Drug-resistant tuberculosis

Drug resistance represents a significant global challenge to tuberculosis control efforts. Approximately 50 million people worldwide are infected with drug-resistant tuberculosis strains, though not all will develop active disease. *Primary drug resistance* refers to resistance in those never previously treated, while *secondary drug resistance* occurs following prior drug exposure. The use of molecular fingerprinting has enabled us to separate re-infection with a new drug-resistant strain from strains that have evolved while on medication.

The term *multiple drug resistant tuberculosis* (MDR-TB) refers to strains resistant to at least isoniazid (INH) and rifampin. MDR-TB has reached worrisome levels in Kajistan (56%), Lithuania (53%), and the Russian Federation (43%). Between 1994 and 2000, Estonia's rate of MDR-TB rose from 19% to 45%. Thankfully, MDR-TB still remains unusual in BC, representing less than 2% of our active cases. The most common resistance pattern seen for a single drug is INH, while monoresistance to rifampin is rare. MDR-TB is seen most frequently in the foreign-born and rarely in the aboriginal population. Mutations that control resistance to antituberculous medications occur spontaneously and independently and account for most resistant strains of tuberculosis, though resistance can occur without any known mutations.

Factors that foster the development of drug resistance include poor compliance, incorrect dosage, poor absorption, inadequate regimens, drug interactions, and the free availability of antituberculous medication without prescription. Drug-resistant disease is of particular concern in HIV-infected individuals. Important predictors of drug resistance include previous treatment for TB, progressive clinical and radiological findings while on therapy, origin from a country with high drug-resistance rates, and exposure to an infectious, drug-resistant TB case.

The laboratory plays a key role in the diagnosis of drug resistance as prompt identification of drug susceptibilities can guide treatment. Resistant mycobacteria sometimes exhibit slow growth—leading to exposure of an inappropriate regimen for several weeks. Susceptibility testing to second-line drugs is required in all cases of MDR-TB. These second-line agents include amikacin, capreomycin, levofloxacin, ethionamide, and cycloserine. An expanded empiric regimen consisting of four first-line drugs and two or more additional drugs may be appropriate in certain circumstances where the suspicion of drug resistance is high and in the event of life-threatening disease.

Predictors of good treatment outcomes include susceptibility to pyrazinamide, ethambutol, and the respiratory fluoroquinolones, as well as sputum culture conversion at 2 months. A study from 1983–1998 in a tertiary care referral centre reported a mortality of 12% in drug resistant TB.

The basic principles of treatment involve selection of any of the first-line drugs the patient is known to be susceptible to, plus the addition of at least a fluoroquinolone and an injectable agent such as amikacin or capreomycin. Moxifloxacin has shown superior in vivo activity against *M. tuberculosis* in a mouse model and is currently undergoing trials in active cases. Second-line drugs such as cycloserine, ethionamide, or para-aminosalicylate (PAS) are added until the patient is on four to six drugs to which the isolate is susceptible. High levels of drug resistance will require the use of third-line drugs such as clofazamine, linezolid, or macrolides. Potential cross-resistance occurs between certain drug classes, for example between isoniazid and ethionamide and between amikacin and kanamycin as drug resistance is associated with the same mutation. In general, there is complete class effect or cross-resistance among the fluoroquinolones, though some activity has been described with more potent drugs, such as the newer quinolones moxifloxicin and gatifloxacin.

As each regimen has to be individually tailored to available sensitivity patterns, predicting efficacy and length of treatment is based mainly on expert opinion rather than randomized clinical trials. All drug-resistant cases require directly observed therapy, particularly if secondary drug resistance resulted from prior poor compliance. High-level drug resistance requires 24 months of treatment beyond culture conversion, which is a considerable challenge for the patient and physician as many of these drugs are poorly tolerated. In cases that continue to be culture positive 4 to 6 months into treatment or if no suitable drug regimen is available, surgery should be considered if the disease is sufficiently localized to allow lobectomy or pneumonectomy. Successful lung resection does not preclude the completion of a full course of treatment, if available, nor does it allow shortening of the course.

While the treatment of drug resistant disease presents major challenges, novel agents are currently being studied, which we hope will allow cure in almost all cases.

—Richard K. Elwood, MB, BCh, MRCP(UK), FRCPC
—Victoria Cook, MD, FRCPC
BC Centre for Disease Control