TRAVEL MEDICINE ADVISOR

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Malaria in Post-earthquake Haiti

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

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

Synopsis: *Malaria cases have occurred in U.S. residents who traveled to Haiti post-earthquake, including emergency responders and a traveler. Some resulted in severe illnesses. Individuals traveling to Haiti should use personal protection measures and take a recommended malaria chemoprophylaxis.*

Source: CDC. Malaria acquired in Haiti — 2010. *MMWR* 2010;59(8):217-219.

A 7.0 MAGNITUDE EARTHQUAKE STRUCK HAITI ON JAN. 12, 2010, WITH AN epicenter 10 miles west of Port-au-Prince, the capital. Approximately 200,000 fatalities occurred, and 500,000 people were left homeless. From Jan. 12 to Feb. 25, 11 laboratory-confirmed cases of *Plasmodium falciparum* malaria acquired in Haiti were reported to the CDC. Among the patients were seven United States residents who were emergency responders, three Haitian residents, and one American traveler. Six of the seven emergency responders were U.S. military personnel, and four had uncomplicated malaria treated in Haiti. The other two were moderate to serious cases that required transfer to the United States for intensive care, including one who developed acute respiratory distress syndrome necessitating intubation and mechanical ventilation.

Chemoprophylaxis would have been recommended for the seven emergency responders and the American traveler. However, six of the eight did not comply with the recommended chemoprophylaxis, including the two who required hospitalization. The three Haitian residents with malaria who traveled to the United States included a Haitian adoptee.

COMMENTARY

The current Haitian government estimates of fatalities and displaced persons are 217,366 and 511,405, respectively.[1] Because of the massive collapse of buildings and resulting lack of housing, most emergency responders to Haiti have slept in tents or other temporary structures. The main vector of malaria in Haiti, *Anopheles albimanus*, like other Anopheles species mosquitoes, is active at night. Therefore, sleeping outdoors at night, or staying in a shelter that does not keep out mosquitoes, increases an individual's chance of mosquito bites.

Haiti, with a population of 9,876,401, reported 36,774 cases of outpatient

malaria cases to the World Health Organization in 2008: 6 cases of *P. vivax*, and the remaining cases were *P. falciparum*.[2] A study of 274 Haitian refugees arriving by boat in Jamaica in 2004 identified, by microscopy, *P. falciparum* (30 isolates), *P. vivax* (13 isolates), *P. malariae* (1 isolates), and unidentified Plasmodium species (31 isolates).[3] When additional testing was performed using the polymerase chain reaction, 15 samples were positive for *P. malariae*, including 7 that were also positive for *P. falciparum*; PCR did not identify any *P. vivax*.[3]

The rainy season in Haiti occurs from May through October and is associated with peak malaria transmission from November to January and a lesser peak in May-June.[4] A population-based PCR survey in the Artibonite Valley of Haiti estimated a prevalence of 3.1% for *P. falciparum* infection during the high transmission season in 2006.[4]

Approximately 1300-1500 cases of malaria occurring in the United State are reported to the CDC annually. In 2007, 1505 cases were reported, of which 34 cases were acquired in Haiti. Among the reported cases attributed to Haiti, 29 isolates were *Plasmodium falciparum*, 1 isolate was *P. vivax*, and 4 were unknown species.[5] Among the 34 reported cases, 23 were in U.S. residents (civilians, not military personnel or foreign residents). *P. falciparum*, the primary species associated with severe malaria, is the predominant species that causes malaria in Haiti.

Occasionally, cases of malaria co-infection with other pathogens have been reported, such as malaria and dengue. One case of *P. falciparum*, *Clostridium perfringens*, and Candida spp. co-infection occurred in a German traveler to Haiti, which led to the demise of the patient.[6]

The currently recommended regimens for malaria chemoprophylaxis for U.S. travelers to Haiti are either chloroquine, mefloquine, atovaquone-proguanil, or doxycycline.[7,8] Although the *P. falciparum* parasites are still considered sensitive to chloroquine, which is one of the regimens recommended for chemoprophylaxis, concern is rising about the potential development of resistance. In 2006 and 2007, amplification of the *P. falciparum* chloroquine resistance transporter (pfcrt) gene on blood samples that had been positive by microscopy or PCR for *P. falciparum* detected several samples that possessed the chroloquine-resistant haplotype.[9]

A medical surveillance of the U.S. Joint Task Force, which served in Haiti during the spring of 2004, found only one case of malaria during the 17,938 person-weeks deployment.[10] However, any cases reported after return to the United States would not have been included in the report. Despite the routine guidance in the military to take doxycycline for malaria chemoprophylaxis in addition to using repellent and insecticide-treated uniforms and nets, several emergency responders from the military adhered poorly to prevention.

In summary, malaria cases have occurred in emergency responders to post-earthquake Haiti. *P. falciparum* is the predominant species, and rare cases of *P. malariae* and *P. vivax* have been identified. Individuals planning to travel to Haiti, whether for earthquake relief or to visit family and friends or other activities, should understand the status of their accommodations. For malaria prevention, travelers should sleep in tents or under mosquito nets to reduce nighttime mosquito exposure, apply repellent appropriately, and use a recommended chemo-

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prophylaxis.

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Transmission of Yellow Fever Vaccine Virus: Blood Products and Breast-feeding

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

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

Synopsis: *Two recent reports highlight the potential risk of transmission of yellow fever vaccine virus through blood products and breast-feeding.*

Sources: Centers for Disease Control. Transfusion-related transmission of yellow fever vaccine virus — California, 2009. *MMWR* 2010:59;34-37.

Centers for Disease Control. Transmission of yellow fever vaccine virus through breast-feeding — Brazil, 2009. *MMWR* 2010:59;130-132.

In March 2009, 89 active-duty U.S. trainees received yellow fever (YF) vaccination as part of standard preparation for potential travel to sub-Saharan Africa and Central and South America. All the trainees were first-time recipients of YF vaccine. Four days later, these trainees took part in a blood drive. Standard blood bank screening procedures were followed, including questioning about recent vaccinations; however, none of the 89 trainees reported having received YF vaccine four days earlier. On April 10, 2009, a blood bank supervisor discovered the error during a routine record review in preparation for a subsequent blood drive. Despite a prompt recall, six units of blood products were transfused into five patients.

No clinical illness occurred in four blood recipients within a month of transfusion. The fifth patient was an 82-year-old male who was in hospice care for terminal prostate cancer and end-stage, transfusion-dependant, B-cell lymphoma. He died 20 days after receiving a platelet transfusion derived from one of the implicated lots. No pre-mortem blood specimens were available for testing in this patient, and no autopsy was performed. In three of the remaining four recipients, YF virus IgM antibodies were detected by plaque neutralization in serum samples taken between 26 and 37 days post-transfusion. No evidence of potential cross-reactive flavivirus infections, such as West Nile virus or St. Louis encephalitis virus antibodies, was detected. The one surviving patient who did not have serologic evidence of exposure to the YF virus was a pre-term infant who received 4 aliquots of irradiated red blood cells (30 cc in total). Two possible reasons for the lack of immune response in this case might be the immaturity of the pre-term infant's immune system and lower levels of YF vaccine virus in red blood cells as opposed to the other serum-containing products.

In April 2009, during epidemic YF activity in Rio Grande do Sul, Brazil, a 22-year-old mother was vaccinated for YF during a routine postpartum visit. Her infant was 15 days old, and she was exclusively breast-feeding. Eight days later, her infant was hospitalized with seizures and meningoencephalitis. Yellow fever-specific IgM was detected in the infant's serum and CSF, thus confirming yellow fever vaccine-associated neurologic disease. Other causes of meningoencephalitis (dengue, herpes simplex, cytomegalovirus, varicella, and enteroviruses)

were ruled out by testing of serum and CSF. The infant did recover and at 6 months was without neurologic sequelae. This is the first laboratory-confirmed case of YF vaccine-associated neurologic disease (YEL-AND) in an infant as a result of transmission of YF vaccine virus through breast milk.

COMMENTARY

These reports confirm what has always been suspected on theoretical grounds but never documented: first, that transfusion-related transmission of YF vaccine virus can occur and, second, that YF vaccine virus can be transmitted through breast milk and cause YEL-AND in infants. The infant recovered without sequelae, and in the transfusion cases, no clinical illness was noted in the four recipients who could be followed. The outcomes might have been very different if the affected blood lots had not been promptly recalled and instead transfused into many more immunocompromised or older patients. Despite its excellent track record for prevention of YF, we are increasingly aware of the potential complications including both YEL-AND and YF Vaccine-Associated Viscerotropic Disease (YEL-AVD) with the various strains of the 17D YF virus lineage. Both of these adverse events occur almost exclusively in first-time recipients of yellow fever vaccine.[1]

The documentation of YF vaccine virus transmission through breast milk has repercussions in parts of the world where epidemic YF activity occurs and breast-feeding is the predominant mode of infant feeding. The actual risk for 17 DD virus transmission through breast milk is difficult to estimate without knowing the numbers of breast-feeding women who are vaccinated without any adverse consequences for their infants. Nonetheless, it is recommended to avoid YF vaccination of nursing mothers unless travel into high-risk yellow fever-endemic areas simply cannot be avoided or postponed.[2] Breast-feeding mothers who need YF vaccination should be made aware of the potential transmission issue so that an alternative mode of infant feeding could be considered during time of expected YF viremia.

Eligibility requirements for blood donation are in place to prevent inadvertent acceptance of donors with the possibility of illness or latent infections. With regard to immunizations, the American Red Cross specifically advises people to defer blood donation for two weeks after receiving either YF vaccine or oral polio vaccine, which is no longer available in the United States, and for four weeks after MMR (measles, mumps, rubella), varicella (chickenpox), and herpes zoster (shingles) vaccination. The complexities of smallpox vaccination require special considerations, but generally a minimum eight-week interval is recommended, assuming no vaccine complications have occurred. There is no deferral period after receipt of influenza, pneumococcal, tetanus (including Td or Tdap), meningitis, hepatitis A, injectable typhoid, injectable polio, or human papillomavirus (HPV) vaccination as long as the donor is in good health without any symptoms. Of note, the American Red Cross suggests a 21-day deferral after routine hepatitis B vaccination (i.e., not given for an exposure) to avoid any potential for a false-positive testing for hepatitis B carrier status.[3]

Although blood bank screening techniques are in place for prevention of transfusion-related illnesses, travel medicine physicians can help reinforce these recommendations at the time pre-travel vaccinations are given. Patients often ask about blood donation deferral policies after travel to malaria-endemic areas (generally one year after travel to a malaria risk area, 3 years if the person lived in a malaria area or had disease). The pre-travel visit, during which live virus vaccines such as yellow fever vaccine are administered, gives us an excellent opportunity to review with our patients the policies on blood donation deferral after immunizations.

Full eligibility requirements for blood donation are available at www.redcrossblood.org.

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Sources for Post-travel Pediatric Illness

By Phil Fischer, MD, DTM&H

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

Synopsis: *Following international travel, children are more likely than adults to require hospitalization for travel-related illnesses. Diarrhea, skin problems, and febrile illness are common presenting problems. Pre-travel care is frequently neglected, and pre-travel interventions likely could have been helpful for many*

ill returned travelers.

Source: Hagmann S, Neugebauer R, Schwartz E, et al. Illness in children after international travel: Analysis from the GeoSentinel Surveillance Network. *Pediatrics* DOI:10.1542/peds.2009-1951, published online April 5, 2010.

The characteristics and morbidities of 1591 children who presented to travel and tropical medicine clinics for care in 19 countries following international visits to 218 destinations were investigated as part of the GeoSentinel Surveillance Network research activities. Pediatric data were compared to findings in 32,668 adults who presented similarly for post-travel care.

While tourism was the most common reason for travel, children, especially young ones, were more likely than adults to have traveled to visit friends and relatives. Compared to sick adult travelers, children were more likely to present earlier, to require hospitalization, to have had a shorter international trip, and not to have received pre-travel medical input. Children traveling to visit friends and relatives were less likely to have received pre-travel advice (32%) than were children traveling for other reasons (51%).

Presentation for post-travel care among children commonly was due to diarrhea. It accounted for 28% of the total cases, 80% of acute cases, and was almost evenly split among bacterial, parasitic, and unknown etiologies. For skin problems, fully 25% of the total cases were associated with animal bites, half of which were caused by dogs, about one-fifth by cats, and one-fifth by monkeys, followed by cutaneous larva migrans and insect bites. Febrile illnesses accounted for 23% of total cases, one-third of which were due to malaria, or respiratory disorders (11% of the total) mostly unrelated to tropical infections. Two percent of children had a vaccine-preventable infection. Compared to adults, children were more likely to present with animal bites, cutaneous larva migrans, and bacterial diarrhea.

Dermatologic diagnoses were more likely after travel to Latin America. Diarrheal diseases were most common after travel to the Middle East and North Africa. Malaria was the most common etiology of febrile illness in children returning from Africa, but typhoid fever and dengue were more common than malaria among children returning from Asia.

COMMENTARY

Since 1995, the GeoSentinel Surveillance Network has been gathering information about returned travelers presenting for health care at specialized travel and tropical medicine clinics.[1,2] Along the way, the network has produced dozens of research papers informing readers about post-travel health issues, including malaria,[3] animal-related injuries,[4] skin problems,[5] and diarrhea.[6,7] Having looked at post-travel problems in other specific sub-populations of travelers, including those visiting friends and relatives,[8] people visiting China,[9] and long-term travelers,[10] this current report provides additional very helpful data relevant to pediatric travelers.

These data are quite relevant to the sorts of travelers who would be seen by practitioners of travel medicine. Of course, primary care providers would be more likely than specialists to see many of the patients who present following travel with common problems, such as respiratory infections and diarrhea. Up to 40% of children experience diarrhea during or shortly after international trips,[11] and many of these would not be seen in a specialty GeoSentinel type of clinic. Nonetheless, the GeoSentinel pediatric data do provide a good perspective on severe post-travel health problems as they might present to professionals caring for returned travelers.

The GeoSentinel pediatric findings are directly relevant to the pre-travel practice of travel medicine. Only about half of all children, and only about one-third of children visiting friends and relatives, had received pre-travel care. Pre-travel care including interventions to prevent malaria, information about diarrhea management, and education about avoiding skin contact with animals, insects, and parasites would likely have been time-effective and cost-effective for these ill returned-traveler children. Efforts should be made to better attract internationally traveling children for pre-travel care. Some success has been realized in a hospital-based clinic dealing with underserved populations traveling overseas to visit friends and relatives.[12] Multi-lingual handouts to facilitate pre-travel care are widely available. (http://www.tropical.umn.edu/TTM/VFR/index.htm)

Nearly half of the children with cutaneous larva migrans[13] in this study had traveled to the Caribbean area. Pre-travel visits for Caribbean travelers should include advice about avoiding skin contact with sand where cats and dogs have defecated. Using sandals to walk on potentially contaminated beaches and sitting on towels or lounge chairs can decrease the risk of infections.

Millions of children cross international borders each year. The provision of adequate pre-travel care will help many of them avoid illness, hospitalization, and costly post-travel care. Those who are ill following their trips often have diarrhea, skin problems, and febrile diseases amenable to thoughtful medical care.

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Schistosomiasis Treatment Failures with Single-dose Praziquantel

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD, and Paul Trowbridge, MD

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Dr. Mileno and Dr. Trowbridge report no financial relationships relevant to this field of study.

Synopsis: *Of 30 patients re-examined post-treatment with praziquantel (PZQ) for new schistosomiasis, only 10 were free of signs and symptoms, suggesting ongoing infection. Two-thirds of patients re-evaluated had an elevated blood eosinophil count or serum IgE level, increased antibody titer, or symptoms. Detectable ova were found on evaluation of urine or rectal biopsy in 20%. Re-evaluation is complicated by the lack of a diagnostic gold standard for schistosomiasis, especially for those with low parasite burdens.*

Source: Helleberg M, Thybo S. High rate of failure in treatment of imported schistosomiasis. *J Travel Med.* 2010;17:94-99.

A RETROSPECTIVE OBSERVATIONAL STUDY WAS CONDUCTED on 30 individuals from a possible 49 persons who were treated for schistosomiasis between 2003 and 2008 at Copenhagen University Hospital, Denmark. All patients had traveled to endemic areas and had been previously diagnosed by detection of ova or positive serologic studies associated with symptoms. All patients had subsequently been treated appropriately with at least 1 dose of praziquantel (40-60 mg/kg) at least 12 weeks post-exposure to avoid treatment at the invasive infection phase during which PZQ has limited effectiveness. Patients were offered re-evaluation 3 to 36 months post-treatment (mean 16 months). Nineteen of the 30 patients who accepted actually required re-evaluation, as 11 had already done so. Evaluation consisted of microscopy performed on 24-hour urine samples and/or rectal biopsies for direct visualization of ova, measurement of eosinophil count, IgE levels, and schistosomiasis serology by indirect hemagglutination assay and/or immunofluorescence testing. All patients were screened by history for potential re-exposure to freshwater from schistosomiasis-endemic regions prior to re-examination.

Viable schistosome ova were detected in 6 of 30 (20%) patients during re-examination following initial treatment, and these cases were considered treatment failures. This level of treatment failure is largely congruent with previous studies of schistosomiasis treatment among travelers. Notably, all of these patients had initially been diagnosed by detection of viable ova, not by a positive serology alone, potentially indicating higher initial parasite load. In addition, these patients were all tourists, expatriates, or immigrants from endemic areas. Treatment

of schistosomiasis with praziquantel in patients from endemic areas has produced lower treatment failure rates. It has been hypothesized that this occurs because praziquantel only exposes parasitic antigens and requires host immunity in order to clear the adult organisms and obtain a cure. The latter would be more likely to occur in sensitized individuals from endemic areas than in travelers who were previously uninfected with the parasite.

In addition to known treatment failures, additional treatment failures were suspected in patients who did not have detectable schistosome ova, but were symptomatic 2 years after treatment and showed a rise in antibody titer of at least eightfold with an elevated serum IgE level. Only one-third of the study population (10 patients) had no confirmed ova or signs/symptoms suggesting potential ongoing schistosomiasis.

Other than direct detection of schistosome ova, no other parameters such as eosinophil count, serum IgE levels, or clinical symptoms could be shown to be a reliable indicator of infection, as none of them were found to show significant differences between patients in whom ova were detected and those in whom ova were not detected. Antibody titer, notably, was actually decreased in one patient who was subsequently found to have ova present on rectal biopsy. The diagnosis of schistosomiasis among individuals who do not have a heavy parasitic burden, and thus have limited excretion of ova, can be difficult; detection of ova, by any means, is fairly insensitive, elevations in serum IgE levels or eosinophil counts are non-specific, and serologic markers can remain elevated long after effective therapy. Although polymerase chain reaction (PCR) testing for parasite DNA may aid diagnosis in the future, empiric repeat treatment of travelers with schistosomiasis may be the best strategy, given the general safety of PZQ use.

COMMENTARY

There are several interesting aspects to this study. First of all, the high rate of treatment failure with PZQ is somewhat disturbing. With at least a 20% treatment failure rate in this study and the possibility that up to two of every three patients treated failed to clear the parasite, the drug of choice for schistosomiasis may require some new guidelines for its effective use, or it even may need to be replaced.

What may be of more interest than the results from this study is what we learn about what we simply do not know. Interestingly, even though this study points out that PZQ may be failing to treat some cases of schistosomiasis, we do not even understand how this medication works, much less how or why it fails. One of the hypothesized mechanisms of action is disruption of the parasitic surface membrane, allowing antigen exposure to the host's immune mechanisms. This hypothesized mechanism potentially could explain why there seems to be a higher rate of treatment failure among people exposed while traveling, including children, than among adults from endemic areas. However, this is not yet clear. Additional research on a larger scale than performed in this study would be useful for detailing the range of risk factors for treatment failure.

In addition to highlighting our lack of knowledge about treatment, this study also indicates that we currently lack a reliable method for choosing whom to treat or even retreat. Our gold standard for detection of infection is quite insensitive, and our serologic methods often are not helpful during re-evaluation. PCR tests looking for parasitic DNA may be helpful in the future, but have not yet been studied sufficiently.

CME Questions

8. The following medication is a recommended malaria chemoprophylaxis for travelers going to Haiti:
   a. primaquine phosphate
   b. artemether-lumefantrine
   c. proguanil monotherapy
   d. chloroquine phosphate
   e. pyrimethamine-sulfadoxine
9. Temporary deferral of blood donation is recommended for:
   a. two weeks after yellow fever vaccination
   b. four weeks after influenza vaccination
   c. four weeks after MMR vaccination
   d. all of the above
   e. a and c only

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.

10. Returned pediatric travelers, regardless of itinerary, will frequently seek medical care for which of the following problems?
    a. cutaneous larva migrans
    b. diarrhea
    c. fever
    d. animal bites
    e. all of the above

11. Which of the following represents a reliable method for ruling out active disease in travelers who were previously treated for schistosomiasis and may have low parasite burdens?
    a. stool and urine examination for for ova
    b. rectal biopsy and examination for ova
    c. serological examination for anti-schistomsomal antibodies
    d. serum IgE level
    e. none of the above

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the questions at the end of the articles. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Web Site Updates

Visit www.travelmedicineadvisor.com to view the latest country maps with disease and vaccination updates. Recently updated countries include Haiti, India, Guatemala, Sudan, and Uruguay.

CME Evaluation

The CME evaluation for the period ending in June is included in this issue. Be sure to complete the evaluation and send it in to obtain your CME credits.

Answers: 8. d; 9. e; 10. e; 11. e

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.*

Atypical Fractures and Bisphosphonate Therapy

In this issue: Fractures and bisphosphonate therapy, warfarin anticoagulation and influenza vaccine and cotrimoxazole, antiplatelet therapy with clopidogrel and aspirin, FDA Actions.

Bisphosphonates and atypical fractures

Atypical fractures of the femur have been linked with bisphosphonate therapy in several recent news stories. A recent industry-sponsored study looks to quell these concerns. Secondary analysis from three large randomized bisphosphonate trials with more than 14,000 women showed that among 284 hip or femur fractures recorded, a total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient years. As compared with placebo, the relative hazard ratio for the three trials did not meet statistical significance, although confidence intervals were wide. The authors conclude that the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare even among women who had been treated with bisphosphonates for as long as 10 years (*N Engl J Med*; published on-line March 24, 2010). An accompanying editorial published on-line at the same time by Elizabeth Shane, MD, Columbia University, acknowledges that despite excellent safety profiles, bisphosphonates have been associated with "atypical" fractures of the femur that occur with minimal or no trauma, generally affecting the proximal third of the femoral shaft. Most of these fractures have occurred in women on long-term alendronate therapy, occasionally taken together with other antiresorptive drugs, corticosteroids, or proton pump inhibitors. Shane points out that while these fractures represent concern, they are uncommon and actually occur more frequently in patients who are not on bisphosphonates. The results of this study "provide assurance that subtrochanteric fractures are extremely rare" and many more hip fractures are "prevented by bisphosphonates than are potentially caused by the drugs." Treatment with bisphosphonates up to 10 years is more effective than shorter-term treatment in preventing new vertebral fractures and nonvertebral fractures, but she also suggests that patients should be considered for "drug holidays with careful observation" if they have been on long-term therapy.

Warfarin, flu vaccine, and cotrimoxazole

Anticoagulation with warfarin requires careful monitoring. Concomitant use of medications may result in changes in the international normalized ratio (INR), which may increase the risk of bleeding or decrease the effectiveness of therapy. Two studies in the April 12 issue of *Archives of Internal Medicine* clarify the risk of two commonly used medications, influenza vaccine and the antibiotic trimethoprim-sulfamethoxazole. Patients on warfarin have been told that they need careful monitoring after the influenza vaccine, although the effect is not clear. Some guidelines have suggested that flu shots prolonged INRs, while others suggest the vaccine reverses the anticoagulation effect.

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In this study, 104 patients on a stable warfarin regimen were randomized to receive influenza vaccine and subsequent placebo administration or vice versa. All patients were tested for coagulation variables and followed for clinical events. The influenza vaccine had no effect on anticoagulation compared to placebo. There were no fatal or major bleeding events. The authors conclude that the influenza vaccine has no significant effect on INR values or warfarin weekly doses in patients on chronic warfarin therapy and that close monitoring of INR values after influenza vaccine is not required (*Arch Intern Med* 2010;170:609-616).

Conversely trimethoprim-sulfamethoxazole (cotrimoxazole) may significantly prolong INRs with adverse clinical outcomes. In the population-based, nested case-controlled study using health care databases in Canada, residents 66 years or older who were treated with long-term warfarin were evaluated for upper gastrointestinal (GI) tract hemorrhage. Of the more than 134,000 patients on warfarin, 2151 patients were hospitalized for upper GI hemorrhage. Recent use of cotrimoxazole was almost four times more common in those hospitalized (adjusted odds ratio, 3.84; 95% CI, 2.33-6.33). The odds ratio for treatment with ciprofloxacin also was higher (1.94), but no significant association was observed with amoxicillin, ampicillin, nitrofurantoin, or norfloxacin. The authors conclude that among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of upper GI tract hemorrhage. Ciprofloxacin was also associated with risk and whenever possible clinicians should prescribe alternate antibiotics in patients receiving warfarin (*Arch Intern Med* 2010;170:617-621).

Clopidogrel and aspirin

What is the optimal duration of dual antiplatelet therapy with clopidogrel and aspirin in patients with drug-eluting stents? In previous studies, early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis. A new study seeks to determine whether dual antiplatelet therapy for more than 1 year is of value. In a study that merged data from two concurrent randomized, clinical trials, 2701 patients who had received drug-eluding stents and had been free of major adverse cardiac events, cerebrovascular events, or major bleeding for a period of at least 12 months were randomized to receive clopidogrel plus aspirin or aspirin alone. The primary endpoint was a composite of myocardial infarction (MI) or death from cardiac causes. The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy as compared with 1.2% with aspirin monotherapy (hazard ratio, 1.65; 95% confidence interval, 0.80-3.36; $P = 0.17$). The individual risks of MI, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death did not differ significantly between the two groups. However, there was a trend toward higher risk for these outcomes in the dual therapy group ($P = 0.051$ for MI, stroke, or death from any cause; $P = 0.06$ for MI, stroke, or death from cardiac cause). The authors conclude that use of dual antiplatelet therapy for longer than 12 months is not more effective than aspirin alone in patients who have received drug-eluding stents (*N Engl J Med* 2010; 362:1374-1382).

FDA Actions

Rifaximin, Salix Pharmaceutical's minimally absorbed (nonsystemic) oral antibiotic has been approved to reduce the risk of recurrent hepatic encephalopathy in patients with advanced liver disease. Rifaximin was previously approved to treat traveler's diarrhea. The drug, which is taken orally twice a day, appears to reduce ammonia levels by reducing gut flora. It is marketed as Xifaxan®.

The FDA has approved Pancreaze, a new pancreatic enzyme product for patients who do not produce enough pancreatic enzymes (due to cystic fibrosis, chronic pancreatitis, pancreatic surgery, etc.). Pancreaze is the third approved pancreatic enzyme product on the market after Abbott's Creon® and Eurand's Zenpep®. The approval coincides with the FDA's deadline to cease marketing unapproved pancreatic enzyme products that have been available for many years. In October 2007, the FDA announced a deadline of April 28, 2010, after which time unapproved products would no longer be available.

The FDA has approved the first generic version of the popular antihypertensive losartan (Cozaar®) as well as the combination of losartan and hydrochlorothiazide (Hyzaar®). This represents the first generic angiotensin receptor blocker on the market, a development that has been anxiously awaited by consumers. Losartan carries a boxed warning against using the drug during pregnancy. Generic losartan is available in 25 mg, 50 mg, and 100 mg strengths, while losartan/hydrochlorothiazide is available in 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg strengths.