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Southern Chad—The Forgotten Crisis

SPECIAL FIELD REPORT

By Mary-Louise Scully, MD

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

ONE OF THE TRULY ENJOYABLE ASPECTS OF PRACTICING TRAVEL MEDICINE and preparing patients for travel is learning about the diversity of volunteer programs and nongovernmental organizations throughout the world. Even more intriguing is hearing the details about the personal motivations that lead a person to go off and dig a well in an African village, teach women in Afghanistan to be hairdressers, or deliver solar backpacks to children in rural Rwanda. The range of volunteers extends now from high school students right up to retirees, and no corner of the world is off-limits, even areas with political unrest and personal safety concerns.

So, when Bill Felstiner, former Associate Dean of the Yale Law School, arrived in my office for his pre-travel visit to southern Chad, I was curious about his motivations. Needless to say, Chad is not a popular travel destination. Bill and co-founder Catherine Swysen had formed a non-profit organization, Chad Relief Foundation, whose mission was to provide assistance to the people of southern Chad. Significant media attention is given to the 250,000 western Sudanese refugees in eastern Chad, but it is less well known that there are also about 40,000 refugees in southern Chad who have been displaced from their homes in northern Central African Republic (CAR) because of fighting between governmental troops and armed rebel groups. These refugees in southern Chad are sometimes referred to as the "forgotten refugees." Chad Relief Foundation (CRF) asked me to travel to southern Chad in October to help assess the medical needs in this area. The trip also was intended to follow up on the progress of previous CRF-sponsored projects and to hand-carry $26,000 of donated medications from Direct Relief International.

Chad is one of the 10 poorest countries in the world. It is estimated that 80% of its 10.1 million people live with less than $1 per day, mostly as subsistence herders and farmers. At 496,000 square miles, Chad is slightly smaller in size than Peru with mostly desert and mountains in the north but savanna and grasslands in the south. Transparency International, a global coalition against corruption, lists Chad among the 10 worst countries of the world on its corruption index. Oil production in Chad began in 2003 but, unfortunately, very little, if any, oil revenues trickle down to actually improve the living conditions of the

local population. President Idriss Deby has remained in power despite numerous rebel coup d'état, most recently in February 2008. Some volunteer groups (Engineers without Borders) have set Chad "off limits" for volunteer efforts due to security threats from rebel activity and rogue bandits.

Our specific destination was Gore, Chad, which is about a 10-hour car drive south from the capital of N'Djamena. (*See Map.*) In Gore, the United Nations High Commission of Refugees (UNHCR) has facilities that direct operations in the three nearby refugee camps. Amboko camp was first opened in June 2003 (12,045 refugees), the Gondje camp was opened in 2005 (12,600 refugees), and the most recent camp, Dosseye, opened in 2006, has about 8,318 refugees. The UNHCR contracts with the Cooperazione Internazionale (COOPI) and UNICEF to provide health care to the residents of the camps. Other NGOs in the area providing relief include Africare, CARE, ACRA, and the World Food Program.

Malaria is the largest health threat. During the peak rainy season, May through October, about 80% of consultations to the camp health clinics are for malaria. The WHO estimates one out of five children younger than age 5 die in Chad, and about 22% of these deaths are attributed to malaria. There are only two doctors to oversee the camp health clinics (> 32,000 refugees), so trained nurses and assistants maintain the daily triage of patients. Patients with a fever over 103°F are tested with rapid diagnostic test malaria tests (RDTs) provided by the Mentor initiative. If positive, presumptive antimalarial treatment is given. Artemisinin-based combination therapy (ACT) medications such as artemether-lumefantrine or artesunate-amodiaquine are in high demand, but many patients still receive chloroquine or Fansidar when supplies for ACTs run short, as they often do.

HIV in Chad is an unfolding story. A 2005 national survey found an adult HIV prevalence of 3.3%, but this is likely a gross underestimate as voluntary testing is not routinely available. A new facility at the Amboko camp and the local hospital in Gore (presently staffed by Médecins Sans Frontières) have begun programs to provide voluntary testing for HIV. Patients diagnosed with HIV, especially pregnant women, are to be educated on their disease with focus on the available strategies for prevention of maternal-fetal transmission. These programs are newly initiated and in great need of financial support.

Vaccine clinics in the refugee camps teach a valuable lesson. In the United States, high vaccination rates led to a low prevalence of measles, hepatitis, and tetanus, making these diseases seem just "words" to American mothers. But Chadian mothers know these as real diseases, having watched non-immunized children suffer or even die. These mothers will wait in line for hours in the 100-degree heat and sun at a vaccine clinic just to insure that their children are among those immunized. Standard immunizations include BCG and polio at birth; tetanus, hepatitis B, Hib, and polio at 6 weeks, 10 weeks, and 14 weeks. Yellow fever and measles are given at 9 months. Vitamin A, nutrition supplements, and nutrition clinics focus effort on improving the extensive malnutrition problems, especially in pregnant women and infants.

Health care and vaccination programs for the refugees are better, at the moment, than for most of the local

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Map

Chad

Source: United Nations High Commission for Refugees

Chadian population who need to rely on local health clinics run by the government whose support and funding are sorely lacking. Eventually the UNHCR and other NGOs in southern Chad will need to transition southern Chad to self-sustaining health and education programs. But most local health and education administrators feel that with the present state of the government, the internal and external conflicts of the area, and the relative lawlessness of rebel groups and bandits, the prospect for the future is grim.

The story of onchocerciasis (river blindness) illustrates these problems. Chad was one of the 16 African countries receiving regular ivermectin treatment support through the African Programme for Onchocerciasis Control (APOC) and ongoing donation of drugs from Merck & Co. Launched in 1998, the Chad program received $1.639 million and, despite there being only one APOC site in Chad (Cameroon has 15 sites), the positive effects of the community-directed treatment programs in decreasing river blindness was apparent. However, as the 2012 APOC deadline to end financial support in Chad approaches, the government is failing to fill the void. We visited a small rural village in the far southwestern corner of Chad near the border of Cameroon and CAR where the incidence of river blindness is increasing again. Community treatment programs formerly in place have declined, and the village chief explained simply, "no one comes anymore."

For the moment, the people of southern Chad are fortunate to have the UNHCR and several NGO groups in the area working to improve health, education, and the living conditions of both locals and refugees amidst immense obstacles. These people are often assigned to this remote area for one- or two-year contracts, and because of safety concerns no family members are allowed to join them permanently. I came away from Chad and the experience now understanding that the real unsung heroes are those who commit years and sometimes even their entire lives to the complex world of humanitarian relief.

For more information on humanitarian relief in Chad, please visit www.chadrelief.org. ■

For updated travel and health information on Chad, please see the Travel Medicine Advisor web site's Country Maps (www.travelmedicineadvisor.com).

Response to Hepatitis B Vaccine

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

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

Synopsis: *The combined hepatitis A and B vaccine successfully produces antibody response in previous hepatitis B vaccine nonresponders, and offers another method to manage at-risk nonresponders.*

Source: Cardell K, Akerlind B, Sallberg M, et al. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. *J Infect Dis* 2008;198:299-304.

The investigators administered a series of double-dose combined hepatitis A and B vaccine at 0, 1, and 6 months to 48 nonresponders and 20 controls (HBV-naïve subjects). Nonresponders were defined as persons who did not have an anti-HBs titer of ≥ 10 mIU/mL despite receiving at least 4 doses of recombinant hepatitis B vaccine. Anti-HBs and anti-HAV were measured before vaccination and 1 month after each dose, with ≥ 10 mIU/mL considered to be protective.

Among 44 nonresponders who completed the study, the following developed protective anti-HBs after each dose of the vaccine: 26 (59%) after the first dose, 35 (80%) after the second dose, *and 42 (95%) after the third dose*. Among the 20 in the reference group, the following developed protective anti-HBs: 2 (10%) after

dose 1, 19 (95%) after dose 2, and 20 (100%) developed protective anti-HBs after the third dose. All subjects developed anti-HAV. Two subjects did not respond after the series. One subject had no detectable anti-HBs and the other had an anti-HBs level of 8.5 mIU/mL.

Comparison of the seroconversion rates between the nonresponders and the reference group supports anamnestic response to revaccination in the nonresponders. Additionally, anti-HBs and anti-HAV titers were lower in the nonresponder group, which suggests that there could be a more general immune responsiveness factor. Investigators analyzed other factors that may influence responsiveness and found that high body mass index (BMI) and smoking were associated with lower anti-HBs. Similarly, they found an association between high BMI and lower anti-HAV.

COMMENTARY

Hepatitis B is caused by a DNA virus in the *Hepadnaviridae* family that is transmitted via percutaneous or mucosal exposure. Following exposure, the virus spreads in the blood to reach the liver, where it replicates. Liver function abnormality (ALT) manifests after about 60 days of incubation, and jaundice may present following 90 days of incubation.

Worldwide, 350-400 million persons are chronic HBV carriers.[2] Prior to the initiation of the childhood hepatitis B immunization program in the United States in 1991, 200,000-300,000 new cases of hepatitis B were reported annually.[3] Since the initiation of the hepatitis B immunization program, the incidence of acute hepatitis B declined dramatically. However, 95% of an estimated 51,000 new HBV infections in 2005 occurred in adults.[1] Among the reported cases of new HBV infections in 2005, the highest incidence occurred in adults 25-45 years of age; 79% were associated with high-risk sexual activity or IV drug use, 5% were associated with occupational exposure, healthcare, travel, and household contact, and 16% denied any known risk.[1]

CDC recommends post-vaccination testing for "persons whose subsequent clinical management depends on knowledge of their immune status, including certain healthcare and public safety workers; chronic hemodialysis patients, HIV-infected persons, and other immunocompromised persons; and sex or needle-sharing partners of HBsAg-positive persons."[1] The generally accepted protective anti-HBs level is a titer of ≥ 10 mIU/mL, and approximately 5-10% of vaccines do not develop this level of response. Factors associated with poor or nonresponse to hepatitis B vaccine include: male gender, tobacco smoking, obesity, age > 30 years, immunosuppression, HIV infection, chronic liver disease, alcoholism, chronic renal disease, site of injections (gluteal rather than deltoid), length of needle, and genetic predisposition.[4]

Strategies to induce anti-HBs of ≥ 10 mIU/mL include: revaccination with hepatitis B vaccine intramuscularly (single dose or series); intradermal administration of hepatitis B vaccine[5]; administration of a double-dose hepatitis B vaccine; and administering a triple-antigen hepatitis B vaccine (Hepacare, not available in the United States).[6,7] Among nonresponders to the 3-dose primary vaccine series, 25-50% responded to an additional vaccine dose, and 44-100% responded to a 3-dose revaccination series.[1] Possible infection with HBV should be assessed if nonresponse persists after revaccination.[1,4] The response rates of 59% after one double-dose combined hepatitis A and B vaccine and 95% after three doses would offer one more method to induce a protective level of anti-HBs. Results of this study support the possibility that the hepatitis A component acts as an adjuvant to hepatitis B vaccine.

Waning immunity is a natural phenomenon in which anti-HBs levels decline after HBV vaccination, with the quickest decline during the first year. Due to immune memory, an individual who develops protective anti-HBs level after HBV vaccine may remain protected against acute hepatitis B infection in spite of declining anti-HBs. Long-term follow-up of recipients of hepatitis B vaccines in high-endemicity populations have reported breakthrough HBV infection by 15 years after primary hepatitis B vaccination, although the infections were asymptomatic.[8-10]

The European Consensus Group on Hepatitis B Immunity published a statement in 2000 that immune memory appears to last at least 15 years in immunocompetent persons. The group recommended postvaccination testing specifically in healthcare workers and immunocompromised patients after primary hepatitis B series, and testing the latter group every 6-12 months.[11] Among immunocompetent individuals tested (see CDC recommendation above) who have shown adequate anti-HBs levels postvaccination, currently there is no recommendation to test routinely. ■

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Treating Travelers' Diarrhea

ABSTRACT & COMMENTARY

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric & Adolescent Medicine, Mayo Clinic, Rochester, MN.

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

Synopsis: *In conjunction with oral hydration, medications can help decrease the degree and duration of symptoms in patients with travelers' diarrhea. The combination of loperamide and an antibiotic is particularly effective. Either a fluoroquinolone or azithromycin may be used.*

Source: Drugs for travelers' diarrhea. *The Medical Letter* 2008;50 (issue 1291): 58-59.

Travelers' diarrhea is usually a self-limited illness caused by noninvasive enterotoxigenic *Escherichia coli*. Antimicrobial therapy, in conjunction with adequate oral hydration, can decrease the frequency and duration of excessive stooling. For traveling adults and older children with mild diarrhea, loperamide, a synthetic anti-motility opioid agent, may be administered for one to two days. For travelers with moderate to severe diarrhea, diarrhea lasting more than three days, bloody diarrhea, or fever, an antibiotic is usually recommended. A fluoroquinolone (ciprofloxacin, levofloxacin, norfloxacin, or ofloxacin) is generally given as the first choice for non-pregnant, non-pediatric travelers. Azithromycin is an alternative choice that actually has some advantages over fluoroquinolones. Rifaximin is approved for afebrile travelers older than 12 years of age with noninvasive *E. coli* and no blood present in the stool.

COMMENTARY

Up to 40% of travelers experience bothersome diarrhea, and even short-term trips may be significantly compromised by this common illness. The *Medical Letter*, in its usual clear, concise, practical way, gives direct guidance about the use of medications in patients with travelers' diarrhea. Nonetheless, some questions remain.

At what point should presumptive therapy with antibiotics be started? The guidelines suggest that "mild" diarrhea be treated with loperamide and that an antibiotic be given for "moderate to severe," persistent, febrile, or bloody diarrhea. For many travelers, the practical definition of "severity" depends more on their itinerary, schedule, mode of transportation, and their awareness that even physically mild diarrhea would significantly interrupt their plans. Some travel medicine practitioners would substitute "significantly bothersome" as the criteria by which a traveler would choose to begin antibiotic therapy.

Usually, the uses of loperamide and antibiotics are not mutually exclusive. Data from adults in Mexico[1] and from military personnel in Turkey[2] suggest that combination therapy is more effective than antibiotic therapy alone. Loperamide, however, should be avoided in young children and in individuals with invasive disease, as suggested by the presence of either blood in the diarrhea or fever.

Which antibiotic should be available for presumptive treatment of travelers' diarrhea? The new *Medical Letter* guidelines suggest that a fluoroquinolone is still the first

choice—except for pediatric and pregnant travelers—but wisely acknowledge that an alternative, azithromycin, does have advantages. Azithromycin seems equally effective to fluoroquinolones in treating *E. coli*, and azithromycin offers the advantage of also covering other microbes, such as fluoroquinolone-resistant *Campylobacter*, that account for some cases of travelers' diarrhea. If there is reasonable certainty that an individual adolescent or adult traveler's symptoms are due to *E. coli*, another option would be treatment with rifaximin.

How long should the antibiotic be given? There are data suggesting that a single initial dose of either a fluoroquinolone or azithromycin is as effective as the previously utilized three-day dosing. For azithromycin, however, it is not yet known whether a standard single dose of 500 mg is as effective as the studied single dose of 1000 mg.

What if the treatment is incompletely effective? In that case, one must be cognizant of other microbial causes of diarrhea in travelers. *Campylobacter* is increasingly resistant to fluoroquinolones. Multi-drug-resistant enteroaggregative *E. coli* might be a problem in some cases of travelers' diarrhea.[3] In addition, seemingly prolonged travelers' diarrhea actually could be due to a subsequent bout of *Clostridium difficile* diarrhea complicating initially treated *E. coli* diarrhea.[4] Also, parasites such as *Cryptosporidium* account for about one-tenth as much travelers' diarrhea as enterotoxigenic *E. coli*.[5] Clinicians must consider these other possibilities, and other specific treatments, in the case of travelers' diarrhea that continues despite standard antibiotic therapy.

What would be better than presumptive treatment? An effective vaccine. Unfortunately, even though there is some efficay of current cholera vaccines against enterotoxigenic *E. coli*,[6] this protection is incomplete. Other vaccines are being evaluated.[7] ■

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New Treatment Approach for Indian Visceral Leishmaniasis

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP

Dr. Barry is a Professor of Medicine and Public Health; Director of International Health Program, Department of Medicine, Yale University School of Medicine, New Haven, CT.

Dr. Barry reports no financial relationships relevant to this study.

Synopsis: *A new treatment approach to visceral leishmaniasis, or kala-azar, using single-dose liposomal amphotericin B followed by short-course oral miltefosine has been demonstrated in the Bihar area of India where 90% of India's cases, and 45% of the world's cases, occur.*

Source: Sundar S, Rai M, Chakravarty J, et al. New treatment approach in Indian visceral leishmaniasis: Single-dose liposomal amphotericin B followed by short-course oral miltefosine. *Clin Infect Dis* 2008;47:1000-1006.

Bihar, India, is the source of nearly one-half of the world's burden of visceral leishmaniasis and, unfortunately, drug resistance has ended the usefulness of pentavalent antimony (Sb) therapy. Early reports of miltefosine resistance have prompted investigation of alternative, cost-effective, practical regimens. This group postulated that a single infusion of IV liposomal amphotericin B (L-AmB) could be curative and, if followed by short-course oral miltefosine, potentially could prevent future drug resistance. They randomized 181 subjects to treatment of 5 mg/kg L-AmB alone (group A: 45

Table.

Responses to treatment for patients treated for Indian visceral leishmaniasis using single-dose liposomal amphotericin B (L-AmB) followed by short-course oral miltefosine.

Variable	Group A	Group B	Group C	Group D	Group E
L-AmB dose, mg/kg	5	5	5	3.75	5
Duration of miltefosine treatment, days	0	10	14	14	7
Enrolled	45	46	45	45	45
Completed treatment	45	46	45	45	45
Apparent cure on day 16	45	46	45	45	45
Relapse	3	1	2	2	1
Death	1	0	0	0	0
Lost to follow-up	0	0	0	0	0
Definitive cure at 9 months[a]	41	45	43	43	44
Percentage of patients with definitive cure at 9 months[a] (95% CI)	91 (78-97)	98 (87-100)	96 (84-99)	96 (84-99)	98 (87-100)

NOTE: Data are no. of patients, unless otherwise indicated. Group A received 5 mg/kg of L-AmB administered once. Group B received 5 mg/kg of L-AmB administered once plus miltefosine for 10 days. Group C received 5 mg/kg of L-AmB administered once plus miltefosine for 14 days. Group D received 3.75 mg/kg of L-AmB administered once plus miltefosine for 14 days. Group E received 5 mg/kg of L-AmB administered once plus miltefosine for 7 days. All subjects received a single infusion of the indicated dose of L-AmB on day 1.

[a] Patients who experienced relapse (n = 9) or died (n = 1) by month 9 were designated as having experienced treatment failure.

subjects), 5 mg/kg L-AmB followed by miltefosine for 10 days (group B: 46 subjects) or 14 days (group C: 45 subjects), or lower dose L-AmB 3.75 mg/kg followed by oral miltefosine for 14 days (group D: 45 subjects), and L-AmB 5.0 mg/kg followed by oral miltefosine for 7 days (group E: 45 subjects). (*See Table.*) Patients were eligible if they were older than 12 years of age with symptoms and signs of kala-azar (e.g., fever, weight loss, and splenomegaly) and parasites demonstrated by microscopic examination of splenic aspirate smear at time of diagnosis. Pregnant or breast-feeding women and individuals who were seropositive for HIV were excluded. Patients with severe pancytopenia (wbc < 1000, plts < 40,000, hgb < 3.5 g/dL) or liver or renal insufficiency were excluded.

Each regimen was satisfactorily tolerated, and all 226 subjects showed initial cure responses with negative splenic aspirates at 16 days. Nine months after treatment, final cure rates (defined as feeling healthy without signs or symptoms of relapse) were similar; group A, 91% (95% confidence interval [CI], 78%-97%]; group B, 98% (95% CI, 87%-100%); group C, 96% (95% CI, 84%-99%]; group D, 96% (95% CI, 84%-99%); and group E, 98% (95% CI, 87%-100%).

A single dose of intravenous liposomal amphotericin B (L-AmB) was tested, as was intravenous L-AmB followed by several randomized treatment regimens of short-term oral miltefosine therapy. All randomized regimens in this pilot study resulted in 100% parasite-free splenic aspirates at 16 days and symptom-free patients at 9-month follow-up. The authors postulate that potential advantage of 2-drug combination therapy includes lowered toxicity, better compliance, and less likelihood of developing drug resistance that has made traditional first-line monotherapy with pentavalent antimony obsolete in this part of the world.

These results suggest that treatment with single-dose L-AmB as well as single dose L-AmB followed by 7, 10, or 14 days of miltefosine is active against Indian visceral leishmaniasis or kala-azar. The authors postulate a short-course, sequential regimen has the benefit of preventing drug resistance in areas where miltefosine resistance is already beginning to be reported.

COMMENTARY

Leishmaniasis, spread by the bite of the female sandfly, is caused by a heterogeneous group of protozoan

parasites belonging to the genus Leishmania. Leishmaniasis, also known as kala-azar or black fever, is caused by three parasite species of *L. donovani* complex; *L. donovani*, *L. infantum,* and *L. chagasi*. In 1903, Leishman and Donovan separately described *Leishmania donovani* in splenic tissue from patients in India with a life threatening disease called visceral leishmaniasis. Unfortunately, almost a century later epidemics of this sandfly-borne disease persist and pentavalent antimony (Sb) therapy has now been made obsolete due to drug resistance in this part of India.[1] In India and Bangladesh, *L. donovani* has no animal reservoir, and humans serve as both the natural reservoir and host for infection. Kala-azar means "black sickness" and refers to the earthen-gray skin color that is common among infected individuals in India. Most patients do not recall a primary cutaneous lesion from the vector bite, but present with five characteristic hallmark features:

- hepatosplenomegaly;
- fever;
- cachexia;
- pancytopenia; and
- hypergammaglobulinemia.

Examination often reveals massive splenomegaly and moderate hepatomegaly. Concomitant HIV infection can produce unusual features in kala-azar with involvement of the central nervous system, respiratory tract, and gastrointestinal tract.

The results of this pilot study indicate the feasibility and cost-effectiveness of combination therapy in Indian kala-azar. A single intravenous dose L-AmB followed by oral miltefosine mitigates the cost of traditionally longer and more expensive regimens. A 28-day cost of the traditional course of oral miltefosine remains fairly expensive, even at the discounted price offered to the World Health Organization (US $84 for a patient weighing > 25 kg). Although inexpensive, paromomycin requires 21 days of intramuscular injection. Inpatient 5-day course L-AmB (total dose 15 mg/kg) is also expensive despite its discounted price, and treatment with intravenous amphotericin B deoxycholate usually requires 30 days in the hospital. Thus, the simplified regimens reported in this study could encourage drug compliance and be cost saving.

It is important to note that this trial was not designed to identify whether addition of miltefosine meaningfully improves the over 90% cure rate of single dose L-AmB alone or whether any of the tested combinations are as effective as the traditional 28-day oral course of miltefosine alone. It is also important to note all HIV-infected patients were excluded from this study. However, this pilot suggests outpatient single infusion of L-AmB followed by brief self-administered miltefosine may produce high cure rates inexpensively and might theoretically prevent drug resistance, although that was not proven in this study. Future confirmatory studies are eagerly awaited. ■

CME Questions

19. According to recent guidelines, travelers' diarrhea may be treated presumptively with:

a. loperamide alone in the event of bloody diarrhea in a febrile traveler.
b. rifaximin if the traveler is younger than 12 years of age.
c. azithromycin if the traveler is pregnant.
d. levofloxacin if *Campylobacter* is a likely etiology of the diarrhea.

20. The following method(s) can produce protective levels of anti-HBs in previous nonresponders:

a. Revaccinate with the hepatitis B vaccine series intramuscularly.
b. Revaccinate with the hepatitis B vaccine series intradermally.
c. Administer double-dose hepatitis B vaccine series intramuscularly.
d. Administer double-dose combined hepatitis A and B vaccines intramuscularly.
e. All of the above

21. Visceral leishmaniasis is:

a. a disease caused by a sandfly vector with both human and animal reservoirs in India.
b. a disease which is common in parts of India and has been traditionally treated with a 28-day course of oral miltefosine or IV amphotericin.
c. a disease which this study showed can be treated by single dose IV amphotericin B deoxycholate.
d. a disease presents with cutaneous ulcers followed by hepatosplenomegaly and fever.

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 fo the world; and

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

CTH® Review and Travel Medicine Update, sponsored by the ISTM, will be held March 8, 2009, in Philadelphia, PA. Please see **www.istm.org** for details.

Answers: 19. c; 20. e; 21. b

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*.

Are 5-α Reductase Inhibitors Associated with Hip Fractures?

In the issue: 5-α reductase inhibitors and hip fracture in men; the effects of drug-reimbursement policy on outcomes; new guidelines for type 2 diabetes; beta-blocker-associated bradycardia is linked to CVD events; FDA Updates.

DO 5-α REDUCTASE INHIBITORS AFFECT BONE DENsity in men? These drugs, which include finasteride (Proscar®) and dutasteride (Avodart®), have been used for more than a decade to treat benign prostatic hyperplasia (BPH). The drugs block the conversion of testosterone to dihydrotestosterone, the more powerful androgenic agent, which is responsible for secondary sex characteristics, but also adverse effects such as BPH, acne, and male pattern baldness. The 5-α reductase inhibitors shrink prostatic tissue and improve BPH symptoms over time and also can be associated with erectile dysfunction and gynecomastia. Recently researchers looked at the correlation between use of finasteride and bone health, which is highly dependent on steroid pathways. Researchers from Kaiser Permanente in Southern California performed a population-based case-control study of 7076 men age 45 and older with incident hip fractures over a 10-year period. Control patients were 7076 men without hip fracture. The rate of BPH was the same in both groups. There was no suggestion of a dose-response relationship between exposure to 5-α reductase inhibitors and hip fracture (P = 0.12). Interestingly, there was slightly higher rate of α-blocker use in the hip fracture group. The authors conclude that exposure to 5-α reductase inhibitors is not associated with increased risk of hip fracture; in fact, there was a trend toward a protective effect. The increased risk associated with exposure to α-blockers (which can cause orthostasis) needs further investigation (Jacobsen SA, et al. Association between 5-alpha reductase inhibition and risk of hip fracture. *JAMA* 2008;300:1660-1664).

Effect of drug-reimbursement policy on health care outcomes

Researchers recently looked at clopidogrel use and health outcomes for cardiac patients before and after a Canadian provincial government changed its prior-authorization policy for medications to a more liberal limited-use policy. Researchers looked at all patients 65 years or older with acute myocardial infarction who underwent PCI with stenting. The primary outcome was composite rate of death, recurrent acute myocardial infarction, PCI, and coronary artery bypass grafting at one year. After the change in benefits, the rate of clopidogrel use for 30 days after hospitalization increased from 35% to 88% and the mean time to first dispensing of clopidogrel decreased from 9 days to 0 days. The one-year composite cardiovascular outcome decreased from 15% in the prior-authorization

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group to 11% in the limited-use group ($P = 0.02$). The authors conclude that removal of prior-authorization leads to improvement in timely access to clopidogrel after coronary stenting and improved cardiovascular outcomes (Jackevicius CA, et al. Cardiovascular outcomes after a change in prescription policy for clopidogrel. *N Engl J Med* 2008;359:1802-1810).

Updated guidelines for type 2 diabetes

The American Diabetes Association and the European Association for the Study of Diabetes have updated their treatment guidelines and algorithms for the treatment of type 2 diabetes. Published simultaneously in *Diabetes Care* and the European journal *Diabetologia*, the guidelines update the initial August 2006 guideline and the January 2008 update to reflect safety issues surrounding the thiazolidinediones (TZDs) and also introduces new classes of medications to the algorithm. Retained as step 1 therapy are lifestyle interventions and metformin. Step 2 therapy includes insulin and sulfonylureas, while TZDs have been dropped as initial therapy. Of the two TZDs, only pioglitazone (Actos™) is recommended by the guideline. Safety concerns regarding rosiglitazone (Avandia®) have resulted in the guideline group to state: "…given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone." The GLP-1 agonist exenatide (Byetta®) is elevated to tier 2 with the guideline pointing out the advantage of weight loss associated with the drug, but also noting it is given by two injections per day, has frequent GI side effects, is very expensive, and does not have an established long-term safety history. Other drugs newly mentioned in the guideline include the α-glucosidase inhibitors (starch blockers), acarbose (Precose™) and miglitol (Glyset®); the glinides, repaglinide (Prandin®) and nateglinide (Starlix®); the amylin agonist primlintide (Symlin®); and the DPP-4 inhibitor sitagliptin (Januvia®) (Nathan DM, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm of the initiation and adjustment of therapy. *Diabetes Care* 2009;32:1-11; Available at: http://care.diabetesjournals.org/misc/dv08-9025.pdf).

Beta-blockers and hypertension

Beta-blockers have come under increasing fire for treatment of hypertension. Now a new study links beta-blocker-associated bradycardia with increased risk of cardiovascular events. Researchers from Columbia University performed a meta-analysis of 9 randomized controlled trials evaluating beta-blockers for hypertension and from which heart rate data were reported. The compiled studies included more than 34,000 patients taking beta-blockers and more than 30,000 on other antihypertensive agents, as well as nearly 4000 patients receiving placebo. Lower heart rate associated with beta-blocker use was linked to a greater risk for all-cause mortality ($r = -0.51$; $P < 0.0001$) and cardiovascular mortality ($r = -0.61$; $P < 0.001$). There was also a statistically significant increase in myocardial infarction, stroke, and heart failure associated with lower heart rates. The authors conclude that in contrast to patients with myocardial infarction and heart failure, beta-blocker-associated reduction in heart rate increases the risk for cardiovascular events and death for hypertensive patients. The authors even suggest that beta-blockers may no longer be indicated for treatment of hypertension in the absence of compelling indications (Bangalore S, et al. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. *J Am Coll Cardiol* 2008;52:1482-1489).

FDA Updates

The FDA has approved a new selective α-blocker for the treatment of benign prostatic hyperplasia. Silodosin is an α-1 receptor blocker with high affinity for prostate, bladder, and urethra. It will be marketed in an 8 mg dose to be given once daily; however, 4 mg should be used in men with hepatic or renal impairment. Silodosin will be marketed by Watson Pharmaceuticals as Rapaflo™.

The FDA will investigate a report for the Institute of Safe Medication Practices regarding varenicline (Chantix®), Pfizer's smoking cessation drug. For the second straight quarter, varenicline accounted for more reported serious injuries than any other prescription drug with a total of 1001 new cases reported to ISMP, including 50 deaths. The FDA has previously issued a Public Health Alert about psychiatric side effects from the drug, but the new report sites numerous cases involving vehicular or other accidents, or syncope with a high potential to cause accidents. The federal government has already taken action to ban airline pilots and military missile crews from using the drug. Sales of varenicline have dropped sharply this year as a result of these reports. ■