost weight regained euglycemia more often.

We can encourage our patients that efforts to prevent diabetes can do that and, in some cases, even restore glucose regulation to normal. ■

Does Metformin Affect Thyroid Function?

Source: Cappelli C, et al. *Diabetes Care* 2009;32:1589-1590.

DIABETES COMMONLY IS COMORBID with other endocrinopathies, including hypothyroidism and hypogonadism. The most common first-line pharmacotherapy for diabetes is metformin, which has been heretofore been considered an essentially benign drug, when proscriptions for its use (e.g., renal insufficiency, heart failure) are observed. Recent reports have suggested that metformin might have an effect on TSH even when levothyroxine replacement doses are kept constant; since many hypothyroid patients are diabetic, such effects may be worthy of note.

Capelli et al evaluated in a pilot study 11 diabetic patients with hypothyroidism who initiated therapy with metformin. All had been on stable doses of levothyroxine. Thyroid studies (TSH, free T4 and T3, and total T4 and T3) were performed at baseline, 6 hours, 24 hours, 72 hours, and 3 and 6 months after initiation of metformin. They included in their analysis additional data from another study population comprised of diabetics receiving thyroid for various indications, diabetics with subclinical hypothyroidism not receiving levothyroxine replacement, and diabetics with normal thyroid function.

During the pilot study, despite continued stable levels of levothyroxine replacement and other thyroid parameters, the mean TSH dropped from 2.11 to 1.5 mIU/L. Omission of metformin in one patient who had experienced a more dramatic TSH decline resulted in a return of TSH to baseline. Particularly in the diabetic group with subclinical (non-replaced) hypothyroidism, the decline in TSH was apparent: from a mean of 4.5 to 2.93 mIU/L at 1 year. The mechanism by which metformin lowers TSH is not known. ■

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®. ■

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." ■