

Resistant TB May Spur WHO Guideline Revision

Currently recommended first-line TB treatments may be contributing to drug resistance.

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MIAMI BEACH — An effective fight against increasing resistance to tuberculosis treatment worldwide may require rethinking of the World Health Organization's recommended standard treatment regimen, David Olson, M.D., said at the annual meeting of the American Society of Tropical Medicine and Hygiene.

"The feeling now is that the standardized retreatment regimen is going to cause greater drug resistance. We're going to have to abandon that protocol and start patients on second-line therapies sooner with susceptibility testing," said Dr. Olson of Médecins Sans Frontières in New York City. However, second-line agents come with their own challenges.

Of the estimated 8 million people infected with tuberculosis worldwide, there

are 300,000 with multidrug-resistant infections, according to the WHO. "It means we're not all going to die tomorrow, but it means these people can infect other people," Lee B. Reichman, M.D., executive director of the New Jersey Medical School National Tuberculosis Center at the University of Medicine and Dentistry of New Jersey, Newark, said in an interview.

In 2003, foreign-born individuals accounted for 53% of all tuberculosis in the United States. "Every American doctor has to be concerned, especially if they see foreign-born individuals," Dr. Reichman said. Tuberculosis acquired abroad poses a risk of infection to Americans when these individuals enter or return to the United States. The risk is greatest at ports of entry—in particular, Hawaii, California, Massachusetts, Florida, and New York.

Many factors contribute to multidrug-resistant tuberculosis (MDRTB). For example, a physician who does not recognize

a resistant case might prescribe first-line treatment and delay more effective, second-line therapy. Also, patient noncompliance can be an issue, as can HIV coinfection or patients who require repeated treatment.

Duration of treatment also affects compliance. Recommended first-line treatment is prescribed for 6 months, compared with 18 months-2 years for second-line agents. Watching patients take their medication is a strategy in the WHO's Directly Observed Treatment, Short-Course-Plus (DOTS-Plus) initiative.

"Studies have shown that many patients with MDRTB can be cured by combinations of reserve second-line anti-TB drugs. Unfortunately, these drugs are weaker than standard therapy, cause adverse reactions difficult for patients to tolerate, have to be taken for prolonged periods to prevent relapse, and are very expensive," WHO experts noted in a 2000 report, "DOTS-Plus Pilot Projects for the Management of Multidrug-Resistant Tuberculosis."

The WHO-recommended regimen for

new cases of tuberculosis is isoniazid, rifampin, pyrazinamide, and ethambutol taken daily or 3 times a week under direct observation. Isoniazid and rifampin are the most powerful weapons against tuberculosis bacilli, but growing resistance—particularly to isoniazid—may necessitate a different approach for the WHO to meet its goal of 85% cure of sputum smear-positive cases by 2005.

There have been no new classes of drugs approved specifically for tuberculosis in more than 40 years. Experts agree that the availability of new tuberculosis agents would help combat resistance, especially shorter duration treatments. "A drug that would work in 2 months would decrease costs by 65%, expand access to treatment, slow or stop resistance, and allow health personnel to be redeployed," Joelle Tanguy, director of advocacy for the Global Alliance for TB Drug Development, New York City, said during a separate presentation at the meeting. ■

Visit www.umdj.edu/ntbcweb for more information on tuberculosis.

Many Symptoms, Long Duration: Think Lyme Disease

BOSTON — Persistent musculoskeletal pain, headache, fatigue, and cognitive dysfunction that occur for no apparent reason over a prolonged period of time are key elements of a clinical diagnosis of chronic Lyme disease in children, results of a retrospective study has shown.

"While there have been reports on the clinical manifestations of chronic Lyme disease in adults, there has not been a detailing of the clinical aspects of the condition in the pediatric population, making the diagnosis especially challenging," said Sam T. Donta, M.D., at the annual meeting of the Infectious Disease Society of America.

In an effort to identify the most telling clinical symptoms, the reliability of serologic studies, and the ef-



fects of drug therapy, Dr. Donta reviewed the clinical histories, serologies, and treatment results of 101 patients aged 2-19 years who were evaluated at Falmouth Hospital in Massachusetts for possible chronic Lyme disease. Tick bites were known to have occurred in 24% of the patients included in the review.

Musculoskeletal symptoms occurred in approximately 90% of the patients, and fatigue, headache, and cognitive dysfunction were reported in 84%, 78%, and 74% of the patients, respectively. Other diagnostically indicative symptoms that occurred with some frequency included stomach pains or nausea (48%), paresthesias (46%), eye symptoms (40%), and fevers or sweats (39%), Dr. Donta noted. Typical and atyp-

ical rashes were reported in 15% and 25% of the patients, respectively. Approximately 79% of the patients had multiple additional symptoms, such as dizziness, palpitations, and tremors, said Dr. Donta, who has private practices in infectious disease in Boston and Falmouth.

Bell's palsy, which is often the first neurologic symptom of Lyme disease, was reported in five patients. Of the total study population, 29 patients had undergone a brain SPECT (single photon emission computed tomography) scan, eight

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DR. DONTA

of which showed some changes in blood flow to various parts of the brain. Such changes, primarily to the temporal and frontal lobes, are present in about 75% of patients with chronic Lyme disease, Dr. Donta stated.

Western tests showed one or more reactions by IgM in 74% of the patients and by IgG in 82%. Enzyme immunoassay titers were positive in 65% of the patients tested. "Clearly, serologic studies can be helpful in supporting the clinical diagnosis," said Dr. Donta, but they are not definitive on their own.

All of the patients in the cohort were treated with tetracycline or a combination of a macrolide antibiotic with hydroxychloroquine over a 4- to 8-month period, and 75% of them were cured or sustained clinical improvement, Dr. Donta noted.

The key is using appropriate antibiotics, adhering for a long enough period, and the earliest possible treatment. ■

Hantavirus Survivors Have Long-Term Pulmonary, Renal Complications

MIAMI BEACH — Hantavirus survivors commonly experience fatigue, shortness of breath, and myalgias up to 5 years after infection, according to the final summary of a longitudinal, prospective study.

Proteinuria, which may be clinically significant as a predictor of renal disease, is also common in hantavirus survivors, and its incidence rises over time post infection, Diane Goade, M.D., said during a presentation at the annual meeting of the American Society of Tropical Medicine and Hygiene.

Hantavirus pulmonary syndrome is an emerging infectious disease characterized by acute, severe febrile illness and a high mortality rate. At the time of Dr. Goade's presentation, 363 cases had been identified in the United States.

Infected rodents spread the disease through their urine, feces, or saliva.

"We know very little about the long-term effects of this illness. What we found at the end of 5 years was quite striking, even though this was a young cohort who was relatively healthy," said Dr. Goade of the University of New Mexico, Albuquerque.

The study included 33 survivors of acute hantavirus infection. Researchers assessed participants annually using a wide range of clinical measures, including CBC, viral antibody assays, patient history, and self-reported fatigue and exercise capacity. "We were basically doing a major fishing expedition," Dr. Goade explained.

The participants were 18 males and 15 females ranging in age from 10 to 54 years. There were 18 non-Hispanic whites, 5 Hispanics, 9 African Americans, and 1 Native American.

Sin Nombre virus—the most common pathogen responsible for hantavirus in the United States—accounted for the infections in 32 participants; the other patient was infected with Bayou virus.

At 5 years, mild to moderate pulmonary changes were common and affected the patients' ability to exercise. Although most pulmonary function parameters were normal, the researchers found a triad of pulmonary abnormalities: decreased small airway flow in 79% of patients, increased residual volume in 76%, and decreased oxygen diffusion capacity in 66%.

Slightly more than half (55%) reported arthralgias and problems with short-term memory; 67% reported inadvertent weight gain (between 2.5 kg and 30 kg); and 84% each reported myalgias and shortness of breath.

Fatigue and decreased exercise tolerance were each reported by 90%, "including a high school wrestling coach who used to run 5 miles a day, who can now only walk about 2 miles a day," Dr. Goade said.

"Proteinuria is increasingly common in the convalescent period and is of concern," Dr. Goade said. At 5 years, 24-hour urinalysis showed that 11 of 33 participants had proteinuria, "an astounding number in young, relatively healthy people."

"The further out we go in this longitudinal study, the more renal effects we see," she added. Proteinuria typically begins about 1 year after the infection and continues to increase. Age, race, gender, and severity of initial infection were not predictive of renal consequences.

"This started out as a fishing expedition, and we were quite surprised by what we found," Dr. Goade said. ■