XDR-TB: Coming Soon To a Location Near You

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KEYSTONE, COLO. — Epidemiologic trends indicate that U.S. physicians will increasingly encounter extensively drug-resistant tuberculosis in coming years, Dr. Charles L. Daley predicted at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center, Denver.

In the mid-1990s, TB in the United States occurred chiefly in U.S.-born persons. Indeed, U.S.-born patients with TB outnumbered foreign-born patients with TB 2:1. Since then, however, the annual number of TB cases among U.S.-born individuals has declined sharply, while the number of cases arising in the foreign born has remained constant. As a result of these crisscrossing trends, in each year since 2001 foreign-born persons have accounted for more than half of all TB cases in the United States.

"That's an important epidemiologic factor, because most of the XDR [extensively drug-resistant]-TB that's been reported has been outside the United States. With more cases here coming from those areas, no surprise, we're going to see more MDR [multidrug-resistant]- and XDR-TB," said Dr. Daley, head of the division of mycobacterial and respiratory infections at the center and professor of medicine at the University of Colorado, Denver.

The No. 1 risk factor for MDR and XDR is foreign birth in areas where TB is endemic and TB control practices are poor. Russia and many of its neighboring former Soviet republics constitute the biggest problem area worldwide. Astonishingly, more than 40% of people in that part of the world who have previously been treated for TB have MDR-TB.

Drug resistance in Russia was created mainly in the prisons—and mass pardons put many convicts with MDR-TB back into the community. A lot of transmission also took place in hospitals because of the lack of infection control protocols.

In the United States and Western Europe, roughly 6% of MDR-TB strains are XDR. In Russia, the rate is 14%.

South Africa is another hotbed of XDR. However, little TB drug resistance exists elsewhere on the continent. That's because MDR-TB and XDR-TB are caused by inadequate treatment—and for the most part Africans with TB outside of South Africa aren't receiving inadequate treatment, they're simply not being treated, period, Dr. Daley said.

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DR. DALEY

Suspect MDR-TB in a patient with TB symptoms who hails from or has traveled to an endemic area. "The highest risk is, 'I'm from Russia and I was in prison.' That's when you carefully back out the door of the room," Dr. Daley quipped.

Globally each year, there are more than 400,000 new cases of MDR-TB and 40,000 of XDR-TB. "The XDR strains aren't real virulent, so far as we know, but they're almost untreatable," according to Dr. Daley.

A handful of published reports show cure rates of about 30% in U.S. patients with XDR-TB, comparable to what's being reported elsewhere. In contrast, treatment success rates of 60%-80% are reported with systematic treatment for MDR-TB.

A Centers for Disease Control and Prevention case series reported last year highlighted the changing epidemiology of XDR-TB in the United States during 1993-2006. In 1993-1999, 72% of cases in the series were men, 38% were foreign born, and 44% were HIV positive. In contrast, in 2000-2006, only 47% were men, 76% were foreign born, and just 12% were HIV infected.

"You might say, 'Well, this doesn't matter to my practice,' but it turns out the world has a way of reaching into the United States, including low-incidence areas," Dr. Daley observed. He noted that in the past year and a half, a handful of documented cases of MDR-TB diagnosed in Rocky Mountain states, where TB hasn't historically been much of a problem, all involved foreign-born individuals. ■

Aggressive Surgery Improves Outcomes in MDR-TB

KEYSTONE, COLO. — Aggressive resectional surgery has led to markedly improved microbiologic and clinical success in treating multidrug-resistant pulmonary tuberculosis, according to experience with patients at the National Jewish Medical and Research Center in Denver.

The use of surgery to treat MDR-TB patients is associated with a greater than fourfold increased likelihood of an initial favorable response to treatment. Fluoroquinolone therapy also is predictive of an initial favorable response, but only in patients older than 40 years.

"Surgery has become a very significant part of our practice at National Jewish," said Dr. Charles L. Daley, head of the division of mycobacterial and respiratory infections at the center. "We think that in selected patients, surgical resection is really important to consider."

The goal of the surgery is to remove cavitary lesions and sections of destroyed lung with a high bacillary burden. The operation is most likely to be successful in patients with focal disease and adequate pulmonary function, said Dr. Daley at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center.

Good surgical candidates are patients with MDR-TB who remain culture positive after 4-6 months of drug therapy, as well as patients with extensively drug-resistant TB (XDR-TB). The World Health Organization's revised definition of XDR-TB, issued in late 2006, describes it as MDR—that is, resistance to at least isoniazid and rifampin—plus resistance to any fluoroquinolone and one of the second-line injectable drugs, namely amikacin, capreomycin, or kanamycin.

The success of the surgical strategy was shown by a retrospective study published in 2004. The study reviewed outcomes in 205 patients with MDR-TB treated at National Jewish during 1984-1998, and compared the outcomes with those of 171 other MDR patients treated there during 1973-1983. All the MDR patients in the review were severely resistant to a median of six TB drugs and treated with a median of six agents while at National Jewish.

Treatment outcomes were better in the more recent cohort. Analysis identified two reasons why: resectional surgery and fluoroquinolone therapy, the novel elements of MDR-TB management introduced at the center after 1983. Each was an independent predictor of good outcome, said Dr. Daley, who also is a professor of medicine at the University of Colorado, Denver.

The initial favorable response rate, defined as at least three consecutive negative sputum cultures over at least 3 months, was 65% in the 1973-1983 cohort, compared with 85% in those treated during 1984-1998. The overall cure rate improved from 56% in 1973-1983 to 75% afterward. Moreover, the TB death rate fell from 22% to 12%.

In a multivariate analysis, surgery was associated with a 4.6-fold increased likelihood of an initial favorable response. Fluoroquinolone therapy, introduced in the 1980s, also was predictive of an initial favorable response, but only in patients more than 40 years old.

There was a trend toward improved survival in patients who underwent resection. It didn't reach significance, perhaps because of the relatively small sample size (Am. J. Respir. Crit. Care Med. 2004;169:1103-9).

The use of surgical resection climbed steadily at National Jewish as physicians came to recognize that it resulted in improved outcomes and had a low complication rate. Just 4% of patients treated for MDR-TB in 1973-1983 underwent one or more resectional procedures, compared with 44% discharged in 1984-1988, 63% in 1989-1993, and 83% in 1994-1998.

"We used to use a thoracotomy but are now turning to VATS [video-assisted thoracoscopic surgical] resection whenever possible," Dr. Daley said.

Predictors of therapeutic failure in patients with MDR-TB include a low body mass index, comorbid HIV, previous therapy, and poor adherence, according to Dr. Daley.

Tuberculosis Drug Pipeline Contains Several Promising Agents

KEYSTONE, COLO. — New drugs are desperately needed to address the growing problem of extensively drug-resistant tuberculosis—and help appears to be on the way.

Indeed, the drug development pipeline for anti-TB medications is remarkably full as a result of recent, greatly increased global attention to what had long been a seriously neglected disease.

"These investigational drugs are very exciting," Dr. Charles L. Daley said at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center, Denver.

Five new drugs are in or soon to enter phase II clinical trials, including several that are already slated for phase III. And more than a dozen other drugs in preclinical testing or the discovery phase are being developed by the National Institute of Allergy and Infectious Diseases, various universities in the United States and abroad, the TB Alliance, and pharmaceutical companies both large and small, according to Dr. Daley, head of the division of mycobacterial and respiratory infections at the center and professor of medicine at the University of Colorado, Denver.

The drugs now in clinical trials are diarylquinoline TMC207, a Johnson & Johnson molecule with greater activity against *Mycobacterium tuberculosis* than treatment mainstays isoniazid and rifampin; the widely prescribed Bayer antibiotic moxifloxacin; nitroimidazole PA-824, being developed through a collaboration between Chiron Corp. and the TB Alliance; nitroimidazole-oxazole OPC-67683, an Otsuka drug slated to go into phase II trials this summer; and the Lupin Ltd. drug pyrrole LL-3858, which is "probably a couple years behind the others," he said.

These are drugs with novel mechanisms of action against *M. tuberculosis*. Resistance won't immediately be an issue.

Dr. Daley forecasted favorable long-term prospects for an effective TB vaccine, the key words being "long term." At least 10 new TB vaccines are now in phase I or II trials around the world. But because no surrogate markers for immunity exist, the only way to learn if a TB vaccine is effective is to vaccinate people, follow them for 10 years or so, and see how many get TB.

"That means even the vaccines that show promise are still way, way off in terms of routine use. But they're coming," he predicted.

Dr. Daley had no financial conflicts to disclose. ■