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# Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

## ABSTRACT & COMMENTARY

# Maternal TB and Mother-to-child Transmission of HIV

***By Dean L. Winslow, MD, FACP, FIDSA***
*Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;*
*Clinical Professor, Stanford University School of Medicine*
*Dr. Winslow reports no financial relationships relevant to this field of study.*

***Synopsis:*** *In this study, 783 HIV-infected mother-infant pairs were evaluated as part of a randomized, controlled trial of nevirapine (NVP) given for 6 weeks vs. single-dose NVP to reduce mother-to-child transmission (MTCT) of HIV. Thirty percent of mothers with TB vs. 12% of mothers without TB transmitted HIV to their infants.*

**Source:** Gupta A, et al. Maternal tuberculosis: a risk factor for mother-to-child transmission of human immunodeficiency virus. *J Infect Dis*. 2011; 203:358-363.

In this study, 783 HIV-infected Indian mother-infant pairs participated in a randomized clinical trial comparing NVP given for 6 weeks vs. single-dose NVP to prevent MTCT of HIV among breast-fed infants. As a secondary study endpoint, multivariate logistic regression analysis was used to assess the impact of maternal TB occurring during pregnancy through 12 months post-partum. Of the 783 mothers,

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three had prevalent TB and 30 had incident TB by 12 months post-partum. Of the 33 mothers with TB, 10 (30%) transmitted HIV to their infants vs. 87 of 750 (12%) mothers without TB who transmitted HIV to their infants. In multivariate analysis, maternal TB was associated with 2.51-fold increased odds of HIV transmission, adjusting for maternal factors (HIV RNA, CD4+ count, and antiretroviral therapy) and infant factors (breast-feeding duration, infant NVP administration, gestational age, and birth weight).

### ■ COMMENTARY

This is an interesting study done in an area of the world with a high prevalence of TB, and emphasizes the inter-relatedness of TB and HIV in the developing world. While there were no differences at the time of enrollment into the trial in plasma HIV RNA between mothers diagnosed with TB vs. those without TB, the most likely explanation for the increased risk of HIV transmission in mothers with TB would be immune activation and, likely, increased mean HIV RNA levels in the TB-infected mothers, resulting in both increased transplacental, intrapartum, and post-partum transmission. Unfortunately, the design of the study precluded confirming this hypothesis, since post-enrollment maternal HIV RNA levels were not systematically collected. Other potential mechanisms (including maternal immune activation increasing levels of HIV RNA in breast milk and immune activation in the infants leading to increased susceptibility to MTCT) were postulated by the authors, but the design of the study precluded being able to examine these hypotheses.

TB in HIV-infected mothers has been shown to be associated with higher maternal and infant mortality.[1,2] Clearly, it is critical that efforts continue to focus on control of both of these scourges to human health, with particular emphasis on prevention and prompt treatment of maternal TB in HIV-infected women. ■

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## ABSTRACT & COMMENTARY

# And the Bands Played On

***By Stan Deresinski, MD, FACP***

***Synopsis:*** *Physicians may not be able to rely upon their clinical laboratory to accurately report the neutrophil "band count."*

**Source:** Geissal ED, Coffey T, Gilbert DN. Clinical importance of the failure to detect immature neutrophils by an automated hematology analyzer. *Infect Dis Clin Pract*. 2010; 18: 374-378.

KNOWLEDGE OF THE PRESENCE OF AN INcreased proportion of band neutrophils (neutrophils with non-segmented nuclei) is believed by many clinicians to assist them in the diagnosis and management of some patients with suspected or known infection. Automated hematology analyzers, however, are not capable of providing a "band count."

The identification of band neutrophils instead depends upon manual review of a blood smear. The need for such a review may be indicated as a result of the machine having detected a predetermined degree of abnormality, such as in the cell volume, cell number, or light scatter. This may be followed by a rapid visual scan of the smear and, then, if abnormalities are suggested by that review, by a more extensive examination with reporting, among other things, of the proportion of white blood cells (WBC) made up of bands and other earlier immature forms. Greissal and colleagues determined the overall sensitivity of this process in the detection of "bandemia" by comparing the proportion of smears with an increased proportion of band forms when processed with this screening procedure, or by routine visual examination of smears of all blood samples (i.e., the degree of sensitivity of flagging a possible abnormality by the automated analyzer).

In addition to other triggers, specimens were flagged if, in addition to other findings, the machine (Beckman Coulter LH 750) detected a total WBC < 3,000 cells/μL or > 30,000 cells/μL, or an absolute neutrophil count < 3,000 cells/μL or > 20,000 cells/μL. Blood from 101 consecutive patients with positive blood cultures was tested. The need for a quick visual examination of a smear was indicated for 87 of the patients, and complete visual examination confirmed bandemia in 42 of the 46 (91%) whose quick scan had indicated a need for full examination. The rapid exam was deemed to be negative and, therefore, not indicative of a need for a full examination in 41. Performance of a complete examination of these specimens found, however, that 20 had > 13% band forms on their peripheral blood smears. Thus, the rapid screen missed 20 of 41 (49%) patients with bandemia despite automated flagging. Complete smear examination of blood from the 14 patients whose specimens were not flagged found that 4 (29%) had > 13% band forms. Overall, using a conservative threshold for bandemia of > 13%, the standard process missed its detection in 24 of 101 (24%) of these selected patients.

The detection of bandemia is often of particular interest to the clinician evaluating patients who do not have leukocytosis, as was the case in 11 of these bacteremic patients with WBC 2,400-9,800 cells/μL. Four of the 11 were not flagged, and three of these had elevated band counts. In the other seven, rapid scanning of the smear was felt to not indicate the need for a complete examination but, in fact, four had bandemia. Thus, the normal process failed to detect bandemia in seven of 11 bacteremic patients who did not have leukocytosis.

## ■ COMMENTARY

While pathologists seem to often disagree, clinicians commonly believe that measurement of the percentage of band neutrophils is often useful in patient management. While some published evidence suggests that knowledge of bandemia is not useful, others suggest that knowledge of this may provide useful clinical information. One setting in which this may be so is in emergency departments. A very recent evaluation of 289 bacteremic patients seen in an emergency department found that one-third had a normal temperature (36°C-38°C) and 52% had a normal WBC.[1] Of the 210 patients who had a "full differential" performed, 172 (82%) had > 5% bands. The band count was elevated by this criterion in 79% of those with a normal total WBC and 80% with a normal temperature. Fifty-two patients had both normal temperature and WBC; 28 of these had a "full differential" and 21 (75%) had bandemia. Thus, knowledge of bandemia may be helpful as a clue to the presence of sepsis in patients in whom other suggestive findings are absent.

Careful examination of blood smears in order to determine the proportion of neutrophil bands is, unfortunately, time consuming and, therefore, adds significantly to the labor costs of a laboratory procedure that is otherwise totally automated. It would be desirable if automated systems could accurately detect band neutrophils.

The machine used by Greissal et al, the Coulter LH 750, examines 8,000 leukocytes per sample and determines cell volume for each cell type by measurement of direct current impedance, the internal cell composition by measurement of conductivity by radio frequency opacity, and cytoplasmic granularity by measuring light scatter with a laser. Neutrophils of septic patients have increased mean volume, as well as a greater distribution of volumes and decreased light scatter. Measurement of mean neutrophil volume and neutrophil volume distribution width has been reported to be more sensitive and specific as indicators of the presence of sepsis than manual band count, total neutrophil count, and CRP.[2] That, however, cannot be true for the patients in whom bandemia is not detected.

Greissal et al have performed a careful analysis of the sensitivity of a standard laboratory algorithm, starting with an automated analyzer in the detection of bandemia and found it wanting in patients with bacteremia. This finding was perhaps of greatest importance to the clinician in patients without other

common markers suggestive of sepsis, even with the use of a much higher threshold for bandemia (> 13%) than in the study by Seigel and colleagues (> 5%).

Thus, I believe that an accurate band count is of clinical value in the patient with suspected infection with a normal total WBC.[3] Another frequently encountered circumstance in which I, correctly or incorrectly, utilize the band count is in patients receiving corticosteroid therapy, which routinely causes leukocytosis. The detection of bandemia may provide a mechanism for judging whether the elevated WBC observed in a patient receiving corticosteroids is due to the medication alone or whether it is a reflection, at least in part, of inflammation, including inflammation resulting from infection.[4] The leukocytosis associated with prednisone administration consists of mature neutrophils, and one investigation found that the presence of > 6% band forms is suggestive of the presence of infection.[4]

Thus, while our pathology colleagues may not like it, I believe there is good reason to request full visual examination of blood smears to determine the presence of bandemia in selected circumstances. ■

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## ABSTRACT & COMMENTARY

# Leptospirosis in Florida: Recreational Exposures Herald New Serovars and Highlight Environmental Impact


***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 financial relationships related to this field of study.*



***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 one patient. Outbreaks of leptospirosis have become more commonly associated with adventure travel and sports activities, and highlight the effect the changing environment can have on infectious diseases.*



**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 develop 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, Florida. The race involved paddling, cycling, trekking, and orienteering, and took place in a swamp; the race occurred two 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 and, 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 one of three 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 two specimens).

Forty-four (23%) of the 192 interviewed racers met the definition for suspected leptospirosis, with a mean incubation period of about 13 days; three were hospitalized and none died. Cultures were attempted on the blood and urine of four patients, one of whom was positive for a novel serovar of species *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 multi-sport race in Malaysian Borneo.[2-4] This outbreak of leptospirosis in Florida was similar in many ways to past outbreaks, with patients demonstrating many classic signs and symptoms, a relatively high attack rate, and an incubation period of about two 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), most outbreak investigations seem to indicate that infection is most strongly associated 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 better suited to transmission of infectious diseases such as leptospirosis.[5,6] The passage of Hurricane Wilma over the race area two 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 related to recreational exposures 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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## ABSTRACT & COMMENTARY

# Paragonimiasis Acquired in the United States

***By Brian Blackburn, MD***

***Synopsis:*** *Nine cases of human paragonimiasis occurred after ingestion of crayfish in Missouri over a four-year period. Although rarely documented previously, this appears to represent a focus of autochthonous transmission of this parasite within the United States.*

**Source:** Centers for Disease Control and Prevention (CDC). Human paragonimiasis after eating raw or undercooked crayfish — Missouri, July 2006-September 2010. *Morb Mortal Wkly Rep*. 2010;59:1573-1576.

Paragonimiasis is caused by lung flukes of the genus *Paragonimus*, of which *P. westermani* is the best described. Humans acquire paragonimiasis primarily by eating undercooked crabs or crayfish infested with the parasite. Shortly after ingestion, patients may develop diarrhea, abdominal pain, fever, chest pain, eosinophilia, and cough. Subsequently, patients may develop eosinophilic pleural effusions, or bronchiectatic and cavitary lung disease with cough and hemoptysis, sometimes mimicking tuberculosis. Less commonly, lesions develop in the brain, skin, or other ectopic sites. Paragonimiasis is most highly endemic to East and Southeast Asia, but transmission occurs in Peru, Ecuador, Nigeria, Cameroon, and other areas.[1] While imported cases occasionally occur in the United States, infection acquired within the United States has been described only six times in the literature to date.[2] In North America, *P. kellicotti* causes infections among animals, but rarely humans.[1,2]

In Missouri, nine people who had developed paragonimiasis between 2006 and 2010 were identified by public-health officials. The patients were aged 10-32 years, and all had eaten raw or undercooked crayfish from rivers in Missouri (during the months of May-August) four months or less before illness onset. Seven (78%) patients were serologically positive for paragonimiasis (two of whom were also positive for *P. kellicotti* eggs in respiratory secretions), and two (22%) were clinically defined (but seronegative) cases. The patients presented with fever (100%), cough (100%), eosinophilia (100%), weight loss (56%), chest pain (44%), dyspnea (44%), and night sweats (44%). Five had eosinophilic pleural effusions, and other radiologic abnormalities included pulmonary nodules (44%),

pulmonary infiltrates (33%), and pneumothorax (11%). Four patients noted migratory skin nodules, one had cardiac tamponade, and one had cerebral lesions. All patients were treated with praziquantel and noted prompt resolution of their symptoms subsequently.

■ **COMMENTARY**

Paragonimiasis is a parasitic infection that predominantly affects the lungs, but through migration of the parasite can also cause skin lesions, pleural effusions, brain lesions, and eosinophilia. Because of the chronic presentation and cavitary lung disease, with cough and weight loss that often results, the disease is commonly confused with tuberculosis; another common misdiagnosis is eosinophilic pneumonia.

Although highly endemic to Asia, and an emerging infection in other parts of the world (such as Latin America and sub-Saharan Africa), paragonimiasis is rare in North America, with transmission described in only a handful of cases to date.[2] This report more than doubles the number of cases reported in the United States that appear to have resulted from autochthonous transmission. The public should be educated regarding the risk of raw freshwater crayfish or crab consumption, and clinicians should consider the possibility of this infection in patients with a consistent clinical picture, even if they have not left the United States.

Because clinicians do not usually consider paragonimiasis in the differential diagnosis of patients in the United States, this infection is probably underreported, and likely exists elsewhere in North America. A seventh case in North America (in Montreal, Canada) has also been reported, and numerous others have probably occurred that have not been reported.[3]

While the patients in this report presumably acquired their infections within the United States (given the compelling exposure histories and timing of illness onset), the authors did not mention the presence or absence of antecedent international travel in these patients. It is, therefore, at least possible that some of them may have traveled outside the United States in the months leading up to presentation, and acquired their infections abroad. Aside from this limitation, this report offers otherwise compelling evidence for a focus of autochthonous transmission of paragonimiasis in Missouri, and raises the possibility of transmission elsewhere in North America. Both the public and physicians in the United States should be better educated about the presence of this parasite, and measures should be undertaken to prevent exposure and to diagnose and treat those already infected. ■

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## ABSTRACT & COMMENTARY

# Management of Non-tuberculosis Mycobacterial Cervical Lymphadenitis in Children


***By Hal B. Jenson, MD, FAAP***

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*Chief Academic Officer, Baystate Medical Center, Springfield, MA*


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


***Synopsis:*** *A randomized, non-inferiority study of 12 weeks of antibiotic therapy (clarithromycin and rifabutin) versus observation only of non-tuberculous mycobacterial cervical lymphadenitis in children found no significant differences in median healing time (36 weeks versus 40 weeks, respectively).*

**Source:** Lindeboom JA. Conservative wait-and-see therapy versus antibiotic treatment for nontuberculous mycobacterial cervicofacial lymphadenitis in children. *Clin Infect Dis*. 2011;52:180-184.

A RANDOMIZED STUDY WAS CONDUCTED FROM JANUARY 2005 to December 2007 in Amsterdam, among 50 immunocompetent children 14-114 months of age (median age, 35 months) with culture- or PCR-confirmed non-tuberculous mycobacterial cervicofacial lymphadenitis. All children had erythematous, fluctuating lymphadenitis. Cultures were positive for 70% of children, and PCR results were positive for the remaining 30%. *Mycobacterium avium* (70%) and *Mycobacterium haemophilum* (24%) were the predominant mycobacterial species. Children were randomized to receive either a 12-week course of clarithromycin (15 mg/kg in 2 divided doses daily) plus rifabutin (5 mg/kg once daily) or observation only.

The median time to resolution of disease in the antibiotic group was 36 weeks (range, 20-64 weeks; IQR, 20-52 weeks) compared to 40 weeks (range, 20-68 weeks; IQR 31-47 weeks) for the observation group ($p = 0.38$, Mann-Whitney U test). In-vitro testing of isolates showed 91% susceptibility to clarithromycin and 94% susceptibility to rifabutin. Adverse effects of antibiotic therapy included abdominal pain (28%, occurring within 2 weeks), fever (60%, occurring within 2 weeks), and reversible extrinsic tooth discoloration (64%) that required treatment by a dental hygienist.

■ **COMMENTARY**

There have not been controlled clinical trials of surgery (either incisional drainage or excision) vs. antibiotics to guide management of non-tuberculous mycobacterial cervical lymphadenitis in children. Based on anecdotal reports and case series, the consensus-recommended management has been complete surgical excision whenever possible. Incision and drainage procedures have often been complicated by fistula formation and prolonged drainage. Excision is curative, but is also associated with scarring, and may be not be feasible with extensive infection, especially with lymph-node adherence to branches of the facial nerve. Temporary facial nerve weakness is reported in 20% of cases following surgery, with permanent facial weakness in 2% of cases.

Non-tuberculous mycobacterial infection in immunocompetent patients is benign, and all cases ultimately resolve, though spontaneous regression may take several months to 2-3 years. The advantage of surgical excision is faster resolution, which is offset by the adverse effects and cost of a three-month course of antibiotics. This study showed no significant differences in median healing time with antibiotic treatment vs. observation only. This finding confirms the traditional approach of not administering antibiotics. The study also showed that healing and resolution can be expected in approximately 40 weeks with observation alone. This finding suggests that the traditional approach of excision may be unnecessary in many cases. ■

## ABSTRACT & COMMENTARY

# Health Care Workers in the Developing World: Disease Transmission Risk and Mitigation

***By Brian Blackburn, MD, and Michele Barry, MD, FACP***

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*Dr. Barry retained consultant for the Ford Foundation and has received research or grant support from Johnson & Johnson Corporate Foundation, the Doris Duke Foundation, and the National Institutes of Health.*

*This article originally appeared in the February 2011 of* Travel Medicine Advisor. *It was edited and peer reviewed by Frank J. Bia, MD, MPH. Dr. Bia is Professor (Emeritus) of Internal Medicine (Infectious Disease and Clinical Microbiology), Yale University School of Medicine; he reports no financial relationships relevant to this field of study.*

***Synopsis:*** *The recent explosion of overseas training opportunities for health-care workers and medical researchers brings with it unique risks and exposures, such as to needlestick injuries, hemorrhagic fever viruses, tuberculosis, and severe respiratory viruses. These issues require special measures for risk mitigation.*

**Source:** Kortepeter MG, et al. Health care workers and researchers traveling to developing-world clinical settings: Disease transmission risk and mitigation. *Clin Infect Dis.* 2010;51:1298-1305.

Only limited data are available regarding the epidemiology of infectious diseases that occur among traveling health-care workers (HCWs) or medical researchers. Providing prophylaxis and vaccinations, bringing protective personal equipment, and having medical countermeasures, such as post-exposure antiretroviral blister packs and antibiotics, are reviewed. Four special areas are targeted: needlestick injuries, hemorrhagic fever viruses, emerging severe respiratory viral infections (such as SARS-CoV and H1N1 influenza), and drug-resistant tuberculosis.

Regarding needlestick exposures, the authors suggest a pre-travel discussion of management and prevention. HCWs are advised to set up a "sharps" container, even using a soda can or plastic laundry detergent bottle. Not only can HIV and hepatitis viruses be contracted by needlestick, but Ebola and Lassa viruses, syphilis, dengue, and even malaria may be contracted in this way; fatal cases of malaria have occurred after needlestick exposure.[1] The authors suggest administration of hepatitis B immunoglobulin if an injury is sustained by a non-immune HCW. They also suggest considering administration of hepatitis B immunoglobulin for non-immune HCWs prior to travel. Those who suffer needlestick injuries also should be followed for the possibility of hepatitis C infection.

Needlestick transmission of HIV should be addressed with post-exposure prophylaxis, initiated preferably immediately, and not later than three days after exposure. This should be continued for 4 weeks; the World Health Organization recommends two nucleoside reverse-transcriptase inhibitors, and three drugs if there is > 15% antiretroviral resistance in the community. The CDC recommends a three-drug regimen if the source patient is known to be infected with HIV and the source device is a hollow-bore needle or has visible blood contamination; they recommend zidovudine, stavudine, or tenofovir plus emtricitabine or lamivudine, and when a third drug is added, both the CDC and the WHO recommend a ritonavir-boosted protease inhibitor. Follow-up for needlestick injury should include serologic testing for HIV, viral hepatitis, and syphilis at 3 months and HIV RNA testing at 2, 6, 12, and 24 weeks, as well as with any acute febrile illness post-needlestick injury.

The WHO and CDC have developed viral hemorrhagic infection-control recommendations for African health-care settings.[2] In a post-exposure setting, treatment or prophylaxis measures can be instituted with specific antivirals directed at certain hemorrhagic fever viruses.[2]

Infection with some respiratory viruses such as SARS-CoV or influenza (H5N1 and H1N1) can cause severe infections in HCWs. Protective measures to mitigate risk include contact and respiratory precautions, diligent hand-washing, and N95 respirators when high-risk procedures that generate aerosols, such as intubation, are undertaken. Influenza vaccination for HCWs is recommended, and chemoprophylaxis with neuraminidase inhibitors may be indicated in certain settings.

Drug-resistant tuberculosis is a potential threat, and extensively drug-resistant (XDR)-TB has been reported in 58 countries, and both multidrug-resistant and XDR-TB represent serious occupational risks to HCWs working overseas. Before departure, the risk of tuberculosis at the destination should be assessed, and the authors recommend that HCWs should be screened for latent tuberculosis by an interferon gamma release assay (IGRA). If the assay is negative, the authors recommend considering BCG immunization 2-6 months before departure. Rescreening the HCW with a repeat IGRA two months after return is recommended as well. The authors strongly suggest fit testing with a disposable filtering facepiece respirator, as negative air pressure rooms are unlikely to be available overseas. When latent tuberculosis is diagnosed after travel to high-risk areas, the authors emphasize that infection with MDR- or XDR-TB should be considered and treatment might consist of either ethambutol or pyrazinamide plus levofloxacin or moxifloxacin for 6-12 months.

## ■ COMMENTARY

With the explosion of global-health programs in

the United States, the number of HCWs and researchers traveling abroad has increased dramatically. The authors suggest that this type of travel exposes HCWs to different risks than the usual traveler experiences. Although this review provides practical guidance to mitigate potential occupational infectious disease transmission, a few of the recommendations are controversial, or difficult to administer, in a low-resource setting. For example, BCG vaccination has never been shown to be effective in adults, but the authors, and certain advisory boards, recommend using it for HCWs in high-risk areas. In addition, although seronegative HCWs may remain at risk for hepatitis B if exposed, it would be highly unlikely that hepatitis B immunoglobulin would be available in a low-resource setting after a needlestick injury. ■

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## CME Questions

22. Which of the following accurately describes the transmission/epidemiology of paragonimiasis?

a. Ingestion of marine crustaceans can lead to infection with Paragonimus.
b. Paragonimiasis is most highly endemic to the Middle East.
c. Paragonimiasis can be acquired in the United States.
d. A risk factor for paragonimiasis is close contact with farm animals.
e. Paragonimiasis is most commonly acquired through larval penetration of skin.

23. Which of the following is the usual source of leptospirosis infection?

a. Ingestion of leptospira-infested undercooked crayfish
b. Exposure to an individual with leptospirosis
c. Exposure to water contaminated with leptospira
d. Ingestion of contaminated food

24. Which of the following was the most common species causing non-tuberculosis mycobacterial lymphadenitis in Amsterdam in the study by Lindeboom?

a. *Mycobacterium avium*
b. *Mycobacterium haemophilum*
c. *Mycobacterium scrofulaceum*
d. *Mycobacterium xenopi*

Answers: 22. (b); 23. (c); 24. (a)

## CME Objectives

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

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

[IN FUTURE ISSUES]

What's New in the Management of Sexually Transmitted Disease

# UPDATES

By Carol Kemper, MD, FACP

## MDR-TB in South African healthcare workers

**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 TB HOSPITAL in KwaZulu-Natal, South Africa for treatment of MDR- and XDR-TB from 2003 to 2008 were examined for healthcare workers (HCWs) compared with non-HCWs.

During this period of time, 4,151 non-HCWs and 231 HCWs (≥ 20 yrs of age) with either MDR-TB or XDR-TB were admitted. From 2003-2008, the number of hospital admissions for MDR-TB increased from 440 cases to 1,028 cases (43 HCWs) and the number of admissions for XDR-TB increased from 6 cases to 114 cases (12 HCWs). The mean age and HIV status of the two groups were similar (55% of HCWs vs. 57% of non-HCWs were HIV+), although more of the HIV+ HCWs were receiving antiretroviral therapy.

The estimated incidence of MDR-TB in HCW 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%, $p < .0001$), suggesting that while resistance may be acquired in non-HCWs as the result of inadequate treatment or non-compliance, HCWs were more like to acquire organisms already drug-resistant.

Nosocomial transmission of TB represents a significant threat to HCWs, and 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 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%). Although the occupation of the HCWs were not specified, this finding suggests that women were more likely involved in direct patient care and, therefore, at greater risk for exposure.

## Xpert MTB/RIF Assay for TB

**Source:** Boehme CC, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363:1005-1015.

THIS ARTICLE EXAMINES THE SPECIFICity and sensitivity of the Xpert MTB/RIF test, which is an automated molecular test for detecting MTb and resistance to rifampin using real-time PCR in sputum specimen. A total of 1,462 patients were included in this project, 39% of whom had smear- and culture-positive pulmonary TB, 12% of whom had smear-negative and culture-positive pulmonary TB, and 7% of whom had a clinical diagnosis of pulmonary TB with negative smears and cultures. The remaining patients did not have TB and served as controls. Patients contributed 4,386 sputum samples for analysis. To briefly summarize the study's findings, the Xpert MTB/RIF test correctly identified 551/561 smear-positive specimens (98.2%) and 124/171 smear-negative specimens (72.5%). The sensitivity of the assay improved to 90.2% if three specimens were tested. The assay had a high degree of specificity, correctly identifying 604/609 negative specimens (99.2%). It correctly identified 97.6% of rifampin-resistant strains and 98.1% of rifampin-sensitive strains.

In a subgroup of 115 patients with culture-negative tuberculosis with suspected drug resistance, the Xpert MTB/RIF test identified 51 sputum TB specimens, eight with rifampin-resistance. All eight patients were subsequently treated with second-line therapy for suspected drug resistance — although the clinicians were unaware of the results of the Xpert MTB/RIF research test results. Therefore, the assay successfully recognized drug resistance in patients receiving active treatment even after culture conversion.

## Death and Resistance

**Source:** Levin PD, et al. End-of-life treatment and bacterial antibiotic resistance: A potential association. *Chest*. 2010;138:588-594.

LEVIN AND COLLEAGUES EXAMINED THE relationship between prolonged critical-care and end-of-life decisions and the presence of colonization or infection with drug-resistant bacteria. Culture results were reviewed for

423 patients receiving critical care in two different hospitals for more than 48 hours, and risk factors for acquisition of resistant bacteria were examined using logistic regression analysis.

Cultures yielded drug-resistant organisms in 82 patients (19%). Patients with drug-resistant organisms were more likely than those without to be diabetic and to have been transferred from another facility, and to have received a higher number of days of antibacterial therapy (19 vs. 14 days, $p = .005$). Although length of stay in the ICU was similar for both groups, patients with drug-resistant organisms required more prolonged mechanical ventilation (10 vs. 7 days, $p = .03$), had a greater number of central-line days (10 vs. 7 days, $p = .03$), and were significantly less likely to have had limitations of care ordered (11% vs. 26%, $p = .014$). The only independent risk factor identified in multivariate analysis was an order for limitation of care. At the time of death, 11% of those with limitations of care vs. 39% with ongoing critical care had recognized colonization or infection with drug resistant organisms ($p = .003$).

End-of-life critical-care treatment is associated with an increased risk of colonization or infection with resistant organisms. Not stated was whether critical-care patients were routinely screened for resistant organisms (e..g, nares, MRSA, screening cultures), as is being done in some hospitals. And it seems apparent that some bias may be introduced, as patients receiving ongoing critical care are more likely to have cultures performed. And rather than prolonged critical care increasing the risk of resistant bacteria — but bacterial resistance may contribute to the need for more prolonged care and increased risk of death.

The authors suggest that, regardless of the causal relationship, patients receiving prolonged critical care present a "reservoir" for drug-resistant organisms in the hospital. The use of private rooms, contact isolation precautions, augmented surveillance, more aggressive environmental cleaning, and improved hand hygiene have all been demonstrated to mitigate this threat — at significantly increased cost to hospitals.

## MRSA Decolonization for Cardiac Surgery

**Source:** Walsh E, et al. Sustained reduction in methicillin-resistant *Staphylococcal aureus* wound infections after cardiothoracic surgery. *Arch Intern Med*. 2010; (pub. online Sept. 2010).

THE STATE OF CALIFORNIA HEALTH AND Safety Code Regulations now require hospitals to screen certain high-risk groups within 24 hours of hospital admission for MRSA colonization, including patients admitted for total hip arthroplasty, total knee replacement, cardiac surgery, and any patient admitted from a long-term care facility (though expensive, this approach has helped to reduce hospital-onset MRSA rates). Unfortunately, these regulations do not provide guidance to physicians about what to do with a positive result, and often the result is available only after the procedure is completed.

Walsh and his group compared rates of post-operative wound infection 3 years before and 3 years following initiation of a MRSA intervention program. The program began by screening all 98 members of the cardiac surgery team (two nurses with nasal colonization received mupirocin). Subsequently, all cardiac surgery candidates were pre-screened for nasal colonization 24 to 72 hours before admission, or as soon as possible if transferred from an outside facility (swab cultures were performed on chromager plates using standard procedures); beginning the day prior to surgery, mupirocin intranasal ointment was used in all patients and continued for 5 days (regardless of MRSA screening culture results); chemoprophylaxis with parenteral vancomycin was given to all patients with recognized MRSA colonization (in addition to standard cefazolin prophylaxis); mupirocin-soaked dressings were applied to chest tube and mediastinal tube exit sites; and repeat nares screening cultures were done at discharge.

Prior to initiation of the program, rates of cardiac surgical site infection (SSI) were 2.1% (half of which was attributed to MRSA). Once the program was begun, a total of 2,496 patients were screened, and 56 (2.2%) had nasal colonization with MRSA. Three had persistently positive nares cultures at discharge. Following initiation of the program, the overall rate of cardiac SSI fell to 1.2, with a 93% reduction in MRSA SSI.

A difference in this study from other decolonization protocols was the use of mupirocin in all patients requiring cardiac surgery, not just those with MRSA. This eliminates the necessity of having culture results in hand when prescribing mupirocin the day prior to surgery — although this approach increases mupirocin exposure and risk of resistance to this agent. Chemoprophylaxis with vancomycin was reserved for those patients with a positive culture result. The frequency of vancomycin adverse drug reactions and "red-man syndrome" are too great to risk the use of this agent in all patients, and would result in too many aborted procedures.

While the authors admit that hand hygiene rates also significantly improved during the period of observation, no mention was made of changes in pre-surgical scrubs. An alternative to the prophylactic use of antimicrobials, the use of improved chlorhexidine-alcohol pre-surgical scrubs also has been shown to significantly reduce the risk of SSI.[1] ■

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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.*

# Escitalopram for Menopausal Hot Flashes

***In this issue:*** Escitalopram for menopausal hot flashes, rifaximin for IBS without constipation, herpes zoster vaccination, antiepileptics drugs and fracture risk, and FDA Actions.

## Escitalopram for hot flashes

Since the Women's Health Initiative was published in 2003, the use of hormone therapy for the treatment of postmenopausal hot flashes has dropped dramatically. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been studied to relieve postmenopausal symptoms, but no agent has been conclusively shown to be effective. A new study suggests that escitalopram (Lexapro™) may offer some relief.

In a study recently published in the *Journal of the American Medical Association*, 205 menopausal women were randomized to 10-20 mg per day of escitalopram or matching placebo for 8 weeks. The primary outcome was the frequency and severity of hot flashes with the average hot flash frequency at nearly 10 per day at baseline. Escitalopram resulted in 1.41 fewer hot flashes per day compared to placebo ($P < 0.001$), although both the active drug group and placebo groups noted reductions. Escitalopram also reduced hot flash severity. There was no difference among women of different races, and the discontinuation rate was small. The authors concluded that escitalopram 10-20 mg per day compared with placebo resulted in fewer and less severe menopausal hot flashes at 8 weeks (*JAMA* 2011;305:267-274). Whether the same effect can be expected with racemic citalopram (Celexa™) is unknown. ■

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## Rifaximin for IBS without constipation

Rifaximin, an oral, nonsystemic (poorly absorbed) broad-spectrum antibiotic, may help relieve symptoms of irritable bowel syndrome according to two identically designed studies published in the *New England Journal of Medicine*. A total of 1060 patients who had IBS without constipation were randomized to rifaximin 550 mg three times daily for 2 weeks or matching placebo. The primary endpoint was a proportion of patients with adequate relief of global IBS symptoms; the secondary endpoint was relief of bloating. Significantly more patients in the rifaximin group had adequate relief of IBS symptoms during the first 4 weeks of treatment (40.7% vs 31.7%; $P < 0.001$), as well as improvement in bloating (40.2% vs 30.3%; $P < 0.001$). The incidence of adverse events was similar in the two groups. The authors concluded that among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of the IBS symptoms of bloating, abdominal pain, and loose or watery stools (*N Engl J Med* 2011;364:22-32).

An accompanying editorial points out that the benefit from rifaximin was sustained over 10 weeks after a short 2-week treatment course, but also points out that benefit of the drug was a mere 9%-12% improvement over placebo, barely clinically relevant. Still, for patients who have IBS without constipation who have not responded to other therapies, a single treatment

cycle could be tried (*N Engl J Med* 2011;364: 81-82). ■

## Herpes zoster vaccination rates and incidence of shingles

The herpes zoster vaccine cuts the rate of shingles by 55% in the elderly population according to a new report in the *Journal of the American Medical Association*. Researchers at Kaiser Permanente in Southern California performed a retrospective cohort study of health plan members, 75,000 of whom were vaccinated against shingles (age 60 and older) and 225,000 age-matched controls who did not receive vaccine. The rate of herpes zoster was 6.4/1000 person-years in the vaccinated group and 13.0/1000 person-years in the unvaccinated group (hazard ratio, 0.45; 95% confidence interval, 0.42-0.48). Reduction in herpes zoster occurred in all age groups and among individuals with chronic disease. The rate of ophthalmic herpes zoster and hospitalizations for herpes zoster were also significantly reduced.

The authors of the study concluded that among immunocompetent community-dwelling adults age 60 and older, receipt of the herpes zoster vaccine was associated with a lower incidence of herpes zoster (*JAMA* 2011;305:160-166). The study is important because only 10% of those aged 60 and older received the shingles vaccine in 2009, whereas nearly one of three people in the United States will develop shingles in their lifetime. ■

## Fracture risk with antiepileptic drugs

Most antiepileptic drugs (AEDs) are associated with an increased risk of nontraumatic fracture according to a retrospective match cohort study. Nearly 16,000 patients with a history of prior AED use (carphenazine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrogine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, or vigabatrin) were compared to up to three matched controls each. Rates of fractures of the wrist, hip, and vertebrae were measured between 1996 and 2004. A significant increase in fracture risk was found for most AEDs, with an adjusted odds ratio of 1.24 for clonazepam to 1.91 for phenytoin. The only AED not associated with increased fracture risk was valproic acid.

The authors concluded that most AEDs are associated with an increased risk of nontraumatic fractures in individuals age 50 or older. They suggested that the risk of fracture with newer AEDs needs to be determined, as well as the effect of bone protective medications in this population (*Arch Neurol* 2011;68:107-112). The mechanism of increased fracture risk in patients using AEDs is unknown, but may be related to accelerated vitamin D catabolism, calcium absorption, or an effect on osteoblasts. ■

## FDA Actions

**The FDA has approved vilazodone hydrochloride for the treatment of depression in adults.** The drug is a selective serotonin reuptake inhibitor as well as a partial agonist of the 5HT 1a receptor. The drug was approved in dosages of 10 mg, 20 mg, and 40 mg for major depressive disorder or major depression. Vilazodone is touted as having fewer sexual side effects than other antidepressants. It carries the same boxed warning as other antidepressant regarding suicidal thinking and behavior in children, adolescents, and young adults. Vilazodone will be marketed by Clinical Data Inc. as Viibryd™.

**The FDA is limiting the amount of acetaminophen in combination prescription pain medications.** The new requirement limits the amount of acetaminophen to 325 mg in each tablet or capsule. Common medications that will be affected include codeine (acetaminophen with codeine), oxycodone (Percocet®), and hydrocodone (Vicodin®). Over-the-counter acetaminophen products are not affected. This action is being taken to limit acetaminophen-related liver failure. It is felt that lowering the amount of acetaminophen in these products will have minimal effect on efficacy for treating pain. The change will be phased in over 3 years.

**The FDA has approved a new transmucosal form of fentanyl for the treatment of breakthrough pain for adults with cancer.** The drug is indicated for the management of breakthrough pain in patients with cancer ages 18 and older, who use opiate pain medication around the clock. Breakthrough pain is defined as pain that comes on suddenly for short periods of time and is not alleviated by the patient's normal pain management plan. Patients must be opioid-tolerant to qualify for use with transmucosal fentanyl. The drug is available only through a Risk Evaluation and Mitigation Strategy (REMS) program, which is intended to minimize risk of misuse, abuse, addiction, and overdose. Fentanyl sublingual tablets are available as 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg strengths. Fentanyl sublingual tablets are marketed by ProStrakan Inc. under the trade name Abstral®. ■