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Post-earthquake Public Health in Haiti

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

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Synopsis: *At a depth of 13 km, and just 25 km from Port-Au-Prince, Haiti, a fault system along the boundary separating the North American and Caribbean plates abruptly experienced a rapid acceleration of its usual super-slow-motion, lateral strike-slip faulting. On January 12, 2009, at 16:53 local time, the result was the devastation of portions of the western third of the island of Hispaniola by an earthquake of magnitude 7.0 on the Richter scale. This was not the first earthquake to strike Haiti — Port-Au-Prince was largely destroyed by one in 1770 — but it appears to be the strongest recorded. It has been estimated that the number of deaths directly resulting from the event exceeds 200,000, perhaps by many tens of thousands. The injured must be dealt with and the population provided water and food. The conditions created by the devastation, particularly in a country that some considered a disaster before the earthquake, will produce a colossal public health challenge. WHO has posted a preliminary statement aimed at facilitating the response to the challenges presented by this calamity.*

Source: Public health risk assessment and interventions. Earthquake: Haiti. January 2010 World Health Organization. Communicable Diseases Working Group on Emergencies, WHO headquarters Communicable Diseases Surveillance and Response, Pan American. Disclaimer: WHO reference number: WHO/HSE/GAR/DCE/2010.1 http://www.who.int/diseasecontrol_emergencies/publications/haiti_earthquake_20100118.pdf

HAITI, WITH A 2007 POPULATION OF 9.7 MILLION, IS THE POOREST COUNTRY IN the Western Hemisphere, with 55% of households earning less than one $1 U.S. per day. Before the earthquake, 45% of the population lacked access to safe water and 83% lacked access to adequate sanitation. Most health care is provided by traditional healers. Malnutrition is commonplace, and multiple

Table 1. Vaccine coverage at 1 year of age, 2007

Antigen	Coverage
BCG	75%
DPT, 3rd dose	53%
Measles	58%
Polio, 3rd dose	52%

infectious diseases, including HIV and tuberculosis, are endemic. Vaccination rates are inadequate. (*See Table 1.*)

Traumatic injuries, including crushes and burns, are common after earthquakes. These obviously necessitated the availability of surgical facilities and intensive care — which require evacuation to medical facilities in other countries. These will also result in infections, including gangrenous ones. The limited vaccination coverage of the population makes tetanus an important risk, as was seen in Aceh after its tsunami. The injuries and infections, as well as the lack of drinking water in a hot tropical climate, lead to many cases of acute renal failure, necessitating dialysis.

The lack of safe drinking water is not likely to be solved by rain since, during the winter dry season, there are only an average of three days with measurable rainfall, yielding a total of 32 mm in the month of January. Water that is available is often not safe, putting the population at risk of water-borne diseases, such as typhoid, hepatitis A, and hepatitis E. Leptospirosis is endemic in Haiti but, fortunately, cholera is not. Polio has been eliminated from Haiti.

Resettlement of displaced individuals to camps often results in crowding (although crowding in urban Haiti existed already), with resultant transmission of a number of respiratory infections, including measles, diphtheria, pertussis, and a variety of respiratory viral infections. Of note is that pandemic influenza A (H1N1) 2009 is currently circulating in Haiti. Meningococcal disease also may spread under these conditions. Of great concern in conditions of crowding is tuberculosis, which, in 2007, had an incidence of 147 cases per 100,000 population. Approximately 4,000 patients were receiving treatment for tuberculosis in Port-Au-Prince at the time of the earthquake. Many with tuberculosis are coinfected with HIV.

Vector-borne diseases also may pose a risk, especially with the population abandoning their homes for fear of aftershocks and living in the streets. West Nile virus has been detected in Haiti. All four dengue types are endemic in Haiti, where transmission mainly occurs during April through November. Malaria, however, is transmitted year-round throughout the country. Only *Plasmodium falciparum* is present; it has been considered to always be susceptible to chloroquine, and failures of treatment with this drug have not been reported. However, mutations in the pfcrt gene associated with chloroquine resistance were recently identified in some isolates obtained in the Artibonite Valley.[1] Lymphatic filariasis is common. Zoonoses of concern include leptospirosis and rabies. A program of mass rabies vaccination of dogs was in progress at the time of the earthquake.

WHO has enunciated a set of priority interventions for immediate implementation. (*See Table 2.*)

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Table 2. Immediate Priorities

- Ensuring access to surgical, medical, and emergency obstetric care, and proper case management, particularly trauma, wound, and burn care
- Shelter and site planning
- Provision of sufficient and safe water and sanitation
- Priority immunizations, including for measles
- Communicable disease surveillance and response, including outbreak

An element to consider with regard to essential emergent medical and surgical care is appropriate triage. Contaminated or infected wounds or those present for more than six hours should not be closed. Patients with wounds should be given tetanus prophylaxis. Standard infection control precautions should be maintained. Post-exposure prophylaxis should be available for health care, rescue, and other workers. Protection of the blood supply must be maintained. Measures must be taken to prevent interruption of treatment of patients with tuberculosis, HIV, and chronic non-infectious diseases, such as diabetes mellitus. Provisions for mental health and psychosocial support must be made available.

Measles vaccination is an immediate priority for children aged 6 months to 14 years living in crowded or camp settings, regardless of previous vaccination or disease history. Supplementation with vitamin A should be administered to children six months through 59 months of age. Mass tetanus vaccination is not indicated. Hepatitis A vaccination can be considered, and typhoid vaccination may be useful for control of outbreaks.

Large numbers of medical and other workers are entering Haiti to provide relief services. Guidance regarding personal measures for individuals planning on volunteering are addressed in this WHO document, but a more extensive set of recommendations has been posted by CDC.[2]

A medical correspondent on CNN warned of the danger of unburied corpses. As it has indicated before, WHO states, "It is important to convey to all parties that corpses do not represent a public health threat. When death is due to the initial impact of the event and not because of disease, dead bodies have not been associated with outbreaks. Standard infection control precautions are recommended for those managing corpses." ■

References

1. Londono BL, et al. Chloroquine-resistant haplotype *Plasmodium falciparum* parasites, Haiti. *Emerg Infect Dis*. 2009;15:735-740.
2. CDC. Guidance for Relief Workers and Others Traveling to Haiti for Earthquake Response. http://wwwnc.cdc.gov/travel/content/news-announcements/relief-workers-haiti.aspx.

TB Screening Before Anti-TNF-alpha Therapy

By Carol A. Kemper, MD, FACP

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SCREENING FOR LATENT TB INFECTION (LTBI) SEEMS TO have only gotten that much more complicated and, increasingly, infectious disease experts are being asked to interpret the newer tests results, especially in persons with inflammatory disorders or underlying immune suppression. In addition to the different gamma-interferon-based (GIB) assays available on the market, newer versions of outdated tests have been introduced. While GIB assays are more sensitive and specific for LTBI than TST, especially in previously BCG-vaccinated persons, only a minority of healthy individuals with LTBI remain at risk for reactivation TB. What is really needed is a diagnostic test that can tell you who those people are.

On the other hand, GIB results have reportedly waned in some patients with prior TB exposure, suggesting that some patients at risk for reactivation TB may be missed with currently available screening tools. Immunosuppression, such as the use of corticosteroids, not only increases the risk of falsely-negative TST, but increases the risk of indeterminate GIB assay results.

A retrospective analysis examined 50 patients with psoriasis who were screened for LTBI using TST, T-SPOT.TB, and chest radiographs in advance of treatment with an anti-TNF-alpha agent.[1] Risk factors for LTBI, including prior TB exposure, abnormal chest radiograph suggestive of prior granulomatous disease, or residence in a country endemic for TB were compared to TST and T-SPOT.TB results. Ninety percent of the patients reported prior BCG vaccination; 20% had come from a country endemic for TB, 22% had had prior exposure to someone with TB, and 8% had abnormal chest radiographs.

The agreement between the TST and T-SPOT.TB tests, using kappa-quantified statistics, was poor (K =.3). Test results were discordant in 14 persons (28%) (both tests were negative in 28 persons and positive in 8). Twelve persons had a positive TST (defined as > 5 mm), a negative T-SPOT.TB test, and a normal chest radiograph, while two persons had a negative TST, a positive T-SPOT.TB test, and an abnormal chest radiograph. The T-SPOT.TB test strongly correlated with risk factors for LTBI compared with the TST.

Ten of 12 patients with a positive TST/negative T-SPOT.TB and a normal chest radiograph received no treatment for LTBI. This group received anti-TNF therapy with a mean follow-up of 76 weeks, with no evidence of reactivation TB. In contrast, one of 10 patients with a +T-SPOT.TB test developed miliary TB while receiving treatment for LTBI and anti-TNF-alpha therapy. Remarkably, 68% of the patients had received prior immunosuppressive therapy, which, while not further specified, raised the possibility of selection of patients at lower risk for developing reactivation TB.

Similar data were observed using the first-generation Quantiferon TB Gold test compared with TST in a group of 302 patients with inflammatory diseases (ie., rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis) who were candidates for anti-TNF-alpha therapy.[2] Sixty percent of the patients were female, with an average age of 50 years. In those with available histories, 152 of 200 reported prior BCG vaccination (76%), 9% reported prior exposure to TB, 8% were from countries endemic for TB, 4% had abnormal chest radiographs consistent with previous granulomatous infection, and 3% had received prior TB treatment. In all, 69 (29%) of the patients had one or more risk factor for LTBI. Using Danish guidelines, 45/241 (19%) patients had a positive TST (> 6 mm, or > 12 mm for those with prior BCG vaccination), while using U.S. Guidelines, 66 (28%) had a positive TST. In comparison, the Quantiferon was positive in 7%, negative in 88%, and indeterminate in 5%. Higher CD4 counts in patients correlated with a higher level of interferon-gamma production and greater likelihood of indeterminate quantiferon test results. In addition, corticosteroid therapy increased the number of indeterminate test results, while decreasing the sensitivity of the TST.

Using kappa-quantified statistics results, the agreement between the two tests was only K = .2. The Quantiferon TB Gold was significantly associated with risk factors for TB (RR 4.7, p = .002), especially prior residence in a TB endemic area (RR 7.8, p > .0001). Interestingly, 18 of 45 had +TST negative Quantiferon TB Gold test. Of those 18 with a positive Quantiferon results, only nine (50%) had a positive TST. Thus, the authors postulate that by using the TST alone significantly more patients would have received unnecessary treatment for LTBI, especially based on U.S. guidelines, but 50% of those at risk for reactivation LTBI would have been missed. Based on the lower sensitivity of the TST in this group compared with the Quantiferon TB Gold, and despite the discordant results, the authors advocate that both tests should be taken into consideration when screening for LTBI in patients with inflammatory diseases. ■

References

1. Laffitte E., et al. Tuberculosis screening in patients with psoriasis before antitumor necrosis factor therapy: Comparison of an interferon-gamma release assay vs tuberculin skin test. *Brit J Dermatol.* 2009;1-4.
2. Soborg B, et al. Comparison of screening procedures for Mycobacterium tuberculosis infection among patients with inflammatory diseases. *J Rheumatol.* 2009;36:1-9.

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*.

Oral Treatments for Relapsing-remitting MS

In this issue: Two oral medications for relapsing-remitting MS in phase III development; antihypertensives find new uses; *Ginkgo biloba* does not prevent cognitive decline in elderly; and FDA Actions.

Oral medications for relapsing-remitting MS

Two new oral medications are effective treatments for relapsing-remitting multiple sclerosis (MS) according to three studies published on-line in the *New England Journal of Medicine*. Fingolimod and cladribine differ in the mechanism of action but both reduce the number of potentially auto-aggressive lymphocytes that are available to enter the central nervous system. In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial, two different doses of cladribine were compared to placebo with the endpoint being relapse at 96 weeks. Both doses were more effective than placebo at preventing relapses and reducing brain lesion count on MRI ($P < 0.001$ for all comparisons). The drug was associated with lymphocytopenia and a higher risk of herpes zoster.

Fingolimod was compared to placebo in the FREEDOMS trial and compared to injectable interferon in the TRANSFORMS trial. The 24-month FREEDOMS trial compared two doses of fingolimod to placebo and similarly found a lower rate of relapse ($P < 0.001$ for both doses) and disability progression ($P = 0.02$ for both doses). The drug also reduced the number of new lesions found on MRI. Significant side effects included bradycardia, AV block, macular edema, elevated LFTs, and mild hypertension. When compared to interferon, fingolimod was associated with significantly lower annualized relapse rates at both doses tested ($P < 0.001$ for both comparisons), although there was no significant difference with respect to progression of disability. Two fatal infections occurred with the higher dose of fingolimod (disseminated primary varicella zoster and herpes simplex encephalitis). (All three studies published on-line at www.NEJM.org, Jan. 20, 2010).

An accompanying editorial calls the arrival of oral formulations of MS drugs "welcome news for the estimated 2.5 million people worldwide with this chronic, disabling disease." While suggesting these drugs "support a change in treatment approach to directly prevent immune-related injury," the editorial also suggests that long-term goals of MS therapy are currently lacking (published online at www.NEJM.org, Jan. 20, 2010). Both drugs are in phase III trials for treatment of MS; cladribine is currently approved in parenteral form for treatment of hairy cell leukemia. ■

Antihypertension drugs for AF and dementia?

Different classes of blood pressure (BP) medications may have different benefits according to two new studies. In the first study, researchers from the United Kingdom performed a nested

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case-control analysis to evaluate whether different antihypertensive drug classes may alter the risk for atrial fibrillation. The researchers reviewed records from a large patient population, specifically patients who were on a single agent for lowering BP. A lower odds ratio (OR) for atrial fibrillation was noted with ACE inhibitors (OR, 0.75; 95% confidence interval [CI], 0.65-0.87), angiotensin receptor blockers (ARBs) (OR, 0.71; 95% CI, 0.57-0.89), and beta-blockers (OR, 0.78; 95% CI, 0.67-0.92) compared with current exclusive therapy with calcium channel blockers. Although the researchers were unable to assess why patients were receiving one class of blood pressure medicine over another, they concluded that long-term therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for atrial fibrillation compared with calcium channel blockers. These findings generally relate to patients with mild hypertension, since patients on multiple drugs were excluded from the study (*Ann Intern Med* 2010;152:78-84).

In the second study, researchers from Boston set out to investigate whether ARBs reduce the risk of Alzheimer's disease and dementia or reduce the progression of both diseases. More than 800,000 predominately male participants, age 65 or older with cardiovascular disease, were studied. Patients were divided into three cohorts (ARBs, lisinopril, and other cardiovascular drugs as a comparator) and followed over 4 years, with adjustments for age, diabetes, stroke, and cardiovascular disease. Hazard rates for dementia in the ARB group were 0.76 (95% CI, 0.69-0.84) compared to the cardiovascular comparator, and 0.81 (95% CI, 0.73-0.90) compared to the lisinopril group. In patients with pre-existing Alzheimer's disease, ARBs were associated with significantly lower risk of admission to a nursing home. The combination of the ARB and ACE inhibitor was better than ACE inhibitor alone in preventing dementia and reducing admission to nursing home. The authors conclude that ARBs are associated with a significant reduction in the incidence and progression of Alzheimer's disease and dementia compared to ACE inhibitors or other cardiovascular drugs (BMJ 2010;340:b5465, doi: 10.1136/bmj.b5465, published on-line Jan. 12, 2010). An accompanying editorial points out that several studies have shown that treatment with any antihypertensive is associated with a lower risk of cognitive decline or incident dementia in older adults. What is not clear is whether some antihypertensives also have other biological mechanisms that help prevent dementia. It is plausible that ARBs are more neuroprotective than other drugs because of their effect on type 2 angiotensin receptors in the brain (*BMJ* 2010:340;b5409, doi: 10.1136/bmj.b5409, published on-line Jan. 12, 2010). ■

Ginkgo does not prevent cognitive decline

The National Center for Complementary and Alternative Medicine (NCCAM) was founded during the Clinton administration as part of the National Institutes of Health to investigate complementary and alternative medicines. Many of the NCCAM-funded studies, however, have shown no benefit from complementary or alternative treatments, and that is the case with a new study looking at *Ginkgo biloba* and cognitive function in older adults. *Ginkgo biloba*, which is widely marketed as an aid to preventing cognitive decline and dementia, was previously found to have no benefit in reducing the incidence of Alzheimer's disease or dementia overall (*JAMA* 2008;300:2253-2262).

In a new study sponsored by NCCAM, researchers set out to determine whether *Ginkgo biloba* slows the rate of global or domain-specific cognitive decline in older adults. More than 3000 participants age 72-96 years were enrolled and randomized to *G. biloba* 120 mg or placebo twice daily. Rates of change over time in two different objectives cognitive tests, as well as neuropsychological tests, were the primary endpoints. There was no difference in the decline in cognitive scores between *Ginkgo biloba* and placebo in any of the domains including memory, attention, and visuospatial abilities, language, or executive functions. There was also no difference in the rate of change in the standardized cognitive exams. The authors conclude that compared to placebo, *Ginkgo biloba* did not result in less cognitive decline in older adults (*JAMA* 2009;302: 2663-2670). ■

FDA Actions

Novo Nordisk has received approval to market liraglutide, a once-daily injection for the treatment of type 2 diabetes in adults. The drug is a glucagon-like peptide-1 receptor agonist similar to exanatide (Byetta®). The company is required to perform additional post-marketing cardiovascular studies as well as a 5-year epidemiological study to evaluate the risk of thyroid cancer. Liraglutide will be marketed under the trade name Victoza®. ■