Alberta study investigates multidrug-resistant TB

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Resistance to antibiotics used to treat tuberculosis (TB) is a growing concern around the world. The World Health Organization estimates that every year about 650,000 people develop TB that is resistant to at least two key antibiotics—isoniazid and pyrazinamide. Such cases of TB are called multidrug-resistant (MDR). In low- and middle-income countries, cases of MDR-TB are particularly problematic, for these reasons, among others:

- drugs may be improperly prescribed (specifically, an insufficient number of active antibiotics in a regimen)
- doses of antibiotics may be too low
- the supply of antibiotics in a region may be interrupted, insufficient or expensive for patients
- some patients may have difficulty taking antibiotics every day, exactly as prescribed
- TB medicines may not be well absorbed by the intestines

In high-income countries, such as Canada, Australia, the U.S. and regions such as northern Europe, TB, including MDR-TB, is generally less common but does occur in particular populations, including the following:

- people who are homeless
- people living in crowded or substandard housing
- people dealing with addictions
- recent immigrants from regions where TB is relatively common

In Canada some Aboriginal people are at heightened risk for developing TB and this will be the subject of a future CATIE News story.

Managing cases of TB can be expensive for the hospitals and clinics and unpleasant for affected people for at least these reasons:

- prolonged courses of treatment are required
- injectable formulations of antibiotics may be used
- hospital stays may be necessary

In America

A study in the U.S. recently investigated cases of transmission of MDR-TB in that country. There, researchers found that “many individuals acquire MDR-TB before entry into the USA.”

In Canada

Although a high-income country such as Canada has a relatively low burden of TB, outbreaks of MDR-TB may occur in the future because of travel to and immigration from places where TB is common.

Researchers at the University of Alberta reviewed health-related information about cases of MDR-TB that occurred between 1981 and 2011 among Canadian residents born overseas. They focused on cases of TB that were confirmed with laboratory testing (so-called cases of “culture-positive” TB): a total of 2,234 people.

Results
Cases of MDR-TB were distributed over time as follows:

- 1982 to 1991 – 0.65% of TB cases were MDR
- 1992 to 2001 – 0.56% of TB cases were MDR
- 2002 to 2011 – 2.11% of TB cases were MDR

This rise in the proportion of MDR-TB in the recent era was statistically significant.

Overall, researchers found that a total of 27 of the cases (1.2%) reviewed from 1982 to 2011 were MDR-TB.

In all, 82% of cases with MDR-TB were born in countries that had a high burden of TB.

Compared to people diagnosed during the first two decades (1982 to 2001), patients diagnosed with MDR-TB in the last decade (2002 to 2011) were more likely to have the following profile:

- be younger than 35 years
- have new, active cases of TB rather than a case of relapsed TB
- be diagnosed with TB affecting parts of the body other than the lungs (such cases are called extra-pulmonary TB)

Cases of MDR-TB diagnosed within the first two decades were resistant to an average of three out of five commonly used TB antibiotics. However, in the most recent decade, MDR-TB cases were more likely to be resistant to four of five commonly used TB antibiotics. The five drugs tested were as follows:

- ethambutol
- isoniazid
- pyrazinamide
- rifampin
- streptomycin

There were no cases of MDR-TB in people co-infected with HIV.

The vast majority of MDR-TB cases diagnosed in Alberta had what researchers called unique genetic fingerprints. This finding allowed researchers to compare these strains of TB with strains commonly found in Canada. The researchers concluded that cases of MDR-TB infection occurred overseas rather than locally. Moreover, they stated that “local transmission does not appear to be responsible for the four Canadian-born cases of MDR-TB that occurred in the 30-year study period.”

Among these four cases, the researchers found that two were infected “while travelling abroad.” The remaining two cases began treatment with strains of TB that were susceptible to treatment; however, over the course of treatment, these strains became “drug-resistant.”

**Implications**

The findings from the Alberta study have the potential to increase the challenge of “suspecting and diagnosing MDR-TB in foreign-born TB patients,” stated the researchers. This is due to the finding of a small but growing proportion of “younger, new active [vs. relapse] MDR-TB cases in recent years,” they added.

This profile of “younger, new active cases of MDR-TB” is in contrast to what the Alberta researchers stated are the usual predictors of MDR-TB:

- treatment failure with a standard four-drug regimen of antibiotics
- previous TB treatment, particularly if the patient was unable to take medicines exactly as directed
- poor management of patients in a TB program
- past treatment of isoniazid-resistant TB
- exposure to someone who “was known to have infectious MDR-TB”

The more recent cases of MDR-TB described in the study tended to attack tissues outside the lungs. Accurate diagnosis of TB in such cases requires fluid samples taken from the affected body part so that it can be cultured and
analyzed. In the absence of such a sample, and given the symptoms they observe, doctors may presume that the patient has TB and prescribe treatment. However, in such cases of presumptive diagnoses, doctors may not be aware of the presence of MDR-TB and so may not prescribe the right combination of antibiotics.

**Screening for antibiotic resistance**

Ideally, prior to prescribing antibiotics for TB, doctors should be able to request laboratory analysis of a fluid sample from the affected tissue. This analysis can check for the presence of drug-resistant TB.

Resistance testing can be phenotypic; in such cases bacteria are grown in the lab and exposed to different antibiotics to determine their degree of resistance.

The other method of assessing resistance is called genotypic testing. These tests seek the presence of genes in TB that confer resistance to the antibiotic rifampin.

The Alberta researchers note that the presence of rifampin-resistant TB in a patient in Canada is strongly suggestive of MDR-TB (based on data from other studies that suggests rifampin resistance is commonly associated with resistance to another antibiotic, isoniazid).

**What to do?**

The Alberta team’s work underscores the importance of drug-resistance testing prior to prescription of TB treatment. They point out the limited choices doctors and nurses face in their everyday work when they realize that a patient may have MDR-TB. The team suggested the following choices be considered:

- Delay treatment until phenotypic resistance testing results are available. However, the Alberta researchers note that this option is not acceptable if “the patient is ill or highly infectious.”
- “Within reason” make certain that prescribed therapy is sufficient to treat MDR-TB.
- Use available genotypic resistance tests.

As treating cases of MDR-TB are complex, the Alberta team suggests that “decisions about each of these options are best made by physicians experienced in the management of drug-resistant TB.”

**Resources**

- [TB—CDC encourages docs to check for antibiotic resistance](#) – CATIE News
- [Tuberculosis & HIV—background information](#) – CATIE News

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**REFERENCES:**

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