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Blood Donor Screening for Chagas Disease

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD
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Dr. Scully reports no financial relationship relevant to this field of study.

Synopsis: *A newly approved serologic assay for detecting* Trypanosoma cruzi *infection opens the door for universal screening of blood donations to prevent transfusion-transmitted Chagas disease.*

Source: CDC. Blood Donor Screening for Chagas Disease- United States, 2006-2007. *MMWR Morb Mortal Wkly Rep*. 2007;56:141-143.

During August 2006-January 2007 the American Red Cross conducted a clinical trial to evaluate an investigational assay for detecting *Trypanosoma cruzi* infection in blood donations. 148,969 blood samples from 3 collection centers (Los Angeles, CA; Oakland, CA; and Tucson, AZ) were screened using an enzyme-linked immunosorbent assay (ELISA) that uses epimastigote lysate antigens to detect antibodies to *T. cruzi* in serum and plasma. A total of 63 specimens from 61 donors were repeatedly reactive for *T. cruzi* antibodies. Of the 63 positive specimens, 50 donors (79%) were from the Los Angeles collection center, 14% from Oakland, and 6% from Tucson. Repeatedly reactive specimens were further tested using a radioimmunoprecipitation assay (RIPA): those with positive RIPA results were considered confirmed positives. Of these 63 repeatedly reactive specimens, 32 (51%) donations (approximately one in 4,655) were confirmed positive with RIPA testing, and 31 (49%) were considered negative.

On December 13, 2006, the FDA licensed the new *T. cruzi* ELISA Test System to screen blood donors in the United States. The assay is also labeled for use on serum and plasma samples from living cell and tissue donors and from heart-beating organ donors but is not approved for general clinical diagnosis. Use of the test by blood centers is not yet mandatory but the American Red Cross and Blood Systems, Inc. began screening all blood donations for *T. cruzi* on January 27, 2007. These 2 blood collection organizations account for about 65% of the U.S. blood supply. Also, the AABB (formerly known as the American Association of Blood Banks) recommends that all components from blood donations that are repeatedly reactive by the ELISA test be quarantined and removed from distribution. In

addition, confirmed positive donors should be deferred from making any further blood donations and testing offered to at-risk family members who have also had a history of exposure to *T. cruzi* vectors in an endemic area.

COMMENTARY

Chagas disease is named after Carlos Chagas, a Brazilian physician who discovered and described the disease in 1909 while working at the Oswaldo Cruz Institute in Rio de Janeiro. The parasite, *T. cruzi*, is transmitted by triatomine insects (ie, kissing bugs) that are found only in the Americas; hence Chagas disease is also known as American trypanosomiasis. Although acute infection can result in mild symptoms such as fever, lymphadenopathy, headache, fatigue, or a swelling (chagoma) at the site of parasite entry, the infected patient is more often asymptomatic. It is estimated that the majority of the 11 million people in Mexico, Central America, and South America with Chagas disease are unaware they have the infection.

If early infections are not treated, Chagas patients will have low-level, intermittent, often asymptomatic parasitemia during what is referred to as the chronic indeterminate phase. However, an estimated thirty percent of infected patients will develop chronic symptomatic Chagas disease with potentially lethal cardiomyopathy or megasyndromes, such as megaeosophagus or megacolon. Treatment options are limited, but early infection should be treated with either benznidazole, which is not available in the United States, or nifurtimox, which is available from the CDC under an investigational new drug protocol. There is increasing evidence to suggest that treatment of persons with chronic infection may result in seroreversion and prevent progression of cardiac morbidity.[1]

Since even asymptomatic Chagas patients have intermittent low-level parasitemia, they remain potentially infectious. Seven cases of transfusion-associated transmission of *T. cruzi* have been documented in the United States and Canada, and 3 recent cases of transmission of *T. cruzi* through organ transplantation have been reported.[2] Since *T. cruzi* parasitemia is intermittent, the nucleic acid testing method that is used for other pathogen screening is less effective than serology testing. The parasite can survive irradiation of blood products, and even leukoreduction fails to remove all *T. cruzi* parasites. With an estimated 50,000-100,000 *T. cruzi*- infected immigrants residing in the United States the approval of this new assay now makes it possible to move toward universal screening of blood and tissue donors.

Available data on the performance of the new assay suggest high sensitivity (98.9%) and specificity (98.2 to 99.9%) in high-risk populations.[3] However, in areas of lower disease prevalence a greater number of false positives can be expected. Since positive donors will be informed of the results and deferred from further donation, patients will look to their health care providers to identify true positives using further diagnostic testing (eg, diagnostic ELISA tests, immunofluorescence assay, or indirect hemagglutination), clinical evaluation, and exposure risk. In anticipation of questions likely to emerge from this new screening, the CDC

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released a fact sheet for patients and health care providers on February 6, 2007. It is available at www.cdc.gov/ncidod/dpd/parasites/Chagasdisease/.

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Azithromycin for Travelers' Diarrhea in Thailand

ABSTRACT & COMMENTARY

By Barbara E. U. Burkhardt, MD, and Philip R. Fischer, MD, DTM&H

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Dr. Fischer and Dr. Burkhardt report no financial relationship relevant to this field of study.

Synopsis: *In Thailand, where Campylobacter is frequently a cause of traveler's diarrhea, a single dose of 1000 mg of azithromycin is more effective than 3 daily 500 mg doses or 3 days of levofloxacin both in resolving symptoms of travelers' diarrhea and in clearing infection.*

Source: Tribble DR, et al.: Travelers' Diarrhea in Thailand: Randomized, Double-Blind Trial Comparing Single-Dose and 3-Day Azithromycin-Based Regimens with a 3-Day Levofloxacin Regimen. *Clinical Infectious Diseases.* 2007;44:338-346.

Travelers' diarrhea in Thailand is increasingly associated with fluoroquinolone-resistant *Campylobacter jejuni*. This led Tribble and colleagues to study azithromycin as an alternative first-line antibiotic for acute diarrhea.

In a double-blind, placebo-controlled trial conducted in 2000 and 2001, 156 adult military personnel were randomized to receive either single-dose oral azithromycin (1 gram), a 3-day course of azithromycin (500 milligrams daily), or 3 days of levofloxacin (500 milligrams daily). Patients were followed with symptom report cards and repeated clinic visits at 24 hours and 72 hours after initiation of treatment.

Resolution of symptoms at 72 hours occurred in 96% of subjects receiving a single-dose azithromycin regimen as compared to 85% of patients in the 3-day azithromycin group and 70% of those on 3 days of levofloxacin ($P = 0.002$). The mean times to the last unformed stool were 39 vs 43 vs 56 hours, respectively. While not correlated with clinical cure at 72 hours, microbiological eradication of an isolated organism was observed more frequently with azithromycin (100%) than with levofloxacin (21%; $P < 0.001$).

COMMENTARY

Travelers' diarrhea affects an estimated 15 million or more travelers to developing countries every year. Stand-by medications are frequently prescribed for travelers who will not have immediate access to medical care at their destination. Due to increasing microbial resistance against antibiotics worldwide, and especially in some specific parts of the world, it has become difficult to choose an appropriate oral antibiotic for visitors to areas such as Thailand.

The patients studied by Tribble and colleagues were all generally healthy adult military personnel. Therefore, the application of these findings beyond this defined population (eg, to persons with preexisting health problems, elderly travelers, or children) is difficult. Moreover, the majority of the study subjects were using doxycycline for antimalarial prophylaxis. This practice could contribute to the development of resistance among intestinal organisms and might also have caused a relative predominance of Campylobacter (as compared to toxigenic *Escherichia coli*) in study subjects. Most pathogenic isolates identified in subjects with diarrhea were *Campylobacter* (all susceptible to azithromycin), and less frequently Salmonella, but with a higher rate of resistance to azithromycin than against fluoroquinolones. However, most cases of travelers' diarrhea worldwide are caused by *E. coli*, and susceptibilities of *E. coli* strains should be the primary basis for choosing an antibiotic for presumptive treatment. For all of these reasons, the findings of the study should not be overly generalized.

The American Academy of Pediatrics issued a policy statement in September of 2006 addressing safety

and possible uses of fluoroquinolones in children. Due to the potential for musculoskeletal side effects, fluoroquinolones should be avoided unless multidrug resistant bacteria need to be treated orally. Gastrointestinal infections caused by multidrug resistant *Shigella* species, *Salmonella* species, *Vibrio cholerae*, or *Campylobacter jejuni* may fall under this category.[1] As an empirical treatment for travelers' diarrhea in children, however, the use of fluoroquinolones would not be recommended. The same considerations apply during pregnancy. Azithromycin, on the other hand, is considered safe for infants and children of any age and is listed as a class B drug during pregnancy.

The worldwide prevalence of fluoroquinolone resistant human pathogenic bacteria is increasing. *Campylobacter* and *Salmonella* species resistant to fluoroquinolones were isolated in the UK as early as the 1990s,[2,3] and resistance to quinolones among *Salmonella enterica* isolates in Spain steadily increased between 1991 and 2003.[4,5] In Europe, Latin America, and North America, fluoroquinolone resistant *Campylobacter* species were rarely found in a 2003 study.[6,7] Fluoroquinolone resistance affects a significant proportion of *E. coli* among hospital patients in Indonesia.[8] Fluoroquinolone resistant, as well as multidrug resistant, *Shigella* strains were highly and increasingly prevalent between 2001 and 2003 in India[9] and have also been spreading in Japan since 2000.[10] Thailand has an especially high prevalence of reduced fluoroquinolone susceptibility in *Salmonella* strains.[5] Likewise, Campylobacter in Thailand is mostly resistant to fluoroquinolones.[11] While up to 15% of enterotoxigenic *E. coli* in Thailand may be resistant to azithromycin, azithromycin-resistance is less prevalent than is resistance to other antibiotics.[12]

On a large scale, this resistance of enteric pathogens has been attributed to the use of fluoroquinolones in animal food as well as inappropriate prescribing practices for human disease,[3,11] but antimicrobial resistance of enteric pathogens may also be acquired during the acute illness, as shown by Tribble. Interestingly, the presence of antimicrobial resistance is not limited to individuals with prior use of antibiotics.[13]

Acute bacterial or viral gastroenteritis is usually self-limited, requiring only fluid and electrolyte replacement therapy.[11] Travelers are often, however, provided with a prescription for an antibiotic for use in the event of bothersome travelers' diarrhea. The choice of a particular agent to offer to travelers to take along depends on several factors, including local prevalence of pathogens and their resistance patterns, and the person's age and health status. A growing body of evidence suggests that azithromycin is a reasonable first line choice when presumptive treatment of travelers' diarrhea is deemed appropriate[14] - for travelers to Thailand, for children and pregnant women and, likely, for all travelers. A single large dose seems more effective than standard daily doses for 3 days.

Prevention of travelers' diarrhea remains most important, and although not a guarantee for successful avoidance of an enteric infection, water and food hygiene measures should be taught at each pre-travel clinic visit. Immunizations such as rotavirus vaccine for young infants or typhoid vaccine should be used where applicable. ■

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Look for Ocular Findings in Cerebral Malaria and Dengue

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD

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Dr. Mileno is a consultant for GlaxoSmithKline.

Synopsis: *A symposium of the ASTMH meetings in Atlanta last November focused on eye findings which may be the most reliable indication of cerebral sequestration of malarial parasites, short of brain biopsy.*

Sources: 55th Annual Meetings. American Society of Tropical Medicine and Hygiene, Atlanta, Georgia, November 2006. Symposium 53. Terry Taylor, Chair. Malarial Retinopathy: Clinical Features, Pathological Correlations and Implications for the Pathogenesis of Severe Malaria.

Lewallen S, et al. Classifying and grading retinal signs in severe malaria. *Tropical Doctor.* 2006; 36 (suppl. 1): 1-13.

LEWALLEN ET AL DESCRIBED A CLUSTER OF retinal findings upon examination of persons with severe malaria that was termed malarial retinopathy in 1993. Since then studies of childhood malaria have yielded new information on disease prognosis and prediction of death based upon the described clinical features of malarial retinopathy. Dengue, however, has other more readily identifiable findings. A case of dengue-associated maculopathy has been reported and will be described here, although this entity remains rare.

A constellation of retinal changes specific to severe malaria and includes retinal whitening, blood vessel abnormalities and white-centered hemorrhages constitutes one of the most consistent associations with the phenomenon of cerebral red blood cell sequestration available to the clinician caring for patients with severe malaria, according to reports presented by Dr. Susan Lewallen from the Kilimanjaro Centre for Community Ophthalmology Moshi, Tanzania. Studies of severe childhood malaria in Africa over the last 10 to 15 years have led to better diagnosis and treatment of malaria and through this effort detailed studies of these associated eye findings were obtained.

The diagnosis of cerebral malaria is most often made on clinical grounds - coma in the presence of *Plasmodium falciparum* parasites in peripheral blood and absence of other causes for coma. A recent postmortem study of children dying with malaria parasitemia and the clinical diagnosis of cerebral malaria did not have pathological features associated with cerebral malaria and actually had other identifiable causes of death. Many children who present with mental status changes in Africa have incidental parasitemia , however, cerebral malaria carries a 15-50% mortality rate, even with treatment. Further understanding of the clinical significance of malarial parasitemia is needed. Between 1999 and 2005, a group of 879 children who were admitted with malaria parasitemia, a significant coma score, no other obvious explanation for coma was evaluated by an ophthalmologist using an indirect dilated eye exam. It should be noted that undilated eyes reveal approximately 1/100th of retinal surface area. Normal fundi were documented in 326 (37%) while 41% had hemorrhage, 46% had macular whitening and 46% had vessel changes described as tram-lining of the vessels in which an orange or white color is seen at the margin of the vascular blood column. Detailed descriptive indicators gradings and definitions of specific lesions are outlined in the Tropical Doctor publication and the report from Malawi.[1] Ninety-nine patients had more than one abnormality. Only 27% had papilledema, a nonspecific but severe and worrisome change, but one that that may be indicative of other contributing pathology. Of those with a

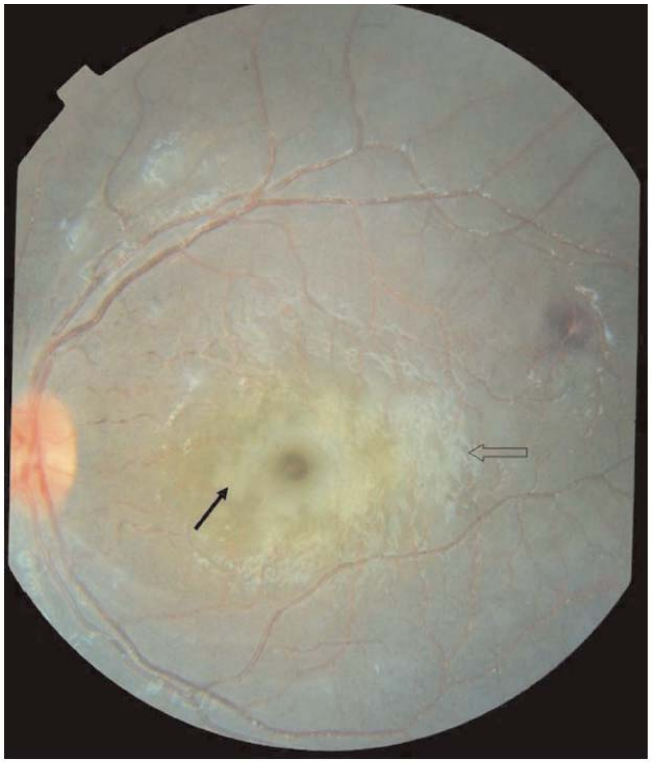

FIGURE 1. Severe macular whitening (**solid arrow**) completely surrounding the foveola of a Malawian child with cerebral malaria. Papilledema is present as well as a white-centered hemorrhage temporal to the macula and cotton wool spots above superior temporal arcade. The **open arrow** indicates glare (photographs provided by Nicholas A. V. Beare).

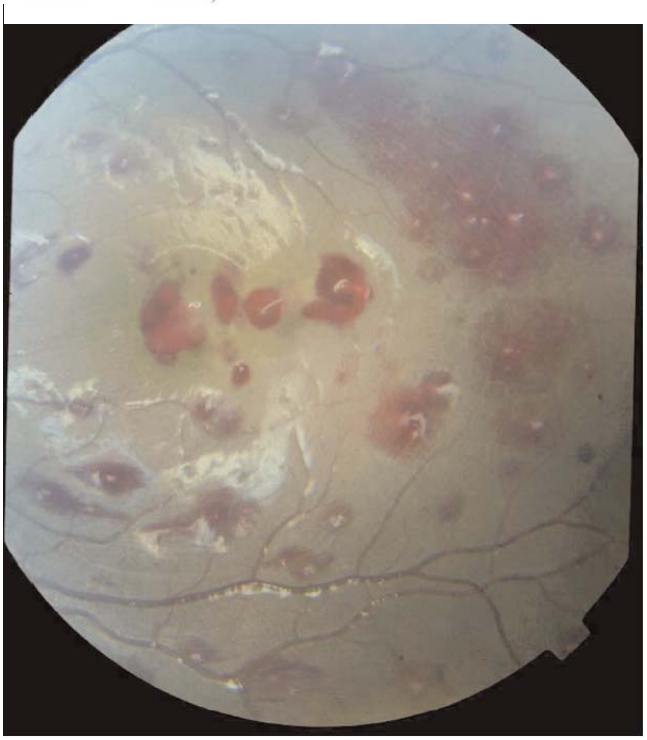

FIGURE 5. Large number of retinal hemorrhages in a child with cerebral malaria.

These images were taken from reference 1, Beare et al, 2006, with permission from the American Society of Tropical Medicine (www.astmh.org).

normal fundus 7% died due to other causes. Patients with malarial retinopathy had a 15% case fatality rate. Persons with papilledema alone, or papilledema with retinopathy had a 44% case fatality rate.

COMMENTARY

In this study ocular findings were the single most reliable indicator of cerebral red blood cell sequestration. Beare et al have indicated that there are four main components of malarial retinopathy; retinal whitening, changes in blood vessels (consisting of discoloration of vessels from orange to white), retinal hemorrhages and papilledema. The first 2 are felt to be specific for malaria. When papilledema is seen without these other changes to suggest malaria alternate causes of increased in intracranial pressure must be considered. Ophthalmologic examination by a straightforward indirect dilated eye exam may aid in a more accurate diagnosis of cerebral malaria and providing a prognosis for adults, as well as children, who present with coma and parasitemia.

A recent report found ocular abnormality in a dengue patient. A 31-year-old man with fever, rash, headache and myalgia presented following a trip to Malaysia. There were no hemorrhagic manifestations. The lowest platelet count was 71,000/µl and dengue serology was positive. On day 8 of his illness he complained of bilateral blurred vision. Detailed visual exam showed diminished visual acuity and fundoscopy revealed dilated veins, hyperemic optic discs, flame and blot hemorrhages soft exudates and macular edema. High-dose corticosteroids were initiated; both visual acuity as well as color vision improved.

Screening returned travelers with fever with more complete ophthalmologic exams may reveal eye ground changes that will greatly influence not only their course of management but also their visual outcomes. ■

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A Randomized Trial for Mucosal Leishmaniasis: Oral Pentoxifylline Combined with Pentavalent Antimony

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP

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Dr. Barry is a consultant for the Ford Foundation, and receives funds from Johnson & Johnson.

Synopsis: *Mucosal leishmaniasis is associated with intense tissue damage and high tumor necrosis factor production. Patients who experience treatment failure often will require greater than one pentavalent antimony (Sb^v) course or alternative drugs to achieve a cure.*

Source: Machado PR, et al. Oral Pentoxifylline Combined with Pentavalent Antimony: A Randomized Trial for Mucosal Leishmaniasis. *Clin Infect Dis*. 2007 Mar 15;44(6):788-793.

This publication describes a double-blind, placebo-controlled trial evaluating the efficacy of adding pentoxifylline to Sb^v treatment of 23 patients with mucosal leishmaniasis caused by *L. brasiliensis*. Eligible patients were between ages 18-65 and had severe mucosal leishmaniasis, defined as the presence of deep mucosal ulcers or nasal septal perforation. A clinical diagnosis was confirmed by either a positive intradermal skin test with leishmania antigen, parasite culture or characteristic histopathological findings. Patients were randomized to parenteral Sb^v (meglumine antimony) at a dosage of 20 mg per kg per day plus oral pentoxifylline (Pentox) at a dosage of 400 mg 3 times daily for 30 days. Controls received Sb^v treatment plus identical placebo pills.

All patients in the pentoxifylline group experienced a cure with one course of Sb^v whereas 5 (41.6%) of 12 patients in the placebo group required a second course of Sb^v ($P = 0.037$). The mean healing time, ± standard deviation, was 83 ± 36 days compared with 145 ± 99 days in the placebo group, $P = 0.049$. No relapses were documented in either group at a 2-year follow-up visit.

COMMENTARY

In Central and South America, cutaneous leishmaniasis is a major health problem with mucosal disease occurring in 3% of all patients with cutaneous disease caused by *Leishmania braziliensis*. Mucosal disease is observed either concomitantly or months to years following cutaneous disease, and is characterized by the presence of destructive lesions that predominantly affect the nose and vocal cord. Standard treatment has been high dose pentavalent antimony, but with clinical treatment failures noted up to 19% of the time.[1] Pentoxifylline is a methylxanthine that was originally licensed for use in peripheral artery disease associated with claudication. Its putative mechanism of action for ischemic claudication was as a rheologic modifier that increased red cell deformity and decreased whole blood viscosity. It has recently been shown to have a role in down-regulating TNF-α production. There is evidence that mucosal lesions in leishmaniasis are related to an unmodulated immune response in the host with increased production of pro-inflammatory cytokines and TNF-α production.[2]

This study demonstrated enhanced resolution of mucosal disease using combination therapy. Previously, these authors had demonstrated in an open label study that Sb^v and pentoxifylline significantly decreased TNF-α levels and resulted in a cure in 9 out of 10 patients refractory to three courses of Sb^v.[3] However, in both this study and the previous one, the numbers were small and statistical significance was not achieved. Thus, these papers present intriguing results that are not quite ready for prime time treatment. As we await larger numbers, pentoxifylline remains a relatively benign off-label consideration for refractory cases needing retreatment. ■

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CME Questions

4. Healthy adult travelers to Thailand:

a. should take prophylactic doxycycline to prevent travelers' diarrhea.

b. might find a single 1000 mg dose of azithromycin more effective than daily 500 mg doses in the event of travelers' diarrhea.

c. should use ciprofloxacin or levofloxacin as presumptive treatment for travelers' diarrhea.

d. should receive pre-travel rotavirus vaccination.

5. Typical ocular findings in cerebral malaria include which of the following?

a. Anterior uveitis

b. Retinal detachment

c. Retinal whitening and hemorrhages

d. Vitreal clouding and detachment

e. Hypopion

6. Which of the following statements is true of mucosal leishmaniasis?

a. It has been successfully treated with 28 days of pentamidine and pentoxyifylline.

b. It is diagnosed by specific serology and increased levels of anti-TNF-α.

c. It has been successfully treated by anti- TNF-α agents, such as etanercept and pentoxyifylline.

d. It has been cured after combination therapy with a pentavalent antimony agent combined with pentoxyifylline.

7. Which of the following statements regarding Chagas disease is incorrect**?**

a. .Patients with chronic *T. cruzi* infection remain potentially infectious for life.

b. *T. cruzi* infected donors are often asymptomatic.

c. Blood donations that test positive with the new *T. cruzi* ELISA will be quarantined and the blood donor notified of the results of testing.

d.. A wide variety of antitrypanosomal medications are available in the United States.

e. *T. cruzi* has been transmitted through blood products and organ transplants in the United States.

Answers: 4.(b) 5.(c) 6.(d) 7.(d)

CME Objectives

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

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

• To alert the readers to recent disease outbreaks and epidemics. ■

PHARMACOLOGY WATCH

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

Which Inhaler Combination is Best for COPD Treatment?

Two recent large studies have looked at the effects of various inhaler combinations on outcomes in patients with COPD. In the first, published in the February 22 issue of the *New England Journal of Medicine*, researchers from the United Kingdom looked at over 6,000 patients with COPD in a randomized, double-blind trial comparing salmeterol plus fluticasone inhaler twice daily (in a single inhaler) vs salmeterol alone, fluticasone alone, or placebo for 3 years. The primary outcome was death from any cause, the frequency of exacerbations, health status, and spirometry values. The all-cause mortality was 12.6% in the combination therapy group, 13.5% in the salmeterol group, 16.0% in the fluticasone group and 15.2% in the placebo group. The hazard ratio for death in the combination therapy group was 0.825 vs placebo ($P = 0.052$), a level that did not reach statistical significance, but was associated with a 17.5% relative reduction in mortality. The mortality rate for salmeterol alone or fluticasone alone did not differ from placebo. Combination therapy was associated with a statistically significant lower rate of exacerbations ($P < 0.001$). The probability of having pneumonia was higher among patients receiving fluticasone alone or medications containing fluticasone (*N Engl J Med*. 2007;356:775-789). An accompanying editorial suggests that the findings show that monotherapy with fluticasone should not be recommended, monotherapy with a bronchodilator may be an option, and that combination therapy "offers statistically significant advantages for health status, frequency of exacerbations, use of oral steroids... and protection against a decline in lung function" (*N Engl J Med*. 2007;356:851-854).

In the second study, 449 patients with moderate or severe COPD were treated with the anticholinergic inhaler tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol. The primary endpoint was COPD exacerbation that required treatment with systemic steroids or antibiotics. After one year there was no difference in the rate of exacerbation between tiotropium alone (62.8%), tiotropium plus salmeterol (64.8%), or tiotropium plus fluticasone/salmeterol (60.0%). Tiotropium plus fluticasone/salmeterol improved lung function ($P = 0.049$), disease-specific quality of life ($P = 0.01$), and reduced the number of hospitalizations for COPD exacerbation and all-cause hospitalization compared with tiotropium plus placebo. The authors conclude that adding fluticasone/salmeterol to treatment with tiotropium did not influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates (early release *Annals of Internal Medicine* 2/20/2007, print date 4/17/2007). So, what is the upshot of these papers? Combination inhalation therapy in patients with COPD works best, bronchodilator plus steroid inhalation therapy should continue to be the recommended regimen perhaps along with an anticholinergic inhaler.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

First Antihypertensive Drug Approved in Last 10 Years: Aliskiren

The FDA has approved the first of new class of antihypertensive drugs, and the first new antihypertensive medication to be approved in more than 10 years. Aliskiren is an oral renin inhibitor, inhibiting the renin-angiotensin system earlier in the cascade than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The drug is a once-a-day oral agent that is approved for use as monotherapy or in combination with other antihypertensives.

Aliskiren's effect is additive with hydrochlorothiazide, and seems to be well-tolerated with other cardiovascular agents. It will be available in 150 and 300 mg doses. The FDA approval was based on 6 placebo-controlled trials in more than 2,000 patients in which the blood- pressure-lowering effect was maintained for up to one year. The drug seems be effective across all age ranges, but is slightly less effective in African-American patients as compared to Caucasians and Asians, as is the case with ACEI's and ARBs. The primary side effect is diarrhea, which was seen in 2% of patients, usually on higher doses. Angioedema was also rarely noted. As with other drugs that affect the renin-angiotensin system, aliskiren should not be used during pregnancy. Aliskiren will be marketed by Novartis Pharmaceuticals, and will be marketed under the trade name Tekturna.

Alternate Treatment for Osteoporosis

Antiresorptive agents are standard therapy for osteoporosis. These drugs, which include the bisphosphonates (alendronate, risedronate, etc.) prevent bone breakdown, but they do not stimulate production of new bone. A new study looks at recombinant human parathyroid hormone (1-84) (PTH), a bone forming agent, as an alternative treatment for osteoporosis. In an 18 month, randomized, double-blind, placebo-controlled, parallel group study, 2,532 postmenopausal women with low bone mineral density at the hip or lumbar spine were randomized to receive 100 µg of PTH or placebo daily by subcutaneous injection. All received additional calcium 700 mg/d and vitamin D 400 U/d. The main outcome was new or worsened vertebral fractures, changes in bone mineral density as well as safety of the medication. PTH significantly reduced the risk for new or worsened vertebral fractures. The relative risk varied depending on the assumptions about women who did not complete the trial, but there was improvement in all subgroups. PTH also resulted in increased bone mineral density compared to placebo of 6.9% at the spine and 2.1% at the hip compared to placebo, but decreased bmd at the forearm. PTH also resulted in increased percentage of participants with hypercalciuria, hypercalcemia, and nausea by 24%, 23%, and 14% respectively compared to placebo. The authors conclude that parathyroid hormone (1-84) reduced the overall risk for new or worsened vertebral fractures in postmenopausal women with osteoporosis, and suggest that PTH provides an alternative therapy option for fracture prevention (*Ann Int Med.* 2006;146:326-339). This study adds a second option for anabolic (bone-forming) agents along with teriparatide.

Roche's Oseltamivir: Scrutiny, Bird Flu, and New Drug Applications

Roche's oseltamivir (Tamiflu) has come under scrutiny in Japan after 2 students who took the drug fell to their deaths in February. The drug has been associated with abnormal behavior in anecdotal reports including a Japanese boy who ran in front of a truck after taking the drug in 2004. Roche counters that influenza can cause abnormal behavior and denies a link between the medication and psychiatric problems. The drug has previously been associated with delirium, and the FDA has required labeling urging close monitoring for abnormal behavior since November 2006. Countries worldwide are stockpiling oseltamivir in case of avian influenza outbreak. Meanwhile Roche has filed a new drug application with the FDA for pediatric doses of the drug for children one year and older. The new capsules and a 30 milligram and 45 mg capsule would join the 75 mg adult strength capsule.

FDA Actions

The FDA has approved duloxetine (Cymbalta) for the treatment of generalized anxiety disorder. The drug is currently approved for the treatment of major depressive disorder in the management of diabetic peripheral neuropathic pain. The FDA approved duloxetine 60 mg once daily for the treatment of anxiety based on three randomized, double-blind placebo-controlled trials in 800 patients.

The FDA has approved lisdexamfetamine dimesylate capsules for the treatment of attention deficit/hyperactivity disorder in children age 6-12. Lisdexamfetamine is a pro-drug of dextroamphetamine that may be associated with less drug abuse than dextroamphetamine. The once-a-day drug will be available in 30, 50, and 70 mg strengths. Lisdexamfetamine is marketed by New River Pharmaceuticals under the trade name Vyvanase. ■