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Leishmaniasis and Human Trafficking

By Carol A. Kemper, MD, FACP

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Dr. Kemper does research for Abbott Laboratories and Merck. This article originally appeared in the July 2011 issue of Infectious Disease Alert. At that time it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.

Source: Cannella AP, et al. A cluster of cutaneous Leishmaniasis associated with human smuggling. *Am J Trop Med Hyg* 2011;84:847-850.

PHYSICIANS AT THE UNIVERSITY OF CALIFORNIA-SAN DIEGO (UCSD) REPORT A CLUSTER of 5 cases of cutaneous Leishmaniasis in illegal immigrants from East Africa, which surprisingly turned out to be consistent with New World Leishmaniasis, although all 5 had come from an area endemic for Old World Leishmaniasis. How did this occur?

Four Somali and one Ethiopian were brought to the Emergency Room at UCSD by Immigration and Custom Enforcement Agents. They had all been found being smuggled across the U.S.-Mexico border about 20 miles south of the city, and had been held in custody for up to 60 days. They each presented with one small cutaneous ulcer, either nodular or pustular, in different locations on the body (thumb, ear, foot, etc.) and in different stages of development. Initially thought to be MRSA folliculitis, prison officials had attempted administration of trimethoprim-sulfamethoxazole and doxycycline without response. The patients were then referred to UCSD for further care.

Skin biopsies were obtained, and the histology was consistent with leishmaniasis, although the presence of a number of features, such as large vacuoles, was more consistent with New World Leishmaniasis. Cultures yielded a *Leishmania* spp. and isoenzyme analysis confirmed *L. panamensis*, which is a member of the *Viannia* group of *Leishmania*. Confirmatory PCR was performed at the Centers for Disease Control and Prevention. All of the patients responded to liposomal amphotericin, although one patient relapsed, requiring a second course of therapy.

The story of how they had arrived at the Mexican border from East Africa was not readily forthcoming, but eventually it was learned that all 5 individuals had been smuggled at different times along an identical route from Djibouti to Dubai to Moscow to Havana, Cuba, and then to Quito, Ecuador, through Colombia, and then by ground via Panama to the U.S.-Mexico border. The trip through Panama required foot travel, and the individuals slept outdoors on the

ground at night in sleeping bags. They described many insect bites.

New World Leishmaniasis occurs throughout Central and South America and is caused by the bite of a sand fly. Only a small number of the 76 sand fly species in Ecuador, Colombia, and Panama can transmit Leishmaniasis, and recent data suggest that up to 1% of female Lutzomyia sand flies are infected. Within 2-8 weeks of a sand fly bite, a small pustule develops, which progresses to a painless ulcer. Fourteen different species of *Leishmania* exist in the New World, a number of which can cause mucocutaneous involvement, including *L. panamensis*. More aggressive therapy with amphotericin is therefore warranted.

Subsequent to this event, 3 individuals from East Africa presented to the physicians in Tacoma, WA, with a similar story. They had been smuggled along the identical route, and skin biopsies yielded the same organism. The discovery of two clusters of Leishmaniasis, in San Diego and in Tacoma, suggest that human trafficking from East Africa through this route must be fairly common with important public health implications for U.S. residents. ■

Tdap for Health Care Workers

By Carol A. Kemper, MD, FACP

This article originally appeared in the August 2011 issue of Infectious Disease Alert. At that time it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.

Source: ACIP Provisional recommendations for health care personnel on use of tetanus toxoid, reduced diptheria toxoid, and acellular pertussis vaccine (Tdap) and use of post-exposure antimicrobial prophylaxis. Available at: www.cdc.gov/vaccines/recs/provisional/default/htm.

Add Tdap to the growing list of recommended (and often required) vaccinations for health care workers (HCWs) in hospital, including MMR, hepatitis B, influenza, and possibly varicella. In April, the American College of Immunization Practices (ACIP) issued provisional recommendations for pertussis vaccination (Tdap) of all hospital HCWs, regardless of age and prior vaccine history (i.e., regardless of the time since last Td dose). Current hospital employees (and future hires) should receive a single dose of vaccine now, in one broad sweep to provide blanketed coverage of every hospital, and then continue to receive the usual booster vaccine recommended for adults.

Pertussis appears to be cycling up in our communities, especially in California, where 8,383 cases were reported in 2010, including 10 deaths in infants. Neonates and infants < 12 months of age are at the greatest risk for severe infection. For this reason, initial ACIP recommendations were to provide vaccination to all caregivers of small children, thus providing a protective "cocoon" of immunogenic individuals. The current recommendations expand on this philosophy, especially to physicians and nurses who provide care for infants and small children.

HCWs are at risk for pertussis exposure — both from their patients and fellow colleagues. Outbreaks of pertussis in the hospital setting can rapidly evolve, resulting

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in significant hours and effort to provide post-exposure prophylaxis to everyone exposed. Those who develop symptoms of pertussis are required to receive antibacterial therapy and are furloughed for a minimum of 5 days. In two separate outbreaks in Minnesota, 12% and 52% of cases occurred in HCWs who were exposed to either an ill index case or to each other. At our county hospital in the 1990s, an outbreak of a pertussis-like illness (pre-PCR test availability) necessitated the administration of chemoprophylaxis to more than 400 HCWs; a supreme effort over a Memorial day weekend, with significant cost to the hospital.[1]

HCWs who have received Tdap vaccine nonetheless require close monitoring for signs and symptoms for 21 days after pertussis exposure. Post-exposure prophylaxis is still recommended for vaccinated HCWs with documented exposure. Even mild respiratory symptoms (e.g., runny nose, sneezing, low grade fever, or cough) should prompt PCR testing for pertussis, receipt of antibiotics, and furlough from work for 5 days. The paroxysmal stage of pertussis, with the characteristic cough, generally only begins 1-2 weeks into the illness. ■

Reference

1. Martinez SM, et al. Azithromycin prophylaxis during a hospitalwide outbreak of a pertussis-like illness. *Infect Control Hosp Epidemiol* 2001;22:781-783.

Bacterial Meningitis: Rarer in Older Patients, but Equally Deadly

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

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Dr. Safdieh reports no financial relationship to this field of study. This article originally appeared in the July issue of Neurology Alert. At that time it was peer-reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Beal reports no financial relationship to this field of study.

Synopsis: *With the advent of new vaccines, the incidence of bacterial meningitis has declined, particularly in children, but the mortality rate has remained the same.*

Source: Thigpen MC, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med* 2011;364:2016-2025.

Bacterial meningitis is a feared medical illness that has a high morbidity and mortality rate. Meningitis can present in any age group, although the predominant pathogenic organisms do vary by age. Prior studies in the 1970s and 1980s have demonstrated that the most common causes of sporadic community-acquired bacterial meningitis in the United States are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, group B streptococcus (GBS), and *Listeria monocytogenes*. The introduction of the Hib vaccine reduced the overall incidence of bacterial meningitis by 55% by 1995. The authors of this study analyzed incidence patterns of bacterial meningitis in the United States from 1998-2007. A number of public health changes were introduced during the study period, including a meningococcal vaccine, a pneumococcal vaccine, and routine screening of pregnant women for GBS.

Coordinated by the CDC, the study authors reviewed a prospectively collected cohort of cases of bacterial meningitis in an infectious disease surveillance program at a number of geographically dispersed clinical sites, which included almost 8% of the United States population. Only cases of meningitis caused by one of the five organisms listed above were included in the study. The cases through the study period (1998-2007) were analyzed for trends and a latter portion of the group (2003-2007) was also analyzed for detailed epidemiology.

For the study period, 3188 cases of bacterial meningitis were identified with a mortality rate of 14.8%. The incidence of bacterial meningitis significantly decreased by 31% from the beginning to the end of the surveillance period (2 cases per 100,000 in 1998-1999 down to 1.38 cases per 100,000 in 2006-2007). The median age of patients significantly increased from the beginning to the end of the study period, from 30.3 years to 41.9 years. The overall case fatality rate over the study period remained unchanged. The most common organisms from 2003-2007 were *S. pneumoniae* (58%), GBS (18.1%), *N. meningitidis* (13.9%), *H. influenzae* (6.7%), and *L. monocytogenes* (6.7%). Through the study period, there were 4100 average annual cases of bacterial meningitis in the United States, with 500 annual deaths.

Rates of bacterial meningitis decreased most dramatically among children, causing the median age to rise. Overall, the pathogen with the most dramatic decrease over the study period was *S. pneumoniae*, which the authors suggest is due to pneumococcal vaccination. Of note, the rate of meningitis in children under age 2 months did not decrease, suggesting that GBS surveillance and treatment does not prevent late-onset disease, manifested as meningitis. *L. monocytogenes* did decrease in infants, which correlates with lower rates of maternal listeriosis, likely due to better education and a safer food supply.

■ **COMMENTARY**

This study demonstrates a number of important points. Bacterial meningitis is certainly becoming rarer over time, due to vaccination as well as better public health measures. Because of the overwhelming success of pediatric vaccines in preventing meningitis, the median age of bacterial meningitis is increasing. It is worth noting that the absolute incidence of bacterial meningitis did decrease in adults older than age 65 in the study period, but not as dramatically as in children. Although bacterial meningitis is less common now than it was in the past, the mortality rate remains unchanged. This is even more important to remember in the setting of declining incidences, as younger physicians may not see as many cases in training and therefore may fail to recognize and rapidly treat patients with meningitis. There is more work to be done, including widespread adoption of the adult pneumococcal vaccine. However, it is certainly encouraging to see the profound positive effects that can occur as a result of public health policies. ■

Hepatitis C Treatment by Primary Care Clinicians

By Louis Kuritzky, MD

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Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda. This article originally appeared in the July 29, 2011, issue of Internal Medicine Alert. At that time it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Roberts reports no financial relationship to this field of study.

Source: Arora S, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med* 2011;364:2199-2207.

In most communities in the United States, hepatitis C (HepC) treatment is provided by gastroenterologists. Because HepC is now the most common cause of end-stage liver disease, and — unless trends reverse — will continue to be so for the foreseeable future, it is important that identification of HepC infection be continued vigorously in the primary care community, since most at-risk persons see primary care clinicians as their point of initial contact with the health care system.

Treatment of HepC offers the opportunity for cure of the disease more than 50% of the time, although persons infected with HepC genotype I have a somewhat lower success rate. Ideally, treatment would be offered to as many infected persons as possible, yet limitations in specialist consultants who traditionally administer the treatment are an obstacle to access for some patients.

The ECHO program (Extension for Community Healthcare Outcomes) is intended to enhance opportunities for provision of health care to underserved populations through, for instance, video-conferencing technology that allows primary care clinicians to receive case-based education with specialist colleagues. Since 2003, ECHO has resulted in 800 HepC patients being treated by primary care clinicians. The primary outcome of this ECHO-based trial was sustained virologic response, which is defined as undetectable HepC RNA 6 months beyond the end of treatment. Encouragingly, analysis of outcomes for patients treated on-site at the University of New Mexico HepC clinic were essentially identical with those of patients treated at distant sites by clinicians guided though case-based video-conferencing. Hopefully, enlarging the spectrum of clinicians who can provide state-of-the-art care for HepC patients will become a goal for other sites that have the capacity for video-conferencing. ■

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.*

ACEIs and ARBs Help Patients with Aortic Stenosis

In this issue: ACEI/ARB therapy for AS; safety alert issued for dronedarone; statins and cancer risk; nesiritide and heart failure; and FDA actions.

ACEI/ARB therapy for aortic stenosis

Drugs that block the renin-angiotensin system are not only safe, they are beneficial in patients with aortic stenosis (AS) according to a new study. This runs counter to current recommendations that suggest that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are relatively contraindicated in patients with AS. The study looked at more than 2000 patients with AS in Scotland, of which the majority had mild-to-moderate stenosis, while about one-quarter had severe AS. Of the total number, nearly 700 were on ACEI or ARB therapy. Over a mean follow-up of 4.2 years, just over half the patients died, of which 48% died from cardiovascular (CV) deaths. Those treated with ACEIs or ARBs had a significantly lower mortality rate (adjusted hazard ratio [HR] 0.76; confidence interval [CI] 0.67-0.92; $P < 0.0001$) and fewer CV events (adjusted HR 0.77; 95% CI: 0.65-0.92; $P < 0.0001$) compared to those not on ACEIs/ARBs. The authors conclude that ACEI/ARB therapy is associated with improved survival and lower risk of CV events in patients with AS. These findings were consistent in patients with nonsevere and severe AS. The rate of valve replacement also was lower in patients treated with ACEIs/ARBs (*J Am Coll Cardiol* 2011;58:570-576). This study was a retrospective observational study and prospective, randomized, controlled trials are warranted to confirm these findings. ■

Drug safety alert issued for dronedarone

The antiarrhythmic dronedarone (Multaq) is again coming under scrutiny from the FDA after review of the company-sponsored PALLAS study of more than 3000 patients, which showed that the drug is associated with an increased mortality rate in patients with atrial fibrillation (AF). Dronedarone currently is approved for treatment of paroxysmal AF and atrial flutter. The new study investigated its use in patients with permanent AF. The study was halted early when the mortality rate in the treatment group was found to be double the rate in the placebo group (32 deaths [2%] in the dronedarone arm vs 14 [0.9%] in the placebo arm). The rate of unplanned hospitalization and stroke also was double in the dronedarone group vs the placebo group. All findings were statistically significant. These findings led the FDA to issue a drug safety alert on July 21, 2011. This follows a January 2011 drug safety alert regarding rare but severe liver injury associated with use of dronedarone. Currently, the FDA is recommending that physicians should not prescribe dronedarone to patients with permanent AF while they further evaluate the data (FDA Drug Safety Communication at www.FDA.gov/drugs/drug safety). ■

Statins do not increase risk of cancer

A new retrospective cohort analysis suggests that statins are not associated with an increased risk of cancer. Researchers used the General

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Electric Centricity electronic medical record database of more than 11 million adult Americans to match nearly 46,000 patient pairs by propensity scores receiving and not receiving statin therapy. With an average time in the database of 8 years, the incidence of cancer in patients taking a statin was 11.37% compared with 11.11% in matched patients not taking a statin (HR 1.04; 95% CI: 0.99-1.09). The authors conclude that this analysis demonstrates no statistically significant increase in cancer risk associated with statins, although they do suggest that more research is needed (*J Am Coll Cardiol* 2011;58:530-537). Lingering fears about cancer risk associated with statins was strengthened by the SEAS trial published in 2008, which showed the combination drug simvastatin/ezetimibe (Vytorin) was associated with a two-fold increase in the rate of cancer in a small group of patients. The FDA has continued to study these data along with data from other studies, but this new analysis adds significant evidence of a lack of association between statins and cancer. ■

Nesiritide and heart failure

Nesiritide can no longer be recommended for use in congestive heart failure based on the findings of a new study. The drug is a recombinant B-type naturetic peptide (BNP) that was approved in 2001 for use in patients with acute heart failure. The approval was based on small studies showing a reduction in pulmonary capillary wedge pressure and improvement in dyspnea 3 hours after administration. However, subsequent data raised questions about the drug's safety, especially with regard to worsening renal function and even increased mortality. Based on the recommendations of an independent panel, the manufacturer performed a placebo-controlled randomized trial of more than 7000 patients hospitalized with acute heart failure to assess the drug's safety and efficacy. Patients with heart failure were randomized to receive nesiritide or placebo for 24-168 hours in addition to standard care. The drug was modestly effective at reducing symptoms of dyspnea at 6 and 24 hours. More significantly, however, the rate of rehospitalization for heart failure or death from any cause within 30 days was no different. Nesiritide was not associated with a worsening of renal function but was associated with worsening hypotension. The authors conclude that on the basis of these results, "nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure" (*N Engl J Med* 2011;365:32-43). ■

FDA actions

The highly anticipated oral factor Xa inhibitor rivaroxaban has been approved by the FDA to reduce the risk of deep venous thrombosis, blood clots, and pulmonary embolism in patients undergoing knee or hip replacement. The once-a-day medication should be taken for 12 days by patients undergoing knee replacement and 35 days for patients undergoing hip replacement. The approval was based on three studies (RECORD 1, 2, and 3) which showed that rivaroxaban is superior to subcutaneous enoxaparin in this role. Bleeding, the primary side effect of the drug, was no more common with rivaroxaban than enoxaparin. Rivaroxaban also has been looked at in phase III trials for stroke prevention in patients with nonvalvular atrial fibrillation, and treatment and secondary prevention of venous thromboembolism, although the FDA has yet to act on approval for these indications. Rivaroxaban was developed by Bayer and is marketed by Janssen Pharmaceuticals as Xarelto.

The FDA has approved ticagrelor, a new antiplatelet drug for patients with acute coronary syndrome, including unstable angina and myocardial infarction (MI). The approval was based on studies that coupled ticagrelor with low-dose aspirin. The approval recommends use with aspirin although it carries a warning that aspirin doses above 100 mg per day may decrease the effectiveness of the drug. Ticagrelor requires twice a day dosing in contrast to the other drugs in this class, clopidogrel and prasugrel, which can be dosed once daily. The approval was based on the PLATO trial, a head-to-head study with clopidogrel which showed that in combination with aspirin, ticagrelor resulted in the lower composite endpoint of cardiovascular death, stroke, or MI (9.8% vs 11.7% with clopidogrel, $P < 0.001$).

The FDA has approved six manufacturers for the 2011-2012 flu vaccine. The strains included this year are A/California7/09 (H1N10), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 — the exact same components as last year's vaccine. One of the manufacturers, Sanofi Pasteur, has received permission to market Fluzone Intradermal, the first flu vaccine administered via a novel intradermal microinjection that is touted as being more comfortable than intramuscular injections. The new intradermal system in approved for adults ages 18-64 years. ■