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Histoplasmosis in Travelers

By Carol A. Kemper, MD, FACP

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

Dr. Kemper does research for Abbott Laboratories and Merck.

This article originally appeared in the April issue of Infectious Disease Alert.

Source: Buitrago MJ, et al. Histoplasmosis and paracoccidioidomycosis in a non-endemic area: A review of cases and diagnosis. *J Travel Med* 2010;18:26-33.

TWICE IN THE PAST 2 YEARS I'VE ENCOUNTERED PULMONARY HISTOPLASMOSIS IN travelers returning from Central America (Mexico and Costa Rica), and both times the diagnosis proved challenging. One case, in particular, was a 60-year-old man who had traveled to Costa Rica for 1 week and then presented with fever, persistent dry cough, malaise, and complaints of memory loss. Only a biopsy of lung tissue confirmed the diagnosis of carcinoid tumor, bronchiolitis obliterans, and histoplasmosis (based on histopathology; cultures were negative).

These authors at the Spanish Mycology Reference Laboratory in Madrid, Spain, describe their experience with the laboratory detection of histoplasmosis and paracoccidioidomycosis (PCM) in returning travelers and immigrants, including the use of a novel PCR-based technique based on DNA amplification of the internal transcriber spacer region of *H. capsulatum* var. *capsulatum*, *H. capsulatum* var. *duboisii*, and *P. brasiliensis*. Precipitating antibodies were detected using immunodiffusion assay.

Since 2006, histoplasmosis was diagnosed in 9 returning travelers and 30 immigrants; most had come from South America (83%), Africa, or both. The 9 travelers had no underlying disease, and were diagnosed with probable histoplasmosis based on positive immunodiffusion test results. The organism was not cultured in any of these patients. RT-PCR was positive in 5, including 3 of 7 serum specimens, 2 of 3 lung biopsies, and 1 of 1 sputum specimen.

In contrast, all 30 immigrants were diagnosed with disseminated histoplasmosis; 97% of these were HIV-infected and the remaining patients had a hematologic malignancy. Of these, 97% were diagnosed with proven histoplasmosis based on a positive culture or visualization of the organism in tissue specimens; only 1 patient was diagnosed based on the results of RT-PCR alone. Im-

munodiffusion testing was performed in 20 patients, and was positive in 8 (40%), whereas RT-PCR was positive in 24 of 27 patients tested (89%; this included plasma or serum, bone marrow biopsy, or other tissue biopsy). Three patients from Africa were found to have *H. capsulatum* var. *duboisii* based on RT-PCR results.

Six patients, all immigrants from South America, were diagnosed with PCM; all 6 had positive immunodiffusion assays for PCM (which were weakly positive in 3), and all 6 had a positive RT-PCR of plasma or serum, bronchoalveolar lavage, lung biopsy, or other biopsy.

Pulmonary histoplasmosis should be suspected in any traveler returning from Central or South America with fever, headache, malaise, dry cough, and chest discomfort (especially if they have visited caves), although confirming the diagnosis may be challenging. Immunodiffusion assays are helpful in many patients, but it may be necessary to obtain tissue. ■

Real-life Efficacy of Herpes Zoster Vaccine

By Louis Kuritzky, MD

Clinical Assistant Professor,
University of Florida, Gainesville

Dr. Kuritzky is a consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Daiichi, Sankyo, Forest Pharmaceuticals, Lilly, Novo Nordisk, and Takeda

This article originally appeared in the March 28, 2011 issue of Internal Medicine Alert.

Source: Tseng HF, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA* 2011;305:160-166.

HERPES ZOSTER VACCINE (ZOSTAVAX) WAS LICENSED IN THE United States in 2006 subsequent to the publication of the Shingles Prevention Study, a large (n = 38,546) prospective trial that demonstrated a 51% reduction in zoster and a 67% reduction in postherpetic neuralgia in vaccines compared to controls. Clinicians may wonder whether the favorable results seen in a major clinical trial would be replicated in their private clinical settings. According to this report by Tseng et al, that may very well be the case.

Enrollees in the Southern California Kaiser Permanente health plan older than 60 years of age who had received zoster vaccine (n = 75,761) were compared with age-matched controls (n = 227,283) in this retrospective analysis. The Kaiser Permanente study population was comprised of healthy, immunocompetent, community-dwelling adults. The primary outcome of interest was incidence of zoster.

The rate of zoster in the vaccine recipients (6.4/1,000 person-years) was significantly less than the rate in unvaccinated study subjects (13.0/1,000 person-years). This 55% relative reduction is highly concordant with the reductions seen in the Shingles Prevention Study, confirming the generalizability of their results. ■

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Leptospirosis in Florida: Recreational Exposures Reveal New Serovar

ABSTRACT & COMMENTARY

By Brian Blackburn, MD

Dr. Blackburn is a Clinical Assistant Professor in the Division of Infectious Diseases and Geographic Medicine at Stanford University School of Medicine

Dr. Blackburn reports no relationship to this field of study.

This article originally appeared in the March issue of Infectious Disease Alert.

Synopsis: *Forty-four (23%) of 192 adventure race participants in a 2005 Florida event developed suspected leptospirosis, with confirmatory serologic testing positive in 45% of the tested individuals. A unique serovar (related to species* Leptospira noguchii*) was isolated from 1 patient.*

Source: Stern EJ, et al. Outbreak of leptospirosis among adventure race participants in Florida, 2005. *Clin Infect Dis* 2010;50:843-849.

Leptospirosis is a zoonosis caused by multiple serovars of bacteria in the genus Leptospira that are widely distributed in the tropics, as well as some subtropical and temperate areas. Although most commonly a self-limited febrile illness, a minority of patients develops severe leptospirosis (Weil's disease), which can result in jaundice, renal failure, or hemorrhagic manifestations.[1] Many non-human mammals serve as the reservoir for this spirochete, which is excreted in the urine of such animals. As a result, infection is acquired predominantly in association with water and moist areas. Recently, infection has been increasingly associated with adventure travel and sporting activities, such as rafting, triathlons, and adventure races; outbreaks may be precipitated by flooding and heavy rainfall and can occur in areas not known to be endemic.[2-4]

In 2005, an adventure race with 200 participants took place near Tampa, FL. The race involved paddling, cycling, trekking, and orienteering, and took place in a swamp; the race occurred 2 weeks after a hurricane passed over the area. Seventeen days after the race, the index case was admitted to a hospital in New York with fever, headache, and myalgias; subsequently, several other racers developed similar illnesses, including a California racer who was diagnosed with leptospirosis based on a positive serologic test. An outbreak investigation conducted by the Centers for Disease Control and Prevention (CDC) and state/local health departments followed. For the investigation, a suspected case of leptospirosis was defined as a race participant who subsequently developed fever plus at least two classic symptoms or signs of leptospirosis (headache, myalgias, eye pain, conjunctival suffusion, jaundice, dark urine, or unusual bleeding). A suspected case was reclassified as laboratory confirmed if 1 of 3 tests was positive (leptospire culture, Dip-S-Tick [DST] test, or a serum microscopic agglutination test [MAT] result of > 400 in a single specimen, or a 4-fold increase in titers between 2 specimens).

Forty-four (23%) of the 192 interviewed racers met the definition for suspected leptospirosis, with a mean incubation period of about 13 days; 3 were hospitalized and none died. Cultures were attempted on the blood and urine of 4 patients, 1 of whom was positive for a novel serovar of *Leptospira noguchii*. Fourteen (45%) of the 31 suspected cases who submitted serum samples were confirmed by laboratory testing. The most common signs and symptoms were fever (100%), headache (91%), chills (69%), sweats (68%), muscle/joint pain (68%), and eye pain or photophobia (39%). Factors significantly associated with leptospirosis included swallowing river or swamp water, eating wet food, and submersion in water. Severe cuts on the legs and wearing shorts were not statistically associated with infection.

■ COMMENTARY

Transmission of leptospirosis is perpetuated by environments that bring humans and animals into contact, especially those that are moist or contain bodies of freshwater. Although most common in the tropics, transmission does occur in temperate areas; in the United States, transmission is most common in Hawaii, and is also seen in the Pacific and southern states.[1] Outbreaks of leptospirosis have been increasingly recognized, including during triathlons in the U.S. Midwest and during an eco-challenge race in Malaysian Borneo.[2-4] The outbreak of leptospirosis in Florida was similar in many ways to past outbreaks, with patients demonstrating classic signs and symptoms, a relatively high attack rate, and an incubation period of about 2 weeks. Not surprisingly, the risk factors associated with infection included ingesting or being submerged in water. Although leptospirosis can be transmitted by many routes (including through mucous membranes, broken skin, and possibly aerosols), infection seems to be associated most strongly with ingestion of water, perhaps reflecting the large inoculum that results from this exposure.[1]

Climate change can affect the epidemiological environment in many ways, and areas that receive increased rainfall as a result of climate change can become bet-

ter suited to transmission of infectious diseases such as leptospirosis.[5,6] The passage of Hurricane Wilma over the race area 2 weeks before the event resulted in heavy rainfall and flooding, and likely contributed to the outbreak. The observed high attack rate was likely in part because of this environmental occurrence, as well as due to the race's location in a swamp. Many outbreaks have heralded the discovery of new endemic areas for infectious diseases and, in this case, the discovery of new infectious agents themselves. With leptospirosis outbreaks becoming more common, chemoprophylaxis should be considered for high-risk events. Doxycycline has been shown to be effective both for pre-exposure and post-exposure prophylaxis for leptospirosis, and should be a consideration for events that place participants at high risk of this infection.[1,7,8] ■

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MDR-TB in South African Health Care Workers

By Carol A. Kemper, MD, FACP

This article originally appeared in the March issue of Infectious Disease Alert.

Source: O'Donnel MR, et al. High incidence of hospital admissions with multi-drug resistant and extensively drug-resistant tuberculosis among South African healthcare workers. *Ann Intern Med* 2010;153:516-522.

Admissions to a public hospital in KwaZulu-Natal, South Africa, for treatment of MDR- and XDR-TB from 2003 to 2008 were examined for health care workers (HCWs) compared with non-HCWs.

During this time, 4,151 non-HCWs and 231 HCWs (≥ age 20) with MDR-TB or XDR-TB were admitted. The number of admissions for MDR-TB increased from 440 to 1,028 cases (43 HCWs) and the number of admissions for XDR-TB increased from 6 to 114 cases (12 HCWs). The mean age and HIV status (55% of HCWs vs. 57% of non-HCWs were HIV+) of the two groups were similar, although more of the HIV+ HCWs were receiving antiretroviral therapy.

The estimated incidence of MDR-TB in HCWs admitted to hospital was 64.8/100,000 vs. 11.9/100,000 in non-HCWs; the incidence of XDR-TB in HCWs was 7.2/100,000 vs. 1.1/100,000 in non-HCWs. A key finding was that HCWs were significantly less likely to have received prior TB treatment than non-HCWs (41% vs. 92%; $P < 0.0001$), suggesting that while resistance may be acquired in non-HCWs as the result of inadequate treatment or non-compliance, HCWs were more likely to acquire organisms already drug-resistant.

Nosocomial transmission of TB respresents a significant threat to HCWs; good airborne transmission precautions and appropriate facilities are essential. Not only are trained HCWs too valuable an asset for these countries to lose, but HCWs infected with TB also present a safety risk to patients. A greater percentage of the HCWs with resistant TB in this study compared with non-HCWs were women (78% vs. 47%), suggesting that women were more likely involved in direct patient care and, therefore, at greater risk for exposure. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Tiotropium for COPD — The New Standard?

In this issue: Anticholinergic drugs for COPD; pioglitazone for diabetes prevention; insulin degludec in Phase 3 trials; and FDA Actions.

Anticholinergic drugs for COPD

Should anticholinergic drugs be first-line agents for preventing exacerbations in patients with chronic obstructive pulmonary disease (COPD)? The answer may be yes, according to a new study in the *New England Journal of Medicine*. Researchers from Europe compared the anticholinergic drug tiotropium to the beta-agonist salmeterol in more than 7000 patients with moderate-to-very-severe COPD. The study was a randomized, double-blind, double-dummy, parallel-group trial in which tiotropium once a day was compared to salmeterol twice a day. The endpoint was the incidence of moderate or severe exacerbations. Over the 1-year study, tiotropium increased the time to first exacerbation compared to salmeterol (187 days vs 145 days, 17% risk reduction, hazard ratio [HR] 0.83; 95% confidence interval [CI], 0.77 to 0.90; $P < 0.001$). Tiotropium also increased the time to first severe exacerbation ($P < 0.001$), reduced the annual number of moderate or severe exacerbations (0.64 vs 0.72; $P = 0.002$), and reduced the annual number of severe exacerbations (0.09 vs 0.13; $P < 0.001$). Adverse events were similar in both groups. There were 64 deaths in the tiotropium group (1.7%) and 78 in the salmeterol group (2.1%). The authors conclude that in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations (*N Engl J Med* 2011;364:1093-1103). This is the first head-to-head study to show benefit for anticholinergics but it must be pointed out that cardiac patients were excluded from the study, and the annual exacerbation rates were lower than has been seen in other trials. The concomitant use of inhaled corticosteroids was evaluated and did not make a difference in the outcomes. The study was sponsored by Boehringer Ingelheim, the manufacturer of tiotropium (Spiriva). ■

Pioglitazone for diabetes prevention

Pioglitazone reduces the risk of development of diabetes among prediabetic patients, according to a new study. Pioglitazone was compared to placebo in a total of 600 patients with impaired glucose tolerance. After a median follow-up of 2.4 years, the annualized incident rates for type 2 diabetes were 2.1% in the pioglitazone group and 7.6% in the placebo group (HR 0.28, 95% CI, 0.16 to 0.49; $P < 0.001$). Conversion to normal glucose tolerance occurred in nearly half of the pioglitazone group and in 20% of the placebo group ($P < 0.001$) and treatment with pioglitazone was associated with significantly lower fasting glucose levels, 2-hour glucose levels, and hemoglobin A1c levels. Pioglitazone also was associated with a decrease in diastolic blood pressure (2.0 mmHg vs 0.0 placebo), reduced rates of carotid intimal-medial thickening ($P = 0.047$), and an increased level of HDL cholesterol (increase of 7.35 mg/dL vs 4.5 mg/dL; $P =$

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. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

0.008). Pioglitazone caused greater weight gain than placebo (3.9 kg vs 0.77 kg; $P < 0.001$), as well as edema (12.9% vs 6.4%; $P = 0.007$). The authors conclude that pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes but was associated with significant weight gain and edema (*N Engl J Med* 2011;364:1104-1115). Thiazolidinediones have been falling out of favor in recent years for the treatment of type 2 diabetes due to association with edema and heart failure. This new industry-sponsored study suggests that pioglitazone (Actos) is more effective than metformin or lifestyle changes in preventing conversion of prediabetes to diabetes. What is unclear is the effect of these various interventions on long-term diabetic complications. ■

Insulin degludec in Phase 3 trials

Insulin degludec is an ultralong-acting insulin that is currently in Phase 3 trials. It forms soluble multihexamer assemblies after subcutaneous injection, resulting in a very long half-life of up to 40 hours. A new study suggests that it can be used three times a week, achieving blood sugar control equivalent to daily insulin glargine. In a 16-week randomized, open-label, parallel group trial, 245 type 2 diabetics aged 18-75 were randomized to insulin degludec once a day or three times a week, or insulin glargine once a day, all in combination with metformin. At the end of the study, mean hemoglobin A1c levels were similar across the treatment groups at 7.3%, 7.4%, and 7.2%, respectively. The rate of hypoglycemia was low in all three groups. The authors conclude that insulin degludec provides comparable glycemic control to insulin glargine without additional adverse events and may reduce dosing frequency due to its ultra-long action profile (*Lancet* 2011;377:924-931). The study was sponsored by its manufacturer, Novo Nordisk. ■

FDA actions

The FDA has approved the first new drug for lupus (systemic lupus erythematosus) since 1955. Belimumab is a fully human monoclonal antibody the targets human soluble B-lymphocyte receptor stimulator protein. It is indicated for the treatment of adult patients with active, autoantibody-positive lupus who are receiving standard therapy. In two pivotal studies, the drug was found to reduce disease activity compared to placebo plus standard therapy. More deaths and serious infections were reported for belimumab compared to placebo, and it does not appear to be effective in people of African or African American heritage (in whom the disease is three times more common), although more studies are needed to confirm this finding. Belimumab is marketed by GlaxoSmithKline as Benlysta.

The FDA has approved a phosphodiesterase type 4 inhibitor to reduce the number of exacerbations from severe COPD associated with chronic bronchitis. Roflumilast is a once daily oral pill that reduces excess mucus and cough. It does not appear to benefit COPD that involves primarily emphysema. The approval was based on two Phase 3 studies of more than 1500 patients. An accompanying medication guide informs patients of the potential risk of mental health problems including changes in mood, thinking, or behavior, as well as unexplained weight loss. Roflumilast is marketed by Forest Pharmaceuticals as Daliresp.

The FDA has approved a new angiotensin II receptor antagonist, the eighth introduced to the American market. Azilsartan medoxomil is approved for the treatment of hypertension in 40 mg and 80 mg once daily doses. The drug is touted as being more effective in lowering blood pressure than valsartan or olmesartan based on clinical trials. Like other angiotensin II receptor blockers, the drug will carry a box warning regarding pregnancy. Azilsartan is marketed by Takeda Pharmaceuticals as Edarbi.

Zostavax, Merck's vaccine for the prevention of shingles, has been approved for use in individuals ages 50-59. It previously was approved only for those 60 and older. The approval was based on a placebo-controlled trial of more than 20,000 individuals 50-59 years of age. The vaccine reduced the risk of developing shingles in this group by approximately 70%.

The FDA has approved ipilimumab for the treatment of late stage (metastatic) melanoma. The drug is a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen (CTLA-4). The approval was based on a single study of 676 patients with melanoma who had stopped responding to other therapies. When compared to an experimental tumor vaccine, those receiving ipilimumab lived an average of 3.5 months longer (10 months vs 6.5 months). Autoimmune reactions were common including fatigue, diarrhea, rash, endocrine deficiencies, and colitis. Severe to fatal autoimmune reactions were seen in 13% of treated patients. Ipilimumab is manufactured by Bristol-Myers Squibb and marketed as Yervoy. ■