EVIDENCE-BASED INFORMATION FOR HOSPITALISTS, INTENSIVISTS, AND ACUTE CARE CLINICIANS

HOSPITAL MEDICINE ALERT

AHC Media LLC Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Rapid Diagnosis of Pulmonary Tuberculosis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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

Dr. Deresinski is on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck.

This article originally appeared in the March 2009 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD. Dr. Price is Assistant Professor, University of Colorado School of Medicine; she reports no financial relationships relevant to this field of study.*

Source: CDC. Updated guidelines for the use of nucleic acid amplification test in the diagnosis of tuberculosis. *MMWR*. 2009;58:7-10.

Synopsis: *Nucleic acid amplification (NAA) testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities.*

NUCLEIC ACID TESTS (NAA) FOR THE DIAGNOSIS OF PULMONARY tuberculosis (TB) have had FDA approval for more than a decade, but their use has been limited, at least in part because of a frequent lack of availability in local laboratories. In addition, previously published guidelines gave less-than-enthusiastic promotion to their use. The CDC has now updated these guidelines for the second time, and their enthusiasm for the test has ballooned.

A major problem in the diagnosis of pulmonary TB is the frequent delay involved. While acid fast smears can have a rapid turnaround time, they are relatively insensitive when compared to culture and, furthermore, lack specificity at a time when the incidence of pulmonary infection with non-tuberculous mycobacteria (NTM) is apparently growing. Culture is specific and sensitive but may require as long as six weeks. In the interval, some patients with tuberculosis may not receive therapy and others with NTM may receive inappropriate therapy. Furthermore, these shortcomings of classical techniques have adverse effects on contact tracing, both in and out of the hospital.

Financial Disclosure

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, has no relevant financial relationship related to the material presented in this issue.

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, selected and reviewed the articles contained within this issue on March 10, 2009.

Table 1

Rapid Diagnosis of Pulmonary Tuberculosis

NAA	AFB Smear	Recommendations
+	+	Presumptive diagnosis of TB; start therapy pending culture result.
+	-	Use clinical judgment with regard to starting therapy; consider repeating testing, including NAA (if > 2 NAA are +, presumptive therapy is indicated).
-	+	Test for inhibitors in specimen (present in 3%-7% of sputum): • Inhibitor detected: NAA of no value; use clinical judgment. • Inhibitor not detected: use clinical judgment, repeat testing; if repeat AFB smear positive but NAA negative, make presumptive diagnosis of NTM infection.
-	-	Use clinical judgment with regard to need for presumptive therapy (sensitivity of NAA only 50%-80% with negative smear).

Adapted from: CDC. Updated guidelines for the use of nucleic acid amplification test in the diagnosis of tuberculosis. *MMWR*. 2009;58:7-10.

The sensitivity of NAA with AFB smear-positive respiratory samples is > 95%, and is 50%-90% with smear-negative samples from patients whose cultures subsequently prove to be culture-positive. In each case, the infection is automatically identified by NAA as being due to *Mycobacterium tuberculosis* rather than NTM.

Because the positive predictive value of the test is < 50% in patients with a low pretest probability of having tuberculosis, NAA tests should not be requested in such patients. On the other hand, a single negative NAA cannot be used to exclude TB in patients with a moderate or high pretest probability of the infection.

Having reviewed the available information, the panel has now recommended that, rather than being a secondary test, NAA testing should become standard practice in the United States. They state that the test should be utilized in the diagnostic evaluation of each patient with suspected pulmonary tuberculosis and for whom the test result would affect either management of the patient or TB control activities, or both. They recommend the following approach:

• In addition to routine collection and processing of specimens for AFB smear microscopy and culture, at least one specimen (preferably the first obtained) be processed for NAA according to the procedure recommended by the manufacturer of the test.

• The result of NAA testing should be interpreted together with the results of AFB smears (*see Table 1*).

The panel also recommends that all clinicians and public health TB programs have access to NAA testing for TB in order to shorten the time to diagnosis from weeks to days. NAA results should be available within 48 hours of specimen collection, and the laboratory should treat the result as a critical value, with immediate reporting to both the clinician and the public health department.

The panel makes no recommendations regarding the use of NAA on non-respiratory specimens, but does acknowledge that "evidence exists for the use of such testing in individual cases." It also makes no recommendations for the use of molecular tests for the detection of drug resistance (no such tests have as yet received FDA approval in the United States). It does, however, indicate that a proposed guideline revision "is likely to support the use of molecular DSTs (diagnostic susceptibility tests) for AFB smear-positive sputum specimens from TB patients who are suspected to have drug-resistant disease or who are from a region or population with a high prevalence of drug resistance."

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Russ Underwood.
MANAGING EDITOR: Leslie Hamlin.
DIRECTOR of MARKETING: Schandale Kornegay.

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA.

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

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.hamlin@ahcmedia.com

Subscription Prices

United States
1 year with Free *AMA PRA Category 1 Credits™*: $249
Add $17.95 for shipping & handling.
(Student/Resident rate: $125).

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *20 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for hospitalists, intensivists and acute care clinicians. It is in effect for 36 months from the date of the publication.

Questions & Comments

Please call **Leslie Hamlin**, Managing Editor, at (404) 262-5416 or e-mail at leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

■ **COMMENTARY**

Overall, as the document indicates, the appropriate use of NAA for the rapid diagnosis of pulmonary TB has the potential to result in earlier initiation of treatment, with resultant improved clinical outcomes, more expeditious interruption of transmission, and more effective public health interventions. It may also lead to reduced inappropriate use of antibacterials, including fluoroquinolones, which could otherwise lead to difficulty in culture recovery of TB and to fluoroquinolone resistance. It also prevents unnecessary isolation and contact investigation, as well as inappropriate therapy in hospitalized patients who prove to have NTM infection. ■

Oseltamivir (Tamiflu) Resistance in Seasonal Influenza A (H1N1) Viruses

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

Sansum-Santa Barbara Medical Foundation Clinic, Santa Barbara, CA.

Dr. Scully reports no financial relationships relevant to this field of study. This article originally appeared in the February 2009 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, and peer reviewed by Philip Fischer, MD. Dr. Bia is Professor of Geographic and Laboratory Medicine, Co-Director, Topical Medicine and International Travelers' Clinic, Yale University School of Medicine, and Dr. Fischer is Professor of Pediatrics, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN. Dr. Bia is a consultant for Pfizer and Sanofi-Pasteur, and receives funds from Johnson & Johnson, and Dr. Fischer reports no financial relationship relevant to this field of study.*

Synopsis: *Preliminary data indicate that the prevalence of influenza A (H1N1) virus strains resistant to the antiviral medication oseltamivir is high. Therefore, interim guidelines issued by the CDC are to use zanamivir or a combination of oseltamivir and rimantidine if influenza A (H1N1) infection is suspected.*

Source: CDC. Health Advisory. CDC issues interim recommendations for the use of influenza antivirals in the setting of oseltamivir resistance among circulating influenza A (H1N1) viruses, 2008-2009 season. http://www.cdc.gov/flu/professionals/antivirals/index.htm. Accessed 12/22/08.

INFLUENZA ACTIVITY HAS BEEN RELATIVELY LOW THUS far in the 2008-2009 season in the United States. However, of the influenza viruses isolated and tested to date, there is significant resistance among the influenza A (H1N1) viruses to the antiviral oseltamivir. As of mid-December 2008, 50 influenza A (H1N1) viruses from 12 states were tested. Ninety-eight percent were resistant to oseltamivir, but all were susceptible to zanamivir, amantadine, and rimantidine. Influenza A (H3N2) and B viruses remain susceptible to oseltamivir.

In light of this information, on December 19, 2008, the CDC issued interim guidelines for antiviral treatment or prophylaxis in suspected cases of influenza (*see Table 2*). The use of influenza tests that can distinguish influenza A from influenza B is encouraged. If a patient has a positive test for influenza A, and treatment is indicated, the use of zanamivir should be considered; alternatively, the combination of oseltamivir plus rimantidine could be used. If the patient has a positive test for influenza B, oseltamivir or zanamivir (no preference) may be given. The same recommendations hold true for persons who are candidates for chemoprophylaxis. Ideally, local or state surveillance data should be used to determine which types (A or B) and subtypes (H1N1 or H3N2) are currently circulating in a given area, but this information may not be available at the time clinical decisions need to be made.

Based on preliminary information, it does not appear that oseltamivir-resistant influenza A (H1N1) viruses cause more severe symptoms compared to oseltamivir-sensitive influenza A (H1N1) viruses. In addition, since oseltamivir-resistant influenza A (H1N1) viruses are antigenically similar to the (H1N1) virus included in the 2008-2009 influenza vaccine (A/Brisbane/59/2007), ongoing influenza vaccination remains an effective strategy to prevent influenza.

■ **COMMENTARY**

In the United States, four antiviral medications are approved for treatment and prophylaxis of influenza. The adamantanes (amantadine, rimantidine) have activity only against influenza A viruses, whereas the neuraminidase inhibitors (oseltamivir, zanamivir) have activity against both influenza A and influenza B viruses. In January 2006, when widespread resistance developed to the adamantanes among influenza A (H3N2) viruses, oseltamivir and zanamivir became the recommended influenza antiviral medications for the United States. Now we are seeing the recommendations shift again in light of the oseltamivir-resistant influenza A (H1N1) viruses circulating this year.

This development is not unique to the United States. The World Health Organization collects data from multiple laboratories participating in the Global Influenza Surveillance Network (GISN), the European Influenza Surveillance

Table 2

Interim Recommendations for the Selection of Antiviral Treatment Using Laboratory Test Results and Viral Surveillance Data, United States, 2008-2009 Season***

Rapid antigen or other laboratory test	Predominant virus(es) in community	Preferred medication(s)	Alternative (combination antiviral treatment)
Not done or negative, but clinical suspicion for influenza	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Not done or negative, but clinial suspicion for influenza	H3N2 or B	Oseltamivir or Zanamivir	None
Positive A	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Positive A	H3N2 or B	Oseltamivir or Zanamivir	None
Positive B	Any	Oseltamivir or Zanamivir	None
Positive A+B**	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Positive A+B**	H3N2 or B	Oseltamivir or Zanamivir	None

* Amantadine can be substituted for rimantadine, but has increased risk of adverse events. Human data are lacking to support the benefits of combination ativiral treatment of influenza; however, these interim recommendations are intended to assist clinicians treating patients who might be infected with oseltamivir-resistant influenza A (H1N1) virus.

** Positive A+B indicates a rapid antigen test that cannot distinguish between influenza and influenza B viruses.

*** Influenza antiviral medications used for treatment are most beneficial when initiated within the first two days of illness. Clinicians should consult the package insert of each antiviral medication for specific dosing information, approved indications and ages, contraindications/warnings/precautions, and adverse effects.

Source: http://www2a.cdc.gov/HAN/archiveSvs/ViewMsgV.asp?AlertNum=00279

Scheme (EISS), and the European Surveillance Network for Vigilance against Viral Resistance (VirGil). In January 2008, Norway reported an increased number of influenza A (H1N1) viruses with resistance to oseltamivir. By June 2008, data from the European region of WHO indicated that 25% of the influenza A (H1N1) viruses tested were resistant to oseltamivir. Finland, France, Luxemburg, the Netherlands, Norway, the Russian federation, and Ukraine all reported a prevalence of 25% or greater, with Norway having the highest prevalence (67%).[1]

The trend of rising oseltamivir resistance does not appear to be correlated with oseltamivir use or abuse since the use of oseltamivir generally is quite uncommon in European countries. Moreover, it does not appear that persons with resistant viruses were in contact with, or linked to, one another. Therefore, the reason for the emergence of these resistant viruses is unknown. However, zanamivir and oseltamivir differ in certain specific aspects of their chemical structures, which explains the lack of emergence of zanamivir resistance.[2] Zanamivir, available only as an inhaled formulation, is indicated for influenza treatment of patients seven years or older, but should not be used in patients with chronic underlying airway disease.

Influenza, be it avian influenza or seasonal influenza, continues to challenge the medical community worldwide. Influenza occurs in the tropics as well as colder climates, affects all age groups, and is highly contagious, placing all of us at risk, including global travelers. The 2008 southern hemisphere flu season just finished and was relatively mild, perhaps reflecting a more appropriate "match" with the vaccine viruses. Vaccination should be encouraged for both travelers and non-travelers throughout the 2009 influenza season since the oseltamivir-resistant viruses appear antigenically similar to the influenza A (H1N1) virus included in both the northern and southern hemisphere vaccines.

As this is an evolving issue, clinicians should check weekly for the updated reports and influenza information at http://www.cdc.gov/flu. ■

References

1. World Health Organization. Influenza A (H1N1) virus resistance to oseltamivir. www.who.int/csr/disease/influenza/oseltamivir_summary/en/index.html. Accessed 12/28/2008.

2. Moscona A. Oseltamivir resistance — disabling our influenza defenses. *N Engl J Med* 2005;353:2633-2636.

Stroke is Associated with Central Periodic (Cheyne-Stokes) Breathing

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

This article originally appeared in the March 2009 issue of Neurology Alert. *It was edited by Matthew Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Vice Chairman, Professor of Neurology, Weill Cornell Medical College; Chief, Division of Stroke adn Critical Care Neurology, NewYork-Presbyterian Hospital, and Dr. Beal is Professor and Chairman, Department of Neurology, Cornell University Medical College. Drs. Fink and Beal report no financial relationships relevant to this field of study.*

Synopsis: *Sleep disordered breathing occurs in most acute stroke patients and may contribute to morbidity*

Source: Siccoli MM, et al. Central periodic breathing during sleep in 74 patients with acute ischemic stroke — m=neurogenic and cardiogenic factors. *J Neurol* 2008;255: 1687-1692.

CHEYNE-STOKES BREATHING (CSB) IS A TYPE OF PERIodic breathing that results from intracranial causes exacerbated by circulatory impairment (prolonged circulation time, congestive heart failure, hypoxia [see Plum and Posner, *The Diagnosis of Stupor and Coma*, 4th Ed, 2007]). Respirographic tracings show alternating periods of hyperpnea, reflecting increased response to CO_2, followed by apnea. The changes in depth of breathing are gradual, so the respirographic tracing has a spindle-like appearance. Unlike sleep apnea, CSB is not sleep dependent.

If the patient happens to be awake when respirations are normal or increased, he may lapse into sleep as they wane. Consciousness returns as respirations increase. The pathogenesis of CSB, then, involves overbreathing in response to CO_2, alternating with post-hyperventilation apnea. Arterial blood gases reflect mild overall hyperpnea. Classically, CSB implies bilateral dysfunction of the cerebral hemispheres or diencephalon, down to the upper pons. It is easy to see that circulatory impairments resulting in delayed feedback of CO_2 or other blood gas information to the respiratory centers can cause or exacerbate respiratory instability such as periodic breathing.

Recently, Siccoli et al at the University of Zurich investigated brain lesions resulting from acute ischemic stroke that were responsible for CSB (termed "central periodic breathing," or CPB, in this report). The subjects were 74 patients admitted within 96 hours after first-ever stroke onset. Sleep-related breathing abnormalities assessed on the first night showed CPB in 53 patients (72%) during 10% of recording time. This may be compared with sleep apnea (obstructive or central), which was found in 41 (55%) patients. Of interest, the severity of CPB was strongly correlated with the severity of sleep apnea, suggesting that they may be pathogenetically related. CPB was much more frequent and severe in anterior circulation hemispheric strokes (six patients) and milder in patients with strokes involving the left insula (n = 5) and mesencephalon (n = 5), as well as those with lower-left-ventricular ejection fraction.

■ COMMENTARY

Acute stroke is nearly always associated with a sleep-related breathing disorder, most often obstructive sleep apnea (OSA), which has been reported to occur in 69%-95% of patients. Because it is associated with transient ischemic attacks as often as completed stroke, CPB is more likely to be a predisposing condition rather than a cause of stroke. Risk factors that are shared by stroke and OSA include obesity, age, and hypertension. Furthermore, sleep fragmentation related to acute stroke may perpetuate and aggravate both central and obstructive sleep apnea.

Regardless of the mechanism, the astonishing frequency of OSA or CSB in stroke should make us wonder how much they may contribute to stroke morbidity and mortality and to what extent stroke burden might be lessened by treatment with continuous positive pressure ventilation (CPAP). Positive effects of CPAP have already been observed in individual patients, and a formal clinical trial of its potential benefits is warranted. ■

Steroids to Prevent Extubation Failure?

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle

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

This article originally appeared in the March 2009 issue of Critical Care Alert. *It was peer reviewed by William Thomspon, MD. Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington; he reports no financial relationships relevant to this field of study.*

Synopsis: *This meta-analysis of studies examining the efficacy of systemic corticosteroids for preventing laryngeal edema following extubation concludes that this treatment is effective. This result differs from those of several previous meta-analyses, and raises practical issues such as whether extubation should be delayed for at least 12 hours after a patient passes a spontaneous breathing trial and qualifies for extubation so that a course of steroids can be given.*

Source: Fan T, et al. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: Meta-analysis of randomised placebo controlled trials. *BMJ*. 2008;337: a1841; doi: 10.1136/bmj.a1841.

POST-EXTUBATION LARYNGEAL EDEMA, ALTHOUGH INfrequent, can necessitate reintubation and lead to other complications. The administration of a course of parenteral corticosteroids prior to extubation to reduce the likelihood of laryngeal edema has been advocated for many years, although the studies published to-date have been small and several meta-analyses of their aggregate findings have failed to show this treatment to be effective. Fan et al at Sichuan University in Chengdu, China, performed a new meta-analysis of those studies, including an additional, recently published series and different selection criteria for the data to use in the meta-analysis, and concluded that steroid treatment is effective in preventing post-extubation laryngeal edema and the need for reintubation.

Using PubMed, the Cochrane Controlled Trials Register, and several other databases, Fan et al searched for randomized, controlled trials comparing parenterally administered corticosteroids to placebo for the prevention of laryngeal edema following extubation. Their search produced six eligible trials, reporting a total of 1,923 patients. They reasoned that, because laryngeal edema was the condition targeted by corticosteroid treatment and, hence, the outcome variable of interest, only those patients with this cause for respiratory distress and reintubation following extubation needed to be included in the meta-analysis. Using data selected in this manner where possible, and including 80 patients from a recently reported study from Taiwan that was not available for the previous meta-analyses, Fan et al found the following results: Compared with placebo, steroids given in multiple doses over 12-24 hours prior to planned extubation decreased the odds ratio for laryngeal edema (0.38; 95% confidence interval [CI], 0.17-0.85) and subsequent reintubation (0.29; 95% CI, 0.15-0.58). A single dose of steroids immediately prior to extubation had no significant effect. They found no adverse effects of steroids as used in the studies examined.

■ COMMENTARY

By the tenets of evidence-based medicine, the only evidence more authoritative than the results of a randomized, controlled trial is a meta-analysis of multiple such trials. Thus, the current study by Fan et al ought to be pretty much the last word on whether corticosteroids are beneficial for preventing post-extubation laryngeal edema, as well as the need for reintubation. But what happens when more than one meta-analysis is available, based on pretty much the same evidence, and they come to different conclusions? Such is the case here. A Cochrane review, also published in 2008, concluded that corticosteroids had not been shown to be effective for preventing either laryngeal edema or reintubation.[1] As pointed out in the editorial accompanying the Fan meta-analysis, methodological differences likely explain the disparate results: "The difference in results comes from a combination of the new data, and a careful selection of the 'most appropriate' data from the five other studies. Where possible, Fan and colleagues included only patients who needed reintubation for laryngeal edema and excluded those who were reintubated for other reasons, who would not respond to corticosteroids and who would dilute any effect. This selection allowed them to use a less conservative (fixed effects) model than that used in the previous review."[2]

Patients fail extubation for a number of reasons, including inability to protect the upper airway because of altered neurological status, the inadequate clearance of lower respiratory tract secretions, and insufficient recovery of ventilatory muscle and airway function after acute respiratory failure to sustain the required work of spontaneous breathing, in addition to laryngeal edema. Only the last of these would be expected to be prevented by a course of systemic corticosteroids. This fact partly justifies the Fan et al strategy of excluding other causes for reintubation in their meta-analysis. However, there are two problems. First, when patients do not do well after extubation and the managing clinician decides that reintubation is necessary, the specific reason is often unclear and, while a

few such patients have clear-cut laryngeal edema, most do not. This makes it unlikely that any post-hoc procedure for classifying reintubation into various causes would be completely accurate, and raises doubts about the appropriateness of selectively omitting some patients in the published studies from analysis. And, second, if laryngeal edema is only one of several potential reasons for reintubation for which steroids can help, a large number of patients would have to receive the preventive therapy for those with laryngeal edema to benefit.

There is another important matter that influences my decision whether to give steroids to all my patients to prevent laryngeal edema: I am not used to deciding that a patient is ready to be extubated 12-24 hours in advance. We make rounds in the morning, assess the patient's status, including the results of a spontaneous breathing trial, and decide on extubation right then based on that information. Waiting until that evening — or the next morning — to carry out the extubation so that several timed doses of steroids could be administered would prolong the period of intubation for a large number of patients who would not benefit from that therapy. Given that a single bolus of steroids immediately prior to extubation does not seem to be effective, the regimen used in the studies included in the meta-analyses (which is either effective or ineffective, depending on which of the latter you prefer) seems ill-suited to current ICU practice.

The use of corticosteroids prior to a second extubation attempt in a patient who had stridor during an earlier failed extubation makes sense. So does their administration to patients who had difficult intubations, who have unusually large endotracheal tubes for their size (particularly women), who have sustained airway injuries or trauma to the head and neck, or who have no cuff leak on repeated measurements — although the required delay while several doses of steroids are administered needs to be factored into the clinical decision. However, I remain unconvinced that more liberal administration of steroids to intubated patients to diminish the likelihood of post-extubation stridor is currently justified by the available evidence. ■

References

1. Markovitz BP, et al. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. *Cochrane Database Syst Rev*. 2008;(2):CD001000.
2. Young D, Watkinson P. Preventing postextubation airway complications in adults. *BMJ*. 2008;337:a1565.

Newer Antipsychotic Drugs and Sudden Death

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

This article originally appeared in the March 2009 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD.*

Source: Ray WA, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;360: 225-235.

RAY ET AL EXAMINED THE COMPUTERIZED FILES OF Tennessee Medicaid recipients to estimate the effects of atypical antipsychotic drugs on the risk of sudden cardiac death. It is well known that typical antipsychotic drugs (for example, thioridazine or haloperidol) block potassium currents in vitro and may prolong QT intervals during clinical use. The typical antipsychotic drugs have been associated with case reports of torsades de pointe (polymorphic ventricular tachycardia with QT prolongation) and sudden death. Atypical antipsychotic drugs were introduced, and have been widely accepted, because they produce less neurologic toxicity, but also because they block repolarizing currents in vitro. The relative toxicity of the two classes of drugs has not previously been examined.

The Tennessee Medicaid database has been extensively used for pharmacoepidemiologic studies in the past by Ray et al. For this report, a cohort was constructed that included patients 30-74 years of age with at least one qualifying day of use of antipsychotic drugs, typical or atypical, during the study period. Two controls for each user of antipsychotic drugs were identified that were matched for age, gender, and days of follow-up; they formed the reference group. The incidence of sudden death was estimated from death certificates stored in the Medicaid database. A secondary analysis was performed using propensity scores to identify a non-user control group with a similar psychiatric illness profile. The use of antipsychotic drugs and other prescription medications was identified from the Medicaid Pharmacy files.

The primary cohort included 93,300 users of antipsychotic drugs, with 186,600 matched controls. There were

approximately equal numbers of users of typical and atypical antipsychotic drugs, 42,218 and 46,089, respectively. The mean age was 45.7 years, with 65% of the cohort women and 70.5% white. As compared with users of typical antipsychotic drugs, the users of atypical agents were slightly younger, less likely to be on disability, and had a higher baseline cardiovascular risk score. Users of atypical antipsychotic drugs were less likely to carry a diagnosis of schizophrenia and were more likely to have a diagnosis of a mood disorder. During more than 1 million person years of follow-up, there were 187 cardiac deaths (17.9 per 10,000 patient years) in the study cohort. Sudden death rates increased with age, and were higher for men than for women. The adjusted rate of sudden cardiac death was higher for users of both typical and atypical antipsychotic drugs than it was in the control population. The incidence ratio was 1.99 for typical antipsychotic drug users and 2.26 for atypical antipsychotic drug users. The increased risk of sudden death was seen only in current users of antipsychotic drugs. The incidence ratio was only 1.13 among former users. Patients on high doses of either typical or atypical antipsychotic drugs had a higher sudden death incidence than patients who received only low doses. Similar findings were seen in a secondary analysis using propensity scores.

Ray et al conclude that users of both typical and atypical antipsychotic drugs have a dose-related increased risk of sudden death of similar magnitude. At least from the standpoint of cardiovascular risk, the atypical antipsychotic drugs appear no safer than the older agents.

■ COMMENTARY

It has been well shown that both the typical and atypical antipsychotic drugs in current use can prolong repolarization due to their effects on potassium currents. The magnitude of the clinical risk of this effect has been difficult to determine. Patients with schizophrenia often have multiple cardiac risk factors, have histories of both poor medication compliance and abuse of non-prescription medications, and manifest a significant rate of suicide. Since most sudden deaths are unmonitored, documented episodes of clear drug-induced arrhythmia have been infrequent.

In this paper, Ray et al use a sophisticated pharmacoepidemiologic approach to further investigate this issue. The same authors have used similar techniques to show that erythromycin, a macrolide antibiotic that also affects potassium currents, is associated with a small increase in sudden death risk. In this report, Ray et al show that the annual sudden death rate increases from 0.14% and 0.16% among non-users and former users of antipsychotic drugs to 0.29% and 0.28% among users of typical and atypical antipsychotic agents. This small risk must be considered in the use of these important agents. Unfortunately, the data show that the risk of sudden death is not diminished with the newer atypical agents, which are often chosen because of lesser neurological side effects. ■

CME Questions

4. According to the new CDC guidelines for the diagnosis of pulmonary tuberculosis, which of the following is recommended?

a. In addition to routine specimens for AFB smear and culture, at least one specimen should be processed for nucleic acid amplification testing.
b. The results of nucleic acid amplification are not helpful in the diagnosis of pulmonary tuberculosis.
c. Nucleic acid amplification testing is most useful in patients with a low pretest probability of pulmonary tuberculosis.
d. In patients with a moderate- or high-pretest probability of pulmonary tuberculosis, a single-negative nucleic acid amplification test can effectively rule out the infection.

5. Based on current epidemiological data from the CDC, the best management of influenza A due to 2008 influenza virus isolates includes all of the following except:

a. oseltamivir for patients infected with H1N1 strains.
b. zanamivir for patients infected with H1N1 strains.
c. oseltamivir plus rimantidine for patients infected with H1N1 strains
d. oseltamivir or zanamivir for patients infected with H3N2 strains.

6. According to the report by Siccoli et al, which of the following types of sleep-disordered breathing can be seen in patients admitted with an acute stroke?

a. Obstructive sleep apnea
b. Central sleep apnea
c. Cheyne-Stokes respiration
d. All of the above.

Answers: 4. (a); 5. (a); 6. (d)

CME Objectives

The objectives of *Hospital Medicine Alert* are to:

• review pertinent safety, infection control, and quality improvement practices;

• discuss diagnosis and treatment of acute illness in the hospital setting; and

• review current data on diagnostic and therapeutic modalities for common inpatient problems. ■