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Vesico-Vaginal Fistula, Violence, and Voluntourism

ABSTRACT & COMMENTARY

By Jennifer S. Hsu and Philip R. Fischer, MD, DTM&H

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Ms. Hsu and Dr. Fischer report no financial relationships relevant to this field of study.

Synopsis: *More than a million women currently suffer with vesico-vaginal fistula. Increasingly, "medical voluntourism" provides a means for compassionate professionals to helpfully visit afflicted people.*

Source: Kirschner CV, Yost KJ, Du H, et al. Obstetric fistula: The ECWA Evangel VVF Center surgical experience from Jos, Nigeria. *Int J Urogynecol J* 2010; 21:1525-1533.

In areas of limited maternal care across Africa, obstructed labor leads to stillbirth and necrosis of maternal tissues. Resulting vesico-vaginal fistulas can be amenable to surgical repair. In central Nigeria, 926 women underwent fistula repair during a six-year period, 90% via a trans-vaginal approach. Continence was achieved in 71% of patients and was most likely if there was an intact urethra, an upper or mid-vaginal fistula, and limited fibrosis. Surgical morbidity was low.

■ COMMENTARY

Obstetric fistula is an abnormal opening either between the vagina and urinary bladder (vesico-vaginal fistula, VVF) or between the vagina and rectum (recto-vaginal fistula, RVF). Generally caused by prolonged obstructed labor, obstetric fistulas affect adolescent and adult females (average age 15 years at marriage), particularly those who are poor, illiterate, and living in rural areas.[1] Underlying child malnutrition and poverty often stunt the growth of affected girls' skeletal structures, including the pelvis, contributing to obstructed labor during childbirth and to obstetric fistula. The World Health Organization (WHO) estimates that there are more than two million young women in sub-Saharan Africa and Asia living with obstetric fistula.[2]

Another, less widely recognized cause of VVF and RVF is sexual violence. Sexual violence often is used as a weapon of war to spread terror, fear, and humiliation among civilians. After being raped by armed groups, a woman may have objects such as tree branches and bottles forced into her vagina. Some are shot, with a gun barrel forced into the genitourinary area. As a result, women suffer from genital injuries and traumatic gynecological fistula. At one hospital in the Democratic Republic of the Congo (DRC), between April 2003 and

June 2006, 702 of the 4,715 women and girls who were victims of sexual violence had genital fistulas.[3] Another study showed that 36 of 2,020 sexual violence survivors seen between 2002 and 2004 had suffered from traumatic fistula.[4] Rape of young adolescents with small pelvises also can lead to obstructive labor and obstetric fistulas, even if the original violent rape did not leave traumatic physical damage.

Fistulas can lead to urinary incontinence and persistent urine or feces leaking uncontrollably through the vagina. The effects on the health and well-being of sexual violence victims are devastating. Besides physical harm, VVF and RVF are also linked to severe psychological consequences for victims, including depression and post-traumatic stress disorder, as well as social and emotional consequences such as social ostracism and rejection by their families and friends. Because of the stench resulting from constant uncontrollable flows of waste, victims who have VVF or RVF often are shunned.

Traumatic gynecological fistula is a problem that remains relatively unknown since it affects those who are powerless in society.[5] Sexual violence is under-reported because women often are reluctant to disclose and receive treatment due to shame, stigma, feelings of self-blame, and fear of reprisals.[6] Thus, the majority of data is based on sexual violence victims seeking treatment at health facilities. Currently, much of the reported work on obstetric and traumatic fistulas comes from Nigeria,[2] Ethiopia,[7] and Democratic Republic of the Congo[3,8-11]; humanitarian groups can be helpfully involved.[12]

Sexual violence is an ongoing global public health issue that not only affects women in every country, but also the communities, making it an "effective" weapon of war. For more than a decade, the Democratic Republic of the Congo has experienced continuous civil conflict and violence. According to UN Emergency Relief Coordinator John Holmes, "sexual violence in the Congo is the worst in the world."[13] According to the United Nations Population Fund (UNFPA), there are roughly 1,100 rape cases reported each month in the DRC.[14] The eastern part of the DRC is likely to have the world's highest number of traumatic gynecologic fistula injuries.[15]

The humanitarian community has an important role to play in preventing and responding to sexual violence crises. The first is to raise awareness of traumatic gynecological fistula, its etiology, and opportunities for treating it. Health care workers should be aware of the problem and know how to respond properly. Comprehensive protocols addressing the medical, psychological, and legal consequences of rape as relevant to victims could also be useful.[16]

Stories of traumatized girls and women touch our hearts. Consider the excerpted testimony of 12-year-old Byamungu: "One day when we were returning from the market, I felt a need to open my bowels. Since the only place to go was in the forest, I entered to relieve myself. But my hour of darkness had come. Suddenly a group of men appeared behind me. One of them grabbed me by the hand. I screamed, but my frightened companions were already running away. I was facing eight beasts who first robbed me, then dragged me into the bush, stripped me naked and raped me repeatedly. When they were done they left me there bleeding until a group of women found me. Feces and urine flowed out of the same opening in

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my body."[3]

Eco-tourism became popular as travelers saw informational and service trips as a means to promote conservation of natural resources. Increasingly now, pre-travel consultation is sought by professionals engaged in "medical voluntourism" as they seek to use their knowledge and skills to help victims of poverty, war, and even sexual violence.

Unfortunately, even well-intentioned individuals can intervene in ways that hurt patients, weaken health care systems, and foster dependency. Written from Christian perspectives, three books can help guide voluntourists either of any, or of no particular faith-base, toward less harmful and more helpful interventions. *Ministering Cross-Culturally*[17] helps travelers identify cultural variations as distinct from compromised values. *Compassion, Justice, and the Christian Life*[18] and *When Helping Hurts*[19] help medical voluntourists appropriately target whether interventions should be focused on rescue and relief (in the early days after an earthquake, for instance), recovery (possibly weeks after a disaster, when services are still compromised), or development (such as when chronic poverty and limited health infrastructure are the main problems). ■

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Occupational Transmission of *Neisseria meningitidis*, California, 2009

ABSTRACT & COMMENTARY

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

Synopsis: *Prevention of occupational transmission of meningococcal disease depends on immediate reporting of suspect cases to local health authorities and the use of proper infection control measures by health-care and emergency responder personnel.*

Source: Occupational transmission of *Neisseria meningitidis*, California, 2009. *Morbid Mortal Wkly Rep* 2010;59(45):1480-1483.

On December 11, 2009, the California Department of Public Health (CDPH) began an investigation into two secondary cases of meningococcal disease following occupational exposure to an unconscious adult. The index case was a 36-year-old male, and the secondary cases were a police officer and a respiratory therapist.

On December 3, 2009, four police officers arrived on the scene to find the index patient in bed, unconscious, with his airway partially obstructed by vomitus. One of the police officers (PO1) turned the patient to the side and adjusted the patient's head to aid in breathing. Immediately after, PO1 left the room and returned once, but never again within 3 feet of the patient. The index patient was then transferred to Hospital A, where a respiratory therapist (RT1) assisted with endotracheal intubation and suctioning. On December 4, gram-negative diplococci were identified in the index patient's CSF and several hours later in blood. On December 6, *N. meningitidis* was isolated from blood, and the following day from CSF. The patient was managed in the intensive-care unit (ICU), treated with appropriate antibiotics, and survived.

Forty-eight hours after PO1 assisted in the case, he began experiencing sore throat and nausea that eventually progressed to fever, vomiting, and muscle pain. He saw his primary care physician 4 days later (December 9), and after a colleague of PO1 called with information about possible meningitis exposure, PO1 was sent directly to Hospital B for admission and IV antibiotics. On Dec 10, gram-negative diplococci were identified in the blood of PO1, and the following day blood and CSF cultures were positive for *N. meningitidis*. PO1 was treated with IV antibiotics and discharged to home after 5 days in Hospital B.

On December 8 (5 days after exposure), RT1 had onset of weakness, chills, and fatigue. On December 11, gram-negative diplococci were identified in the blood and CSF of RT1, and the next day blood and CSF were culture-positive for *N. meningitidis* at Hospital C. After treatment with ceftriaxone, vancomycin, and meropenem, RT1 also survived and was discharged to home after 11 days of hospitalization.

N. meningitidis serogroup C, ST-11 clonal complex was isolated from both the index case and the two secondary cases, PO1 and RT1. The isolates were indistinguishable by pulse-field gel electrophoresis. The state of California requires health-care providers to report immediately by telephone any suspected cases of meningococcal disease to the local health authority. In the case of Hospital A, this report was delayed for 3 days. In addition, Hospital A did not conduct an exposure assessment of affected employees until 8 days post-exposure — essentially after learning of RT1's hospitalization. Hospital B's reporting was actually on time, but Hospital C's reporting was one day late. The other staff in the emergency room of Hospital A (one physician, 2 nurses, and another respiratory therapist) were offered post-exposure chemoprophylaxis (PEP) 8 days postexposure. Ideally PEP should be given < 24 hours or as soon as possible after an identified exposure. Two paramedics at the initial scene were offered PEP 4 days after exposure, and one firefighter at 5 days after exposure. Neither PO1 nor RT1 were ever contacted or offered PEP before their illnesses.

In the emergency room, neither the physician nor RT1 wore any type of mask or respirator during suctioning and the intubation procedure. Neither of the two nurses in the ER administering IV fluids and caring for the index patient wore any type of mask either. Another respiratory therapist caring for the patient did wear a surgical mask with a face shield. The emergency personnel performed better, with both paramedics and both firefighters wearing N95 respirators. PO1 wore only gloves.

■ COMMENTARY

This is the first time more than one occupationally acquired case of meningococcal disease has occurred after exposure from the same index case. These three patients were indeed fortunate in that all survived — especially as case fatality rates for meningococcal meningitis and sepsis range from 10-14%.[1]

There were significant delays in notification to the local health authorities, worker exposure assessment, and timely use of PEP. There were also significant breaches in proper infection control policies by the emergency room staff.

The California Division of Occupational Safety and Health Aerosol-Transmissible Diseases (Cal/OSHA ATD) requires droplet precautions for all contact with suspected or confirmed cases of meningococcal disease.[2] In the case of the index patient, the differential diagnosis included pandemic H1N1, so N95 respirators for airborne protection should have been used. As of September 2010, Cal/OSHA ATD is now recommending that employers provide a powered air-purifying respirator (PAPR) with a high-efficiency particulate air (HEPA) filter, or an equivalent respirator, to all employees who perform high-hazard procedures on patients with suspected airborne infectious diseases. The big obstacle to overcome will still be the human factor, i.e., the use of any such protective devices still will depend on health care personnel to actually wear them. However, the PAPR system seems more acceptable to health-care personnel.

PEP is recommended for close contacts of patients with meningococcal disease. The CDC Advisory Committee on Immunization Practices (ACIP) defines close

contacts as: household members; child-care center personnel; and persons directly exposed to the patient's oral secretions (i.e., by kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management).[1] Therefore, the policeman's (PO1) case is disconcerting, as his exposure was very brief and he did not recall any droplets on his skin or face. Infectious disease doctors often receive phone calls of this nature from our medical colleagues asking for advice. This report will no doubt influence our future decisions on similar cases that are outside the established parameters of meningococcal risk exposure. ■

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

ABSTRACT & COMMENTARY

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Dr. Barry is a 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. Dr. Blackburn reports no financial relationships related 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(11):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 3 drugs if there is >15% antiretroviral resistance in the community. The CDC recommends a 3-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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Sushi Delight: Uncooked Seafood and Anisakidosis

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD

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

Synopsis: *In 1960 Van Thiel identified the nematode responsible for ascarids most often vomited. More recently, anisakidosis has been increasingly identified as the cause of gastric, intestinal, and allergic syndromes in humans who have either occupational exposures to or who consume uncooked seafood.*

Source: Hochberg NS, Hamer DH. Anisakidosis: Perils of the deep. *Clin Infect Dis* 2010;51(7):806-812.

Anisakis simplex and Pseudoterranova decipiens cause most human anisakidosis. The term anisakidosis refers to a dead-end human disease caused by ingestions of any such larvae. Most infections (> 90%) occur in adult Japanese men from coastal regions where people commonly consume raw or inadequately cooked saltwater fish or squid. Many case reports originate from coastal areas of Europe, especially the Netherlands, Germany, France, and Spain. About 60 cases have been described in the United States. Increasing regulatory controls of marine mammal exploitation, increased consumption of raw or lightly cooked food, and improved endoscopic diagnostics all account for a rising incidence of infections and increasing reports from New Zealand, Canada, Brazil, Chile, and Egypt.

All major oceans and seas harbor anisakid-infected marine life. A study of wholesale fish markets in Japan showed that 98% of mackerel and 94% of cod carried the parasite. High levels of infestation occurred among fish caught off the coast of Scotland, Italy, and France, and a fish market in Spain found anisakid infection in more than 39% of fish.

P. decipiens is largely transmitted by the Atlantic or

Pacific cod, and Pacific halibut and red snapper. A substantial proportion of infected cod harvested in the U.S. coastal waters are infected.

In Japan, sushi chefs are experts in identifying and removing larval infestation; although sushi and sashimi are potentially high-risk meals there, the fish served in sushi bars tend to be less contaminated and free of anisakid nematodes. Risk of infection is greater with less expensive marine fish such as cod, herring, and mackerel and squid-fish that are more often consumed in local restaurants or at home.

Other high-risk dishes besides sushi include salted and smoked herring from the Netherlands; Scandinavian gravlax; Hawaiian lomi lomi or raw salmon; South American ceviche, Spanish pickled anchovies known as *boquerones en vinagre*, and raw sardines.

Marine mammals represent the primary hosts for Anisakis simplex and *Pseudoterranova decipiens,* while dolphins, porpoises, and whales host anisakids, and seals, walruses, and sea lions host *P. decipien*s. When marine mammals, acting as final hosts, ingest infected fish or squid, the parasite develops into the 4th-stage larvae and then into adults. Human consumption of raw or undercooked fish places humans as accidental hosts, and larvae most often embed in human gastric or intestinal mucosa and die.

Four major clinical syndromes in humans include gastric, intestinal, ectopic, and allergic disease. Gastric anisakidosis has a presentation of abrupt onset, 1-12 hours after ingestion of raw fish, with severe epigastric pain, nausea, vomiting, low-grade fever, and occasionally, rash. Acute symptoms resolve within a few days, but infected persons report persistent vague abdominal symptoms for weeks to months afterwards. If left untreated, chronic ulcer-like symptoms may continue for months.

Intestinal anisakidosis presents as intermittent or constant abdominal pain beginning 5-7 days after larval ingestion. It predominately involves the terminal ileum, although colon or jejunum are involved less commonly and can be complicated by ascites or peritoneal findings. Rare complications can include small bowel obstruction, ileal stenosis, intussusception, intestinal perforation, and pneumoperitoneum.

Ectopic presentations of anisakidosis include extra gastrointestinal or intraperitoneal infection. These are much less common, yet they can result from larval penetration of the stomach or intestine. If larvae migrate into the peritoneal cavity they may reach the pleural cavity, mesentery, liver, pancreas, ovary, and subcutaneous tissue, causing pneumoperitoneum from perforation of the GI tract. Mesenteric masses have also been described.

Allergic anisakidosis is associated with prominent responses. Manifestations ranging from urticaria and isolated angioedema to anaphylaxis, at times associated with GI symptoms, are documented in several reports from Spain. Symptoms occur approximately 5 hours after exposure.

In Japan, presentation with gastric infections occurs most commonly, whereas intestinal disease is more common in Europe. *Pseudoterranova decipiens* infection usually involves the stomach only and tends to be milder than disease due to Anisakis species. Infected persons may experience "tingling throat syndrome" from a worm crawling in the upper esophagus or oropharynx; the primary symptom is cough. Diagnosis can be made by history, with endoscopic or surgical removal of the larvae providing definite diagnosis.

Besides directly visualizing the worm embedded in gastric mucosa, endoscopy may reveal erythema, edema, severe erosive gastritis, a tumor-like nodule, or ulcerations. The larvae may be found up to approximately 6 days after consumption of seafood, although most degenerate and are either eliminated or pass through the mucosa resulting in ectopic disease. The only signs remaining may be thickened gastric folds and inflammation; chronic infection can result in abscess or granuloma formation in response to degenerating larvae.

Serologic evaluation can be useful in diagnosing intestinal, extra-intestinal, and allergic cases. ELISA, Latex agglutination, or other immunoassays are available, but many cross-react with other parasites including Ascaris, *Toxocara canis*, and unrelated beasts such as insects, including the German cockroach or even shrimp. A compatible history of allergic reactions after either consumption or exposure to fish with positive hypersensitivity testing and serology, as well as a lack of reaction to fish proteins on skin testing, can confirm a diagnosis of allergy to Anisakis.

Treatment is preferably early endoscopic extraction of gastric larvae, although surgical removal may be required. Intestinal infection may be treated conservatively, and limited evidence suggests that oral albendazole 400-800 mg daily for 6-21 days is effective.

■ COMMENTARY

This thoughtful review is replete with references that support this discussion. Marinated and salted foods as well as "smoked" foods can be mistaken as safe methods of food preparation. Visual inspection of fish, extraction of visible parasites, and elimination of heavily parasitized fish all may reduce risk of human infection. The authors also speculate that eviscerating fish immediately after catch may decrease the number of larvae in the flesh of fish by preventing potential migration of larvae from the fish's intestinal tract into edible musculature. Heating kills larvae if temperatures greater than 60°C or 140°F

are sustained for at least a minute.

For fish that will be consumed raw, the key to prevention is freezing. The FDA code recommends freezing to -20°C for 7 days or flash freezing to -35°C for more than 15 hours. The European code recommends freezing at less than -20°C for 4 days only. Travelers should be made aware that these standards are not uniformly enforced. Of note, *A. simplex* antigens are resistant to freezing or heating and so persons may develop allergic responses despite proper preparation. The key to elucidating the culprit causing the varied and complex intestinal symptoms of returned travelers would be to take a detailed food history. ■

CME Questions

1. Vesico-vaginal fistulas:
   a. cause incontinence in more than 2,000,000 worldwide
   b. often occur with obstetric trauma during adolescence
   c. increasingly are caused by violent rape
   d. all of the above are true

2. All of the following statements about meningococcal disease are true *except*:
   a. The case fatality rate of meningococcal bacteremia and sepsis is 10-14%.
   b. *N. meningitidis* cases should be reported in writing to local health care authorities only when culture confirmation is complete.
   c. Droplet precautions should be implemented in all suspect and confirmed cases of meningococcal disease.
   d. Implementation of infection control recommendations ultimately depends on acceptance and adherence by health care personnel.

3. A health care worker traveling to a low-resource clinical setting may have an unusually high risk of occupational exposure to:
   a. hemorrhagic fever viruses in endemic areas
   b. needlestick injuries
   c. multidrug-resistant tuberculosis
   d. needlestick-induced malaria
   e. post-antibiotic-induced colitis

4. Which of the following statements is true concerning anisakidosis?
   a. Ova are often found embedded within the gastric mucosa of infected patients.
   b. Most infections occur in Japanese men living in coastal regions of Japan.
   c. Serological testing using ELISA-based methodology is both sensitive and specific.
   d. Larvae are too small to be identified visually within infected fish.
   e. Therapy with ivermectin is considered first line prior to any attempted endoscopic removal of the nematode.

CME Objectives

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

• discuss the latest data regarding the diagnosis and treatment of various travel-related diseases;

• explain new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world;

• implement strategies in the practice setting to inform patients of disease outbreaks and epidemics relevant to their travel plans.

Answers: 1. d; 2. b; 3. c; 4. b

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.*

Statin Use in Patients with Abnormal Liver Function

In this issue: Statins and liver function; dosing timing for thyroxine; rivaroxaban for VTE, DVT, and stroke; echinacea and the common cold; and FDA actions.

Statins and liver function

Most physicians are hesitant to use statins in patients with abnormal liver function tests (ALT or AST less than three times the upper limit of normal). A new study suggests that not only are statins safe and effective, they may improve liver abnormalities in patients with fatty liver. In a study recently published in the *Lancet*, 437 patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation study population were noted to have moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease. Of that group, 227 were treated with a statin (atorvastatin) and 210 were not. Patients treated with a statin had substantial improvement in liver tests ($P < 0.0001$), whereas the group not treated with a statin had further increases in liver enzyme concentrations. Cardiovascular events occurred in 10% of atorvastatin-treated patients vs 30% of the non-statin group (60% relative risk reduction; $P > 0.0001$). This was a greater improvement in benefit than seen in patients with normal liver function tests. Fewer than 1% of the participants who received a statin had to discontinue statin treatment because of transaminase concentrations more than three times the upper limit of normal. The authors concluded that "statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease" (*Lancet* 2010;376:1916-1922). ■

Dosing timing for thyroxine

When is the best time to take thyroxine? Patients are generally told to take it on an empty stomach in the morning and wait at least 30 minutes before eating. A new study suggests that taking thyroxine at bedtime might be a better option. Over 6 months, 105 patients were randomized to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Taking levothyroxine at bedtime lowered thyrotropin levels and increased free thyroxine and total triiodothyronine levels (the primary outcome). Treatment did not change secondary outcomes including quality of life. The authors concluded that taking levothyroxine at bedtime is a good alternative to morning intake (*Arch Intern Med* 2010;170:1996-2003). This would likely benefit patients who find it difficult to wait 30 minutes to eat after taking their thyroxine each morning. ■

Rivaroxaban: an oral, factor Xa inhibitor

Rivaroxaban is an oral, direct factor Xa inhibitor that is approved in several countries for the prevention of venous thromboembolism (VTE) after orthopedic surgery. It is currently being evaluated by the FDA for this indication. Based on the findings of the EINSTEIN study, it appears the drug is also effective for the treatment of acute deep vein thrombosis (DVT). EINSTEIN consists of three randomized trials of rivaroxaban, one for the treatment of acute DVT, one for treatment of acute pulmo-

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nary embolism, and one for continued, long-term treatment in patients who have received treatment for acute DVT or pulmonary emboli. The results of the first and third wings of the study were recently reported in the *New England Journal of Medicine*.

In the DVT treatment arm, 3449 patients with acute DVT were randomized to rivaroxaban (50 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. In the continued treatment wing of the study, patients were randomized in a double-blind fashion to rivaroxaban 20 mg once daily or placebo for additional 6 or 12 months after completion of 6-12 months of treatment for VTE. The primary outcome for both studies was recurrent DVT. For the treatment of acute DVT, rivaroxaban was non-inferior to enoxaparin-vitamin K antagonist (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; $P < 0.001$). In the continued treatment study, rivaroxaban had superior efficacy compared to placebo (8 events [1.3%] vs 42 events [7.1%] with placebo; HR 0.18; 95% CI, 0.09-0.39; $P < 0.001$). There were four patients in the rivaroxaban group with non-fatal major bleeding vs none in the placebo group. The EINSTEIN authors concluded that "Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation" (*N Engl J Med* 2010;363:2499-2510).

Rivaroxaban is also being evaluated for the prevention of stroke in patients with nonvalvular atrial fibrillation based on the ROCKET AF study, which was presented at the American Heart Association meetings in November 2010. If approved, it will join the recently approved direct thrombin inhibitor dabigatran (Pradaxa®) for this indication. Both drugs have the advantage over warfarin of not requiring ongoing lab monitoring. ■

Echinacea and the common cold

The National Center for Complementary and Alternative Medicine (NCCAM), a division of NIH, has been in existence for nearly 20 years, much of the time under the intense scrutiny of the mainstream medical community. Despite NCCAM's attempts to verify the effectiveness of alternative healing practices, most if not all rigorously studied modalities have been shown to be ineffective. The benefit of another alternative staple, echinacea, is questioned with the publication of a NCCAM-sponsored study testing the benefit of the herbal remedy for treating the common cold. More than 700 patients in Wisconsin with new-onset common cold were assigned to one of four groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded). The primary outcome was severity of the cold by self reporting with secondary outcomes of interleukin-8 levels and neutrophil counts from nasal washes. The comparison of the two blinded groups showed a trend toward benefit for the echinacea group (an average decrease in duration of cold of 7-10 hours out of 1 week; $P = 0.089$), but no difference in mean illness duration. There were no differences in the secondary outcomes. The authors concluded that the differences in illness duration and severity were not statistically significant with echinacea compared to placebo (*Ann Intern Med* 2010;153:769-777). ■

FDA Actions

The FDA is removing the breast cancer indication for bevacizumab (Avastin-Genentech). The somewhat unusual move was made after an FDA advisory panel suggested last summer that the drug did not provide a survival benefit for patients with breast cancer and at the same time caused serious side effects. The drug is still approved for treating cancer of the brain, colon, kidney, and lung.

The **FDA advisory panel is recommending approval for the first new diet pill in a decade. Orexigen Therapeutics' Contrave® is a combination of the antidepressant bupropion and the opioid antagonist naltrexone.** The drug was recommended for approval by a vote of 13-7, with some committee members voicing concern about potential side effects of the drug and recommending close post-marketing follow-up and studies to assess the risk of major cardiac events. The recommendation to approve the drug was based on studies that show an average weight loss 4.2% greater than placebo.

The **FDA has approved denosumab for the prevention of skeletal related events (fracture and bone pain) in patients with bone metastases from solid tumors.** The drug, which is given as a once monthly injection, was approved after a 6-month priority review. Denosumab is a monoclonal antibody to RANKL, a protein essential for the formation, function, and survival of osteoclasts. Denosumab in a lower-dose formulation was recently approved for the treatment of osteoporosis under the trade name Prolia™. Amgen Inc. will market the drug for this new indication under the trade name Xgeva™. It is expected to compete strongly with Novartis Pharmaceutical's zoledronic acid (Zometa®), which is approved for the same indication. ■