Canadian Tuberculosis Standards

7th Edition

Chapter 8: Drug-Resistant Tuberculosis

Public Health Agency of Canada
Agence de la santé publique du Canada

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CHAPTER 8

DRUG-RESISTANT TUBERCULOSIS

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KEY MESSAGES/POINTS

- Globally, the rate of drug-resistant TB is increasing.
- In Canada, two systems are used to track drug-resistant TB: (i) the Canadian TB Reporting System and (ii) the Canadian TB Laboratory Surveillance System.
- The major risk factors for drug-resistant TB in Canada are previous treatment and foreign birth.
- Drug-resistant TB should be suspected in patients who have (i) previously been treated for active TB, (ii) originated from, resided in or travelled to a country where drug-resistant TB is prevalent or (iii) been exposed to a person with infectious drug-resistant TB.
- It is recommended that within programs priority should be given to the prevention, rather than the management, of drug-resistant TB. To prevent resistance it is important to (i) prescribe in proper dosage an appropriate regimen, (ii) ensure that the prescribed regimen is adhered to and that those who abscond from treatment are identified promptly – best achieved by supervising the ingestion of each dose – and (iii) never introduce a single drug to a failing regimen.
- In Canada, it is recommended that all initial isolates of *Mycobacterium tuberculosis* be tested for susceptibility to isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB).
- Further, it is recommended that second-line drug susceptibility tests (DST) should be carried out for all isolates that are RMP-resistant, polydrug-resistant (resistant to two or more first-line drugs other than INH and RMP) and multidrug-resistant (resistant to INH and RMP with or without resistance to other first-line drugs; MDR-TB). Intolerance to these drugs/combinations should also lead to second-line DST.
- For the purpose of these *Standards*, the third- and fourth-generation fluoroquinolones (FQNs) – levofloxacin and moxifloxacin – are considered interchangeable with INH in the treatment of INH-resistant TB.
- It is recommended that the treatment of MDR-TB be individualized, based upon DST results. Treatment should include a minimum of four drugs to which the initial isolate is susceptible; if at all possible one of these drugs should be an FQN and one an injectable agent (for example, amikacin or capreomycin).
- It is recommended that the initial phase of treatment of MDR-TB be administered for at least 8 months.

- The treatment of MDR-TB is a complex health intervention requiring experience and special expertise. Referral to physicians or centres that offer this experience and expertise is strongly recommended.
- The careful monitoring of patients with drug-resistant TB is important to their safe and successful completion of therapy.
- It is recommended that the treatment of LTBI in close contacts of infectious drug-resistant TB be based upon the DST results of the source case.

INTRODUCTION

People with TB are said to have drug-resistant disease if their strain of *Mycobacterium tuberculosis* is resistant to one or more first-line drugs: isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB). The impact of drug resistance on the outcome of TB treatment varies according to which drug, or combination of drugs, is resistant and reflects the different but complementary role each drug plays in the treatment of TB.[1]

Globally, the improper prescription of anti-TB drugs, their proper prescription but unavailability, inadequate supervision or, uncommonly, the malabsorption of these drugs has increased the prevalence of drug-resistant TB. In low- to middle-income countries the resource-driven use of standardized regimens that do not take into account pre-treatment DST results may have inadvertently amplified the problem of drug-resistant TB. In a systematic review and meta-analysis of initial drug resistance and TB treatment outcomes the cumulative incidence of acquired drug resistance with initially pan-sensitive strains was 0.8% (95% confidence interval [CI] 0.5% to 1.0%) compared with 6% (CI 4% to 8%) with initially single drug-resistant strains and 14% (CI 9% to 20%) with initially polydrug-resistant strains.[2]

The fourth global report on *Anti-tuberculosis drug resistance in the world*, produced by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease, describes resistance patterns in 81 countries and 2 special administrative regions of China from 2002 to 2006.[3] The population-weighted mean of resistance to any of INH, RMP, EMB or streptomycin (SM) was 17.0% (95% CI 13.6% to 20.4%) in new cases, 35.0% (CI 24.1% to 45.8%) in previously treated cases and 20% (CI 16.1% to 23.9%) in all TB cases. The global weighted mean of MDR-TB, defined as resistance to at least INH and RMP, the two most important anti-TB drugs, was 2.9% (CI 2.2% to 3.6%) in new cases, 15.3% (CI 9.6% to 21.0%) in previously treated cases and 5.3% (CI 3.9% to 6.7%) in all TB cases. In 2008, an estimated 440,000 cases of MDR-TB emerged globally, India and China accounting for almost 50% of the world's total cases.[4] In the 46 countries that reported continuous surveillance or representative surveys of second-line drug resistance in MDR-TB cases, 5.4% were found to have extensively drug-resistant (XDR) TB, defined as resistance to INH and RMP as well as any fluoroquinolone (FQN) and any one of the second-line injectable agents, amikacin, kanamycin or capreomycin.[3,4]

NATIONAL DRUG-RESISTANT TB TRACKING SYSTEMS

In Canada, two systems are used to track drug-resistant TB.

PHAC CANADIAN TUBERCULOSIS REPORTING SYSTEM (CTBRS)

Provincial and territorial TB control programs participate in the CTBRS national surveillance system by reporting to the Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada (PHAC), all new and re-treatment cases of active TB. Between 2006 and 2010, drug-resistant TB was reported most commonly in people with a past history of TB ("re-treatment cases") and in foreign-born people (see Table 1).[a]

Of 5,807 new active cases of TB, 5.3% had an INH-resistant/RMP-sensitive strain and 0.7% had an MDR strain. Of 427 cases of re-treatment TB, 7.5% had an INH-resistant/RMP-sensitive strain and 2.3% had an MDR-TB strain.[5] Between 2006 and 2010, foreign-born people with TB were 1.9 times more likely to have INH-resistant/RMP-sensitive TB and almost 13 times more likely to have MDR-TB than Canadian-born people. Higher rates of drug resistance among foreign-born people correspond to higher rates of drug resistance in their country or region of birth. Countries in which the majority of the population has access to the DOTS strategy (directly observed treatment, short course; see Chapter 5, Treatment of Tuberculosis Disease) have lower rates of drug resistance.[6] In Alberta the prevalence of MDR-TB was higher among immigrants who arrived in the decade ending in 2011 than in the decades ending in 1991 or 2001 (Figure 1).[7] In Canada, drug-resistant TB cases present earlier after arrival than drug-susceptible TB cases (Figure 2).[8] Immigrants to Canada from the Western Pacific may be at higher risk of MDR-TB due to Beijing/W strains of *M. tuberculosis*.[9] Most TB cases (71.0%) and most MDR-TB cases (84.0%) in Canada were reported in three provinces: BC, Ontario and Quebec.[10]

[a] Before 2008, "re-treatment" cases were referred to as "relapse" cases.

Table 1. Pattern of resistance to INH and RMP in the initial isolate of *M. tuberculosis* complex from TB patients in Canada, by disease type and country of birth, 2006-2010*

		Country of birth							
Resistance pattern	**Disease type**	**Canadian-born**		**Foreign-born**		**Unknown**		**Total**	
		N	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Susceptible to INH and RMP	New active	1,733	84.4	3,600	84.7	89	78.8	5,422	84.5
	Re-treatment	163	7.9	211	5.0	8	7.1	382	6.0
	Unknown	76	3.7	82	1.9	10	8.8	168	2.6
Resistant to INH, susceptible to RMP	New active	66	3.2	268	6.3	3	2.7	337	5.3
	Re-treatment	8	0.4	23	0.5	1	0.9	32	0.5
	Unknown	2	0.1	8	0.2	2	1.8	12	0.2
Resistant to RMP, susceptible to INH	New active	2	0.1	4	0.1	0	0.0	6	0.1
	Re-treatment	1	0.0	2	0.0	0	0.0	3	0.0
	Unknown	1	0.0	0	0.0	0	0.0	1	0.0
Resistant to INH and RMP (MDR-TB)	New active	1	0.0	41	1.0	0	0.0	42	0.7
	Re-treatment	0	0.0	10	0.2	0	0.0	10	0.2
	Unknown	1	0.0	3	0.1	0	0.0	4	0.1
	Total	2,054	100.0	4,252	100.0	113	100.0	6,419	100.0

INH = isoniazid, RMP = rifampin, MDR-TB = multidrug-resistant TB

*Based on the Canadian Tuberculosis Reporting System of TB cases, Public Health Agency of Canada.[5]

Figure 1. Number of foreign-born people with MDR-TB diagnosed in Alberta by year of arrival. The number of cases is represented by the solid line and the trend in MDR-TB case counts by the dashed line.[7]

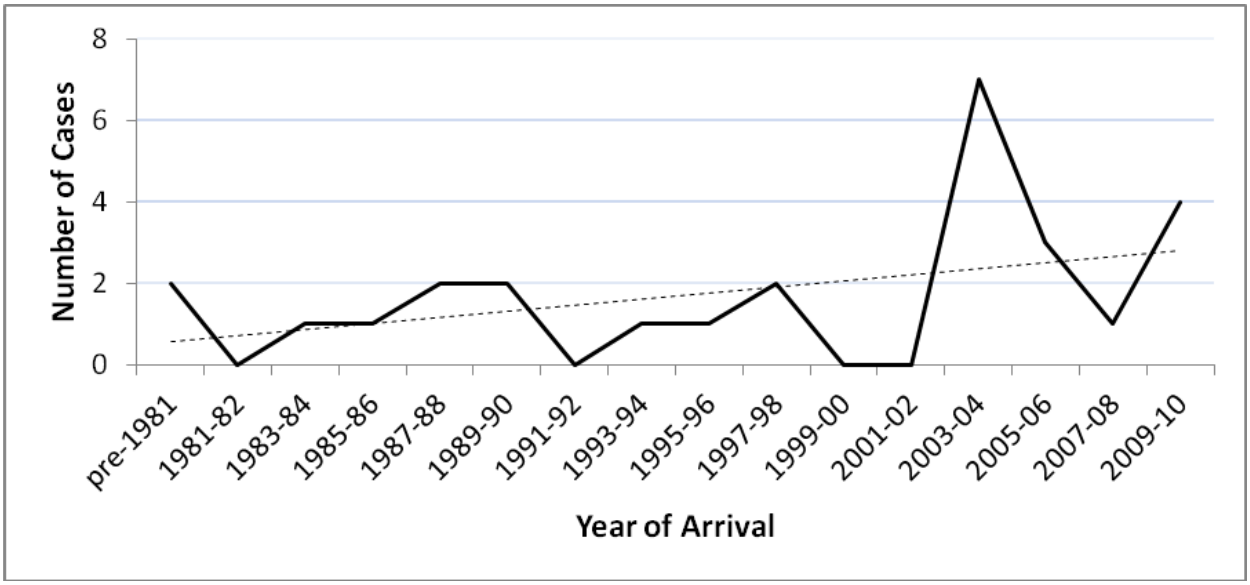
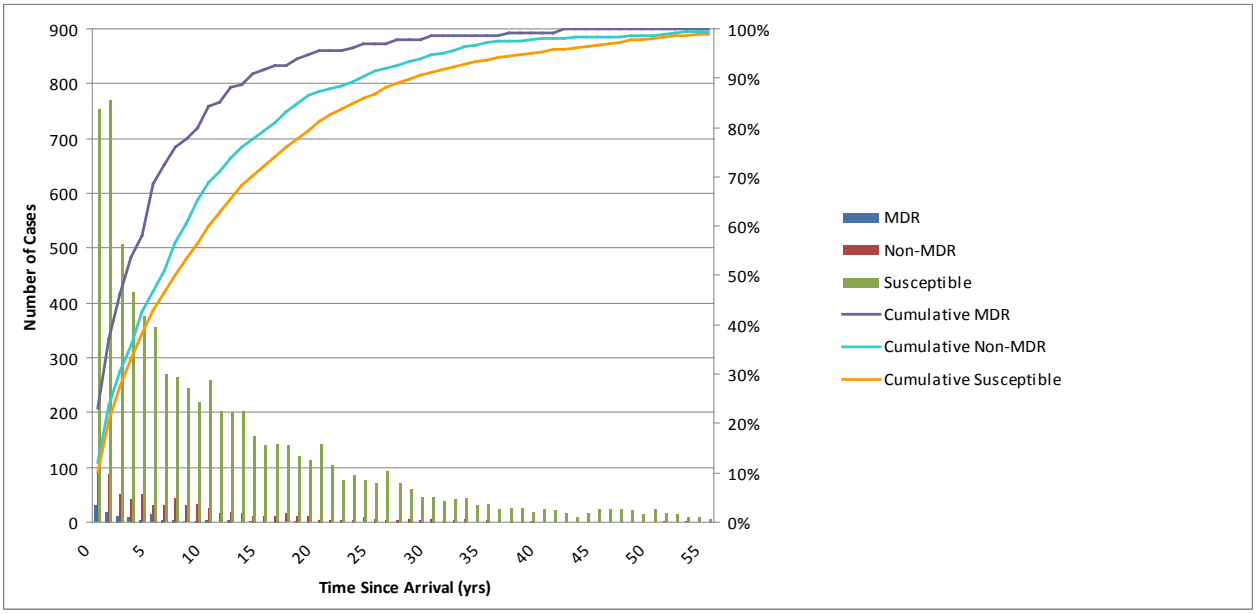


Figure 2. Time from arrival in Canada to diagnosis of foreign-born, culture-positive tuberculosis cases by drug susceptibility pattern of incident case isolate (1997-2008)[8]



Time from arrival to diagnosis was calculated by subtracting year of arrival from year of diagnosis. Year of arrival was known for 6,928 of the 10,589 foreign born cases. Cases with time since arrival between 0 and 55 years displayed.

Bar graph represents the absolute number of cases diagnosed, and line graph represents the cumulative proportion of foreign-born TB cases diagnosed since their time of arrival in Canada.

PHAC CANADIAN TUBERCULOSIS LABORATORY SURVEILLANCE SYSTEM (CTLSS)

This national laboratory-based surveillance system was established in 1998 to collect timely data on TB drug resistance across Canada. Participating laboratories include members of the Canadian Tuberculosis Laboratory Technical Network (covering all provinces and territories). Please see Table 2 for the overall pattern of TB drug resistance in Canada, 2006 to 2010, as reported by this system. For additional reports, see http://www.phac-aspc.gc.ca/tbpc-latb/index-eng.php for annual *Tuberculosis Drug Resistance in Canada* reports.[10]

Drug resistance is detected by the performance of *in-vitro* DST on pure cultures of *M. tuberculosis* complex grown from clinical specimens collected from patients (see Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance). Prompt turnaround times for laboratory results are of paramount importance in rapid diagnosis and appropriate treatment of drug-resistant TB. Recent advances in molecular biology have allowed identification of the genetic loci and biologic mechanisms of resistance to each of the first-line and selected second-line drugs (see next page).

Table 2. Overall pattern of reported TB drug resistance in Canada on initial and follow-up isolates of *M. tuberculosis* complex, 2006-2010*

	Report year											
	2006		2007		2008		2009		2010		2006-2010	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
All isolates	1,389	100	1,267	100	1,356	100	1,331	100	1,276	100	6,619	100
Susceptible isolates	1,263	90.9	1,134	89.5	1,240	91.4	1,204	90.5	1,164	91.2	6,005	90.7
Any first-line drug resistance†												
Any resistance to INH	101	7.3	110	8.7	102	7.5	113	8.5	101	7.9	527	8.0
Any resistance to RMP	24	1.7	13	1	19	1.4	21	1.6	18	1.4	95	1.4
Any resistance to EMB	12	0.9	23	1.8	13	1	17	1.3	10	0.8	75	1.1
Any resistance to PZA	16	1.2	27	2.1	22	1.6	18	1.4	25	2	108	1.6
Resistant to ≥1 first line drug	**126**	**9.1**	**133**	**10.5**	**116**	**8.6**	**127**	**9.5**	**112**	**8.8**	**614**	**9.3**
Monoresistant	107	7.7	111	8.8	94	6.9	98	7.4	88	6.9	498	7.5
Polydrug-resistant	3	0.2	11	0.9	7	0.5	11	0.8	6	0.5	38	0.6
MDR	16	1.2	11	0.9	15	1.1	18	1.4	18	1.4	78	1.2

INH = isoniazid, RMP = rifampin, EMB = ethambutol, PZA = pyrazinamide, MDR = multidrug resistant

*Based on the Canadian Tuberculosis Laboratory Surveillance System's drug susceptibility test results for *M. tuberculosis* clinical isolates.[10] These numbers are slightly higher than those in Table 1 as they also include drug-susceptibility test results on selected follow-up cultures.

†Some laboratories do not routinely report pyrazinamide or streptomycin resistance.

DRUG RESISTANCE THEORY

Traditionally, drug resistance in TB has been classified into three types.[11]

1. Primary drug resistance

When previously untreated patients are found to have drug-resistant organisms, presumably because they have been infected from an outside source of resistant bacteria. Primary drug resistance is uncommon in Canadian-born people unless they have travelled abroad to a country with a high prevalence of anti-TB drug resistance.

2. Acquired drug resistance

When patients who initially have drug-susceptible TB bacteria later become drug-resistant as a result of inadequate, inappropriate or irregular treatment or, more importantly, because of nonadherence in drug taking. Acquired drug resistance is uncommon in Canadian-born people, perhaps because directly observed therapy (DOT) is frequently used to promote treatment adherence.[12]

3. Initial drug resistance

When drug resistance occurs in patients who deny previous treatment but whose history of prior drug use cannot be verified. In reality it consists of true primary resistance and an unknown amount of undisclosed acquired resistance. It may be best to classify drug resistance in the foreign-born who deny previous drug use as *initial* rather than primary, unless their prior drug use can be verified. The following theory relates to acquired drug resistance.[†]

An understanding of acquired drug resistance theory is key to the prevention of drug-resistant TB. In any large population of *M. tuberculosis* bacteria, there will be several naturally occurring drug-resistant mutants.[13,14] Random mutations that confer resistance to each of the major anti-TB drugs occur at predictable frequencies in *nontreated* populations of TB bacteria (Table 3). A 2 cm diameter TB cavity harbouring 10^8 (100 million) bacteria may contain a few (~100) bacteria resistant to INH, a few (~10) resistant to RMP, a few (~10-100) resistant to EMB, etc. This does not mean that when a sample of this population of bacteria is cultured in the laboratory it will be determined to be resistant to these drugs: for resistance to be reported in the laboratory, at least 1% of the bacterial population needs to be resistant to the drug.[13,15,16] When 1% or more of a bacterial population is resistant to a given drug, clinical success with a regimen that is dependent upon that drug is less likely.[13,15,16]

Table 3. Mutation rates (per bacterium, per generation) and average mutant frequencies (in an unrelated population of bacteria, the proportions of resistant bacilli) for several commonly used drugs[15]

Drug	Mutation rate	Average mutant frequencies
INH (0.2 µg/mL)	1.84×10^{-8}	3.5×10^{-6}
RMP (1.0 µg/mL)	2.2×10^{-10}	1.2×10^{-8}
EMB (5.0 g/mL)	1.0×10^{-7}	3.1×10^{-5}
SM (2.0 µg/mL)	2.9×10^{-8}	3.8×10^{-6}

INH = isoniazid, RMP = rifampin, EMB = ethambutol, SM = streptomycin

[†]With respect to the reporting of "disease type" at the time of diagnosis, the terms "new active" and "re-treatment" are used (see Appendix A for definition of terms). Drug resistance among new cases is defined by the WHO as "the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, deny having had any prior anti-TB treatment (for as much as 1 month) and, in countries where adequate documentation is available, for whom there is no evidence of such a history".[3] Drug resistance among previously treated (re-treatment) cases is defined by the WHO as "the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, admit having been treated for tuberculosis for 1 month or more, or in countries where adequate documentation is available in a patient for whom there is evidence of such a history".[3] This category includes patients who have acquired resistance, have been primarily infected with a resistant strain in the past, been treated and subsequently failed or relapsed, as well as patients who have been re-infected.

The sites of resistance within the mutants are chromosomally located and are not linked. Accordingly, the likelihood of a bacterium *spontaneously* developing resistance to two unrelated drugs is the product of probabilities: for example, for INH and RMP resistance, 1 in 10^8 × 1 in 10^{10} equals 1 in 10^{18}. Because the total number of bacteria in the body, even with far advanced disease, rarely approaches this number (10^{18}), spontaneous evolution of MDR-TB is very rare. As Iseman and Madsen have enunciated so clearly:[17] "This is the salient principle of modern TB chemotherapy. Because naturally occurring two-drug resistance is very uncommon, therapy with two (or more) drugs prevents the emergence of progressive resistance in the following manner: some organisms in the population will be resistant to drug A, and some others will be resistant to drug B, but none will be simultaneously resistant to both drugs. Thus drug B will kill those organisms resistant to drug A, whereas drug A will kill those resistant to drug B. In principle this means a two-drug regimen should be adequate to treat the usual case of *drug-susceptible* TB." Because PZA accelerates bacterial killing in the initial phase and shortens the duration of treatment, and because bacterial loads may occasionally be very large, PZA is usually added to INH and RMP; to prevent acquired resistance to RMP in the event the initial isolate of *M. tuberculosis* (MTB) is resistant to INH, EMB is usually added to INH, RMP and PZA.[1,18] Thus, the standard short-course therapy recommended includes four drugs: INH, RMP, PZA and EMB. If the initial isolate is determined to be fully drug-susceptible, EMB may be discontinued (see Chapter 5, Treatment of Tuberculosis Disease).

If infection (latent TB infection or LTBI) and not disease is present, then it is reasonably safe to assume the bacterial load is small, and treatment need only include a single drug, usually INH.[18]

The emergence of drug resistance is due to the selection of pre-existing resistant mutants in the original bacterial population by "drug pressure." [15,17] For example, if INH alone is prescribed (or is the only first-line drug taken in a multidrug regimen), then it will kill all of the bacteria susceptible to it, including those random mutants resistant to drugs such as RMP and EMB, but it will not kill INH-resistant mutants. These will continue to multiply and will eventually dominate the population because they have a selective advantage in the presence of the drug, and INH will be lost to the armamentarium. The likelihood of this happening is influenced by the duration of such monotherapy: 25% among those receiving INH alone for 2 weeks, 60% for those receiving it for 6 months and 80% for those receiving it for 2 years.[19] If RMP alone is now added to the regimen, then by the same mechanism an MDR strain (i.e. resistant to both INH and RMP) will emerge: RMP will kill all bacteria resistant to INH, but it will not kill those few random mutants in the new population that are resistant to both INH and RMP.[15,17]

This classic theory of drug resistance in TB posits a sequence of events in which the patient effectively receives monotherapy. It does not explain how resistance may emerge solely because of irregularity in drug taking and without monotherapy. Other mechanisms have been proposed to explain resistance under these circumstances.[15,20,21] In essence, they require several cycles of killing (when drugs are taken) and regrowth (when drug taking stops). In each of these cycles there is selection favouring the resistant mutants relative to the susceptible bacterial population. Regrowth back to the size of the original population may occur with the consequent presence of increasing proportions of resistant bacteria at the start of each cycle.

WHEN TO SUSPECT DRUG-RESISTANT TB[22]

The possibility of drug-resistant TB should be considered at the time of selection of the initial treatment regimen. Failure to consider the possibility of drug-resistant TB until DST results become available weeks later can result in unnecessarily inadequate treatment regimens.

In patients who have not yet started their anti-TB drugs the most important predictors of drug-resistant TB are the following:

1. Previous treatment of TB disease

Drug-resistant TB should be suspected if the patient was previously treated for smear-positive or cavitary pulmonary TB; or if the treatment regimen was inadequate or self-administered; or if the patient was nonadherent. Conversely, if the patient is reported to have been lost to follow-up when taking multidrug DOT (i.e. stops all medications at the same time) or has relapsed after completion of a directly observed standardized regimen, then theoretically the likelihood of the isolate being drug-resistant is lower.[23]

To quote the Francis J. Curry National Tuberculosis Center:[22] "the soliciting of a history of previous TB treatment requires a great deal of patience and attention to detail. In a culturally sensitive and confidential setting one must allow plenty of time, utilize an accurate and unbiased interpreter (if necessary), and be willing to repeat or rephrase a question to obtain the information. One must give the patient encouragement to review accurate information by asking and responding in a nonjudgmental manner. One must ask the patient if he/she has any written information regarding his or her treatment, any old radiographs, etc." Patients born in Canada may have records of previous treatment at the level of the provincial/territorial TB program. Foreign-born people who have been referred for medical surveillance by Citizenship and Immigration Canada (CIC) because of inactive pulmonary TB, history of TB or another condition that puts them at high risk of active TB may have overseas records of previous treatment that CIC can retrieve (see Chapter 13, Tuberculosis Surveillance and Screening in Selected High-risk Populations).

If active TB disease is not adequately excluded beforehand, treatment of LTBI, even if only for a month, can result in drug resistance.

2. Origin from, history of residence in, or frequent or extended (1 month or more) travel to a country/region with high rates of drug resistance

Although drug-resistant TB is more common in the foreign-born than in other population groups in Canada, transmission of drug-resistant TB from the foreign-born to the Canadian-born is relatively uncommon.[12,24]

3. Exposure to an individual with infectious drug-resistant TB, including exposure in facilities where drug resistance has occurred, e.g. correctional facilities, homeless shelters or other congregate settings

While some data suggest that drug-resistant bacteria are less transmissible or less pathogenic once transmitted than drug-susceptible bacteria,[25-34] other data indicate that this may not be so and the transmission risk is offset by longer periods of infectiousness in drug-resistant cases[34,35] or compensatory mutations in drug-resistant bacteria.[36] Clinical evidence of the transmissibility of drug-resistant strains is compelling.[37-40] For practical purposes, i.e. for the ordering of treatment regimens or for contact tracing, drug-resistant bacteria should be considered just as transmissible and just as pathogenic as drug-susceptible bacteria.

4. Exposure to a person with active TB who has had prior treatment for TB resulting in treatment failure or relapse and whose DST results are not known

Depending upon the circumstances of the individual case (e.g. likelihood of resistance to more than one first-line drug, severity of disease) an expanded, empiric treatment regimen may be indicated from the outset. Although few countries report drug resistance data disaggregated by HIV status, the two with the most robust data (Latvia and Donetsk Oblast, Ukraine) both showed a significant association between HIV and MDR-TB.[3] This association may have more to do with environmental factors, such as transmission in congregate settings, than biological factors.[41]

A drug-susceptible strain of TB may become drug-resistant, or a monoresistant strain may become polydrug-resistant (see below) during treatment. This is more likely to occur under the following circumstances:

- when the treatment regimen is inadequate to begin with,[15,17]
- when there is intermittent or erratic ingestion of the prescribed anti-TB drugs,[15,17]
- when the patient is malabsorbing one or more of the drugs in the treatment regimen,[15]
- when the patient has cavitary pulmonary TB – cavities contain large numbers of bacteria with correspondingly large numbers of drug-resistant mutants,[42]
- when the patient's disease is sequestered, e.g. TB empyema, a rare condition in which differential penetration of anti-TB drugs has been described.[43]

Rare instances of mixed infection, with selection of a drug-resistant subpopulation during treatment with first-line drugs of a dominant drug-susceptible population, have been reported.[44,45] Also reported have been instances of reinfection with a drug-resistant strain during treatment of disease that is due to a drug-susceptible strain.[46]

Among patients with drug-susceptible pulmonary TB who are treated with standard four-drug therapy, approximately 80% will have negative sputum cultures after 2 months of treatment.[47] Progressive clinical and/or radiographic deterioration or failure of smears or cultures to convert in a timely fashion should lead to suspicion of treatment failure (defined as: [i] sputum smears positive after 5 months or more of treatment or [ii] continued or recurrent positive cultures after 4 or more months of treatment in patients in whom medication ingestion was confirmed) and acquired drug resistance.[47,48] Prior DST results should be reviewed and repeat DST performed. Self-administered treatment, if used, should be abandoned in favour of DOT and, in the event of possible drug malabsorption, serum drug concentrations should be measured.[47] Depending upon the circumstances, consideration should be given to a change or expansion of the treatment regimen. If a decision is made to expand the regimen, then a minimum of two new drugs is recommended – it is inadvisable to add a single drug to a failing regimen. It is advisable for the new drugs to be chosen from those to which the organism is known to be susceptible and/or those that the patient has never received.[22]

MANAGEMENT OF DRUG-RESISTANT TB

For the optimal management of drug-resistant TB, particularly MDR-TB, the following is recommended: the performance of state-of-the-art DST, an uninterrupted supply of first- and second-line anti-TB drugs (see below), the capacity to provide DOT, and access to a physician and team experienced in the management of drug-resistant TB. Steps to ensure that there is an uninterrupted supply of drugs should begin 6 months or more in advance of anticipated need, and drug needs should be estimated as accurately as possible.[49]

The WHO "gold standard" method for *M. tuberculosis* DST for first-line drugs uses an automated liquid culture system and an indirect or direct test.[50] Such phenotypic testing systems are most accurate for INH and RMP and less reliable (the extent to which a test result remains consistent when repeated under identical conditions) and reproducible (the ability of a test to be accurately reproduced or replicated under independent conditions) for PZA, EMB and SM. Liquid culture DST for aminoglycosides, polypeptides and FQNs has been shown to have relatively good reliability and reproducibility.[50] The Clinical and Laboratory Standards Institute, which offers practical operating guidelines that lead to consistent laboratory practices, precision and efficient use of resources, recommends that after having been tested for first-line anti-TB drugs, isolates found to be monoresistant to RMP or to demonstrate resistance to any two of the first-line anti-TB drugs should be tested against a panel of second-line drugs.[51] When FQNs may be added to therapy for cases showing monoresistance to INH (see below), it is also recommended that second-line anti-TB drug testing should be performed.[51] In anticipation of possible INH resistance/intolerance many laboratories are now including routine FQN DST at the time of first-line DST. In Canada in 2011, four laboratories conducted second-line anti-TB drug susceptibility testing: the provincial laboratories in Alberta, Ontario and Quebec, and the National Reference Centre for Mycobacteriology in Manitoba.[10,52]

Among patients with the various patterns of drug resistance, definitive, randomized trials of treatment have not been performed. Recommendations for treatment are based upon less than ideal evidence. With few exceptions the treatment regimens for drug-resistant nonrespiratory TB are the same as those for respiratory TB.[49] Generally, the regimens assume that the pattern of drug resistance has not changed between the time the specimen was collected and the time the phenotypic DST results were reported. Unfortunately, this gap can include several weeks during which the patient is receiving standard or empiric therapy. If the initial isolate of MTB turns out to

be polydrug-resistant or MDR, then the standard or empiric regimen may have not only been inadequate in the number and strength of drugs necessary for cure but also have induced resistance to other drugs included in the initial regimen ("amplified" resistance).

There are really only three ways to avoid this scenario: (i) delay treatment altogether until the DST results on the initial isolate are available – rarely an acceptable option, (ii) make certain (within reason) that the empiric regimen is strong enough to cover the possibility that the pre-treatment isolate is highly resistant or (iii) use one of the newer genotypic DST methods that target resistance-conferring mutations and provide an indication, early on, of the existence of resistance to INH and/or RMP (see below).[7]

DIAGNOSTIC CONSIDERATIONS

In Canada, RMP resistance strongly suggests (85% or more of the time) the presence of MDR-TB (see Table 1). Two new WHO-approved molecular tests rapidly detect RMP resistance and by doing so signal the likely presence of MDR-TB: the line probe assays (LPAs) and the Xpert MTB/RIF test.[50] LPAs use a polymerase chain reaction (PCR) hybridization technique to identify members of the MTB complex while simultaneously identifying drug-resistant strains through detection of the most common single nucleotide polymorphisms associated with resistance. The major advantage of LPAs is that they can be performed directly on smear-positive sputum samples, giving rapid (approximately 5 hour) drug susceptibility results without the need for culture. The disadvantages of LPAs are that they are labour intensive and require highly trained personnel, and dedicated laboratory space and equipment. The Xpert MTB/RIF test is a fully automated, closed system that performs both sample preparation and real-time PCR, producing results (detecting MTB complex while simultaneously detecting RMP resistance [targeting the rifampin resistance-determining region of the *rpoB* gene]) in less than 2 hours. The sensitivity and specificity of these two systems for detecting RMP resistance are in the order of 97%-100%.[50,53]

The WHO currently recommends rapid DST of INH or RMP alone over conventional testing or no testing at the time of diagnosis of TB, subject to available resources.[54] The basic assumption is that rapid DST will reduce the delay to the start of appropriate second-line therapy and thus provide benefit to the patient by increasing cure, decreasing mortality, reducing development of additional resistance and reducing the likelihood of failure and relapse. Studies supporting this assumption are just beginning to emerge.[55-57]
With the use of decision analysis modeling,[58] it was found that rapid testing for both INH and RMP at diagnosis rather than later during treatment was the most cost-effective DST strategy available, starting from an MDR-TB prevalence greater than 1% and an INH resistance (other than MDR-TB) greater than 2%, both of which apply to foreign-born TB patients in Canada (Table 1).[8] Origin from, history of residence in or frequent travel to one of the 27 countries[†] with a high MDR-TB burden, especially if residence or travel occurred within recent years, should prompt consideration of rapid testing.[4]

Other patients to consider for rapid testing include those with a history of previous treatment, those who are contacts of MDR-TB cases and those who are HIV coinfected.[4,7] Most Canadian-born TB patients would not be good candidates for rapid testing, given the low positive

[†] The 27 countries with a high MDR-TB burden are the WHO member states estimated in 2008 to have at least 4,000 MDR-TB cases arising annually and/or at least 10% of newly registered TB cases with MDR-TB. These countries are Armenia, Azerbaijan, Bangladesh, Belarus, Bulgaria, China, DR Congo, Estonia, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Myanmar, Nigeria, Pakistan, Philippines, Republic of Moldova, Russian Federation, South Africa, Tajikistan, Ukraine, Uzbekistan and Vietnam.

predictive value of these tests in patient groups in which RMP resistance is rare. It is recommended that use of rapid tests not obviate the need for culture and phenotypic DST. The current status of second-line DST methodology, consensus on reliability and reproducibility, and critical concentrations for different methodologies can be found in a WHO policy document on the rational use of second-line DST.[59] Susceptibility testing to all second-line drugs (cycloserine excepted) is available in Canada.[10,52]

RESISTANCE TO INH WITH OR WITHOUT RESISTANCE TO SM

In Canada, INH resistance is the most common pattern of first-line drug resistance (see Tables 1 and 2). Resistance to INH is usually due to a mutation in either the *katG* or *inhA* gene.[60,61] Less commonly it is due to one or more mutations in other genes, such as the *ahpC* gene.[15]

INH is a prodrug that must be activated by catalase-peroxidase, an enzyme that is regulated by the *katG* gene, in order to be effective against MTB. Mutation of the *katG* gene results in high level resistance to INH (resistance concentration 1.0 µg/mL using solid media [agar proportion method], 0.4 µg/mL using liquid media [indirect proportion method]).[15,62] When the *katG* gene is not mutated, activated INH acts on several *M. tuberculosis* genes, of which those in the *inhA* promoter region are the most important.[62] Mutations in the *inhA* gene or *inhA* promoter region result in low-level resistance to INH (0.2 µg/mL using solid media, 0.1 µg/mL using liquid media). Isolates that have high-level resistance to INH are usually susceptible to ethionamide; isolates that have low-level resistance to INH are usually resistant to ethionamide but susceptible to high dose (15 mg/kg or 900 mg thrice weekly) INH (see below).[62]

In general, on the basis of the research, it is recommended that patients suspected of having INH-resistant TB (with or without SM resistance) should, at a minimum, be started on all four first-line drugs while DST results are pending. An initial four-drug regimen is also advisable whenever the prevailing rate of INH resistance among those in whom there is no history of anti-TB drug use is 4% or more (see Tables 1 and 2).[63]

Recommended regimens for the treatment of INH-resistant TB are listed in Table 4.[64,65] The presence of SM resistance does not affect the efficacy of these regimens. Ideally, each regimen should be regarded as the *minimum* effective therapy, and consideration should be given to administering the regimen as DOT (see Chapter 5).

Direct observation of treatment is especially important in patients with smear-positive pulmonary disease or HIV coinfection. Given that a randomized controlled trial showed moxifloxacin, a fourth-generation FQN, to be equivalent to INH in the initial phase of treatment of smear-positive pulmonary TB, it is assumed that moxifloxacin or, by inference, levofloxacin (a third-generation FQN) would be equally efficacious and therefore could be interchangeable with INH in the treatment of INH-resistant TB.[66]

(Strong recommendation, based on moderate evidence)

Still unresolved is the question of whether an FQN can be used in an intermittent regimen; in theory a thrice weekly regimen of levofloxacin and RMP could be effective as the half-lives of these two drugs tend to be similar. A thrice weekly regimen of moxifloxacin and RMP is not

considered advisable, as the half-life of moxifloxacin is longer than that of RMP, resulting in conditions of moxifloxacin monotherapy.[65]

Table 4. Regimens for the treatment of INH-monoresistant TB

Initial phase	Continuation phase
2 months daily (INH) RMP/PZA/EMB*	4-7 months daily or thrice weekly RMP/PZA/EMB[64]
2 months daily (INH) RMP/PZA/EMB	10 months daily or thrice weekly RMP/EMB[22]
2 months daily (INH) FQN/RMP/PZA/EMB†	4-7 months daily or thrice weekly FQN/RMP/EMB[66]

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, EMB = ethambutol, FQN = levofloxacin or moxifloxacin

*If treatment was started with a standard 4-drug regimen, INH (particularly if the resistance is of a high level) can be discontinued once phenotypic resistance is documented.

†If an FQN-containing regimen is used thrice weekly, it should contain levofloxacin and not moxifloxacin. This is because levofloxacin has a shorter half-life than moxifloxacin and is less likely to result in a condition of FQN monotherapy.[65]

ISOLATED RESISTANCE TO RMP

Resistance to RMP is due to point mutations in the *rpo* gene in the beta subunit of DNA-dependent RNA polymerase in 95% of cases.[67] Resistance to RMP results in cross-resistance to rifabutin (RBT) in most (~80%) and to rifapentine (RPT) in all (100%) cases. With one exception, i.e. the occurrence of acquired RMP resistance in HIV-infected patients, RMP monoresistance is uncommon. It has been described in AIDS patients taking RBT as prophylaxis against *M. avium* complex and in HIV-coinfected TB patients, in whom the consistent associations are advanced HIV disease (CD4 counts in cases of acquired rifamycin resistance have all been <200 cells × 10^6/L and usually <50 cells × 10^6/L) and the use of an intermittent regimen during the initial phase of treatment.[68-74] In general, for HIV-coinfected TB patients it is recommended that intermittent treatment should be avoided altogether in the initial phase and used selectively in HIV sero-negative patients (see Chapter 5). Treatment options for patients determined to be RMP-monoresistant are given in Table 5.[22,47,75-78]

Table 5. Regimens for the treatment of RMP-monoresistant TB

Initial phase	Continuation phase
2 months daily INH/PZA/EMB/FQN*	10-16 months daily or thrice weekly INH/EMB/FQN[22,47,75]
2 months daily INH/PZA/SM (or other aminoglycoside/polypeptide daily or thrice weekly)	7 months daily or thrice weekly INH/PZA/SM[76]
2 months INH/PZA/EMB daily†	16 months daily or thrice weekly INH/EMB[77,78]

INH = isoniazid, PZA = pyrazinamide, EMB = ethambutol, FQN = levofloxacin or moxifloxacin, SM = streptomycin

*For treatment in patients with extensive cavitary disease or to shorten the duration of treatment (e.g. 12 months), addition of an injectable agent for at least the first 2 months is recommended.

† An injectable agent may strengthen the regimen in patients with extensive disease.

ISOLATED RESISTANCE TO PZA AND EMB

Isolated resistance to PZA or EMB is rare. Isolated PZA resistance occurs genotypically in *M. bovis*.[15] In 2003, PZA monoresistance was reported in isolates of *M. tuberculosis* from Quebec.[79] Patients with these strains had worse clinical outcomes than those with fully susceptible strains.[80] In patients with disease due to PZA-resistant isolates, the total duration of treatment should be 9 months or more. EMB monoresistance will not change the efficacy or duration of treatment with standard regimens.[22,47]

RESISTANCE TO TWO OR MORE FIRST-LINE DRUGS (POLYDRUG-RESISTANT TB) NOT INCLUDING MDR-TB

Polydrug-resistant TB is uncommon in Canada (see Table 2); the range of possible resistance patterns and treatment options are outlined in Table 6.[22,47,49] It is recommended that patients with polydrug-resistant TB be treated with daily DOT in the initial phase and daily or thrice weekly DOT in the continuation phase.

Table 6. Treatment regimens for the management of polydrug-resistant TB[22]

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment	Comments
INH and PZA	RMP, EMB, FQN	9-12 mo	A longer duration of treatment should be used for patients with extensive disease.
INH and EMB	RMP, PZA, FQN	9-12 mo	A longer duration of treatment should be used for patients with extensive disease.
RMP and EMB	INH, PZA, FQN plus an injectable agent for at least the first 2-3 months	18 mo	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
RMP and PZA	INH, EMB, FQN plus an injectable agent for at least the first 2-3 months	18 mo	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
INH, EMB, PZA	RMP, FQN plus an oral second-line agent, plus an injectable agent for the first 2-3 months	18 mo	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.

INH = isoniazid, PZA = pyrazinamide, RMP = rifampin, EMB = ethambutol, FQN = fluoroquinolone

MDR AND XDR TB

MDR-TB, and especially MDR-TB that is XDR, represents a grave threat to TB prevention and care.[81,82‡] It is recommended that people with MDR or XDR TB be treated with second-line drugs, here listed as the aminoglycosides (streptomycin, amikacin, kanamycin), polypeptides (capreomycin), the FQNs, ethionamide, cycloserine and *para*-aminosalicylic acid, which on balance are weaker, more toxic and more costly than first-line drugs (see Table 7).[22, 47,49,84-87] Furthermore, the duration of MDR or XDR TB treatment is longer, on average 20-24 months. Four MDR-TB case series have been reported in Canada.[7,8,88-90] In all of them, a high proportion of cases were foreign-born (83.3%-95.2%) and undergoing re-treatment (32.9%-67.7%); of those who were HIV tested few were HIV coinfected (0.0%-27.7%). See Table 8. MDR-TB has also been reported in HIV-seronegative Tibetan refugees in Ontario.[91] Longitudinal data from Alberta suggest that MDR-TB cases that report having arrived in Canada in the near past are more likely to have primary drug resistance than those reporting having arrived in the remote past.[7]

‡ At this time there is no evidence that strains referred to as “totally resistant TB” differ from strains encompassed by XDR TB. Accordingly, for the foreseeable future the term “totally drug-resistant TB” is discouraged.[83]

Table 7. Doses of and common adverse reactions to second-line anti-tuberculosis drugs[22,47,49]

DRUG*	Usual adult daily dosage (pediatric doses)	Peak serum concentration, µg/mL	Recommended regular monitoring	Adverse reactions
Streptomycin	15 mg/kg (20-40 mg/kg daily) (MAX 1 gm)	35-45	Vestibular function, audiometry, creatinine, electrolytes, magnesium and calcium	Auditory, vestibular and renal toxicity. If possible, avoid in pregnancy.
Amikacin Kanamycin Capreomycin	15 mg/kg (15-30 mg/kg daily) (MAX 1 gm)			
Ethionamide	250 mg BID or TID (15-20 mg/kg daily divided BID) (MAX 1 gm)	1-5	Hepatic enzymes, glucose, TSH	GI disturbance, hepatotoxicity, endocrine effects, neurotoxicity. Avoid in pregnancy.
Para-amino salicylic acid	4 g BID or TID (200-300 mg/kg daily in 2-4 divided doses) (MAX 10 gm)	20-60	Hepatic enzymes, electrolytes, TSH	GI disturbance, hepatic dysfunction, hypothyroidism. Avoid if allergic to aspirin.
Cycloserine	250 mg BID or TID (10-15 mg/kg daily divided BID) (MAX 1 gm)	20-35	Mental status, pharmocokinetics of cycloserine	Avoid in patients with epilepsy, mental illness or alcoholism.
Levofloxacin	500-1000 mg OD (< 5 yrs, 15-20 mg/kg daily divided BID) (> 5 yrs, 10 mg/kg OD) (MAX 500 mg)	8-12		GI disturbance, headache, anxiety, tremulousness, prolonged Q-T interval. Avoid in pregnant women or growing children.
Moxifloxacin	400-600 mg OD (10 mg/kg daily OD) (MAX 400 mg)	2.5-4.5		
Rifabutin	300 mg OD		Hepatic enzymes, complete blood count, vision screening	Hepatotoxicity, uveitis thrombocytopenia, neutropenia, drug interactions
Clofazimine	100-300 mg OD	0.5-2.0	Macular pigmentary changes, symptoms	Skin, conjunctiva, cornea, body fluid discoloration, GI intolerance, photosensitivity

BID = twice daily, TID = thrice daily, TSH = thyroid-stimulating hormone, GI = gastrointestinal, OD = once daily

*Kanamycin, capreomycin, ethionamide, *para*-aminosalicylic acid, cycloserine and clofazimine are not available in Canada, except perhaps pursuant to a practitioner's application for treatment of a patient through the Special Access program, available at: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php. Monthly monitoring of body weight is especially important in pediatric cases, with adjustment of doses as children gain weight.[22,85] Pyridoxine may reduce ethionamide and cycloserine neurotoxity.[86]

Table 8. MDR-TB experience in Canada

Reference	Jurisdiction (time period)	No. of cases	No. (%) foreign-born	No. (%) re-treatment	No. (%) HIV coinfected	Mean no. of first-line drugs to which the isolate was resistant*
88,89	AB & BC (January 1989 to June 1998)	24	20 (83.3)†	16 (66.7)	1/17 (5.9)	3.25
90	ON (January 1986 to June 1999)	40	38 (95.0)	26 (65.0)	6/46 (13.0)‡	3.20
8	Canada (January 1997 to December 2008)	177	163 (92.1)	55/167 (32.9)	9/38 (23.7)	NA
7§	AB (January 1982 to December 2011)	31	27 (87.1)	12 (38.7)	0/22 (0.0)	3.35

AB = Alberta, BC = British Columbia, ON = Ontario

*First-line drugs included isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin.

†Two Canadian-born cases were infected with an MDR strain while travelling abroad.

‡ This study reported only HIV uninfected patients; of all patients over the same time period (*n* = 82), 46 were HIV tested and 6 were positive.

§This study included 9 cases from reference #88; there were 31 patients and 32 episodes; one patient (the only MDR-TB case with XDR TB) had a relapse episode.

MAKING A PRESUMPTIVE DIAGNOSIS OF MDR-TB

Prior to the availability of DST results, MDR-TB should be suspected in the following:

- patients who have failed treatment with a standard four-drug regimen;
- patients who were treated for TB in the past and were nonadherent;
- patients who were treated for INH-resistant TB in the past; and
- patients who were close contacts of an infectious MDR-TB case.

In a recent study from California, independent predictors of *acquired* MDR-TB were initial INH resistance, initial RMP resistance, HIV infection and cavitary disease in the absence of DOT throughout therapy.[92] As outlined earlier, the suspicion of drug-resistant TB, and in particular MDR-TB, should precede the introduction of any anti-TB drugs. It should follow meticulous history-taking and the assembly of all available information concerning previous treatment and DST. Patients may recognize drugs as having been taken in the past when they are shown pictures of the drugs or the drugs themselves. Previous treatment with second-line drugs is a strong, consistent risk factor for resistance to these drugs.[93] As informed a prediction as possible should be made about precisely which drugs are likely to be effective in the individual. Great care should be taken to avoid a circumstance whereby an empiric regimen inadequate in the number or effectiveness of drugs allows the emergence of further drug resistance.

Once DST results are available for the current episode, it is recommended that any unnecessary drugs prescribed in an initial surfeit regimen be stopped. Generally, drugs to which there is known *in-vitro* resistance are not recommended. Exceptions to this may be the use of high dose INH in the presence of low-level INH resistance or the use of a fourth-generation FQN in the presence of second-generation FQN (ofloxacin) resistance.[94-98] Previous use of a drug may be associated with reduced clinical response, despite apparent *in-vitro* susceptibility.[19,99]

In a Canadian study, people with MDR-TB were more likely than those with resistant non MDR-TB, and people with resistant non MDR-TB were more likely than those with drug-susceptible TB, to be re-treatment cases.[8] Unless they were infected with a drug-resistant isolate from the outset (primary resistance), it is presumed that some combination of physician error and patient nonadherence to treatment turned fully susceptible organisms, or those with less complex resistance patterns, into MDR-TB.[100] In this regard it is noteworthy that among patients with MDR-TB referred to the National Jewish Medical and Research Center (Denver, Colorado) there were an average of 3.9 physician treatment errors per case.[100] The most common errors were addition of a single drug to a failing regimen, failure to identify pre-existing or acquired resistance, and administration of an initial regimen inadequate in number of drugs or duration of therapy, or both. MDR-TB patients without a history of previous treatment have a better response to treatment than do patients with a history of previous treatment.[101-103]

MDR-TB has been associated with reduced rates of cure and treatment adherence and increased rates of fatality and relapse.[104,105] MDR-TB patients who have XDR TB are yet more difficult to manage, their outcomes yet worse.[106]

TREATMENT REGIMENS FOR PEOPLE WITH A PRESUMPTIVE OR ESTABLISHED DIAGNOSIS OF MDR-TB

The following **recommendations** are based on evidence consisting of multiple observational studies, an individual patient data meta-analysis and expert opinion. *As such, all recommendations below should be considered conditional, based on weak to very weak evidence.* They may change as new and stronger evidence is published. The major sources for the recommendations are the WHO,[54,107] the Francis J. Curry National Tuberculosis Centre,[22] an individual patient data meta-analysis[108] and the Centers for Disease Control and Prevention in Atlanta.[47,109]

- MDR-TB (and de facto XDR TB) should be treated by those with a special interest and expertise in the management of drug-resistant TB.

- Individualized treatment regimens, based upon first- and second-line DST results as opposed to standardized regimens, should be used. If there is reason to question whether resistance to start-up drugs has developed (for example, to PZA or EMB) then repeat DST of these agents should be performed.

- To the extent that it is possible, outpatient (ambulatory) care is encouraged.[54] This recommendation, like the treatment itself and its duration (see below), requires a balance. The aim should be to provide treatment that is optimal in terms of relieving symptoms, reversing infectiousness, preventing further (acquired) resistance, maximizing cure and minimizing mortality while at the same time causing as little inconvenience as possible, e.g. hospitalization, side effects, duration of treatment, surgery. Such a balance serves, among other things, the purpose of promoting adherence. However, it is often the case that a period of hospitalization near the outset of treatment provides an opportunity to achieve rapid control of the infection while securing the patient's future cooperation. Incremental doses of poorly tolerated second-line drugs, such as *para*-aminosalicylic acid, ethionamide and cycloserine, can be introduced under direct observation; peripherally inserted central catheters can be placed for administration of injectable agents; psychosocial issues can be addressed;[110] and the patient and family can be educated. This may have the effect of reducing complications and improving adherence over the long term, justifying the expense of hospitalization.[111]

  Hospitalization is an especially important consideration when the patient is highly infectious (smear-positive) and effective home isolation cannot be provided, when the patient's infection is resistant to many more drugs than just INH and RMP, and when he or she is HIV coinfected. In other patients, and where the necessary program infrastructure, expertise and resources are in place, outpatient care may be possible and has been associated with high cure rates and lower costs.[112] Ideally, patients who require hospitalization should be admitted to specialized centres that meet strict criteria (see Table 9).[113]

- All treatment should be directly observed. DOT for 5 days per week with self-medication on weekends is acceptable if there are no problems with adherence.

- An initial phase of 8 months, followed by a continuation phase of 12-16 months, based upon clinical, radiographic and mycobacteriologic response, and the strength and tolerability of the regimen, is recommended.[54] The minimum total duration of treatment should be 20 months.

- It is suggested that the initial phase should include four or more drugs that are likely to be effective. It is advisable to begin with any first-line agents to which the isolate is susceptible, recognizing that prior use of these drugs in a start-up regimen may, if given for long enough, have induced further resistance and the relative weakness of phenotypic DST for these agents. Then it is recommended that a third- or fourth-generation FQN and an injectable agent be added, on the basis of susceptibilities. This should be followed by the addition of previously unused second-line drugs starting with ethionamide, if there is susceptibility to it, until four to six drugs to which the isolate is susceptible have been prescribed. In adult studies, the inclusion of an FQN is associated with improved outcome.[114] Ideally, the injectable agent should be administered 5-7 days per week (15 mg/kg daily), at least until culture conversion (see below), when thrice weekly dosing (25 mg/kg) is acceptable. The WHO has recently recommended that adults should be given injectable drugs for 8 months because longer durations are associated with better outcomes.[54] This may be appropriate for older children with extensive disease, but for most children 4-6 months of treatment is likely sufficient.[115]

- Administration of injectable agents through a central venous line may avoid irritation and persistent pain at the injection site. Whenever drugs such as ethionamide, *para*-aminosalicylic acid, clofazimine or cycloserine are used one may begin with a small dose and increase gradually to the planned dose over a period of several days.[22] The patient may otherwise experience severe drug intolerance and refuse to continue to take the drugs. Therapeutic drug monitoring to place dosages of second-line drugs in the therapeutic range and to minimize toxicity should be performed whenever possible (see Chapter 5).[22, 116] In general, high-end dosing is preferred.[117] The optimum duration and dose and indeed the utility of clofazimine therapy is still debated.[118] Before therapy is initiated adults and children should have their hearing and vision tested as well as their renal and thyroid function. Children old enough to cooperate (usually from about 5 years of age) can be assessed using Ishihara charts and by pure tone audiometry.[119] In designing a treatment regimen for MDR-TB, the potential toxicities (see Table 7), cross-resistances and drug interactions (see Table 10) should be taken into account.[120-122]

- The continuation phase should include three or more drugs likely to be effective.[22,54]

- Antiretroviral therapy is recommended for all patients with HIV and MDR-TB (or other cases requiring second-line anti-TB drugs) irrespective of CD4 cell count, as early as possible (within the first 8 weeks) after initiation of anti-TB treatment.[54]

- In addition to being followed closely for adverse events, patients should be instructed to report immediately any symptoms that suggest drug toxicity.[49]

- Special drug considerations: if an isolate is resistant to RMP, testing for *in-vitro* susceptibility to RBT should be requested. If cross-resistance is not present on phenotypic testing (ideally confirmed on genotypic testing – most RBT-susceptible isolates have RMP *rpoB* mutations at codons 506-508, 511, 512 and 516; most RBT-resistant isolates have RMP *rpoB* mutations at codons 526 and 531) RBT should be added.[123] RBT is as effective as RMP in the treatment of drug-susceptible TB,[124,125] but data on its use for MDR-TB are limited. Although linezolid, an oxazolidinone, is often not listed as a second-line drug, it has been used as such with some success. It has theoretic advantages in that it is rapidly and extensively absorbed after oral dosing, is readily distributed to well-perfused regions of the body and penetrates well into bronchoalveolar tissue. It has activity against *M. tuberculosis in vitro* and inhibits the growth of *M. tuberculosis* in animal models. Linezolid's safety and tolerability are limited by the dose- and duration-dependent occurrence of reversible myelosuppression and peripheral and optic neuropathy.[126-130] In general, a once daily dose of 300 mg is better tolerated than a once daily dose of 600 mg, which in turn is better tolerated than a twice daily dose of 600 mg of linezolid. Observational data suggest that pyridoxine (50-100 mg daily) might mitigate the myelosuppression associated with linezolid.[127]

When extensive resistance to first- and second-line drugs (XDR-TB) has been documented, better outcomes have been reported in those who received more than five drugs.[131] In these patients or in others, such as MDR-TB patients intolerant of second-line drugs, consideration may need to be given to surgery (see below). Several new anti-TB drugs, for example, bedaquiline (TMC207), delamanid (OPC67683), SQ109, PA824, AZD5847 and PNU100480, have entered human trials and may be available for clinical use within the next few years.[79] Results of Phase II trials of bedaquiline and delamanid have been published; outcomes of treatment when these drugs were added to an optimal background regimen were better than with placebo.[132,133] Compassionate use of and expanded access to new drugs are being explored internationally.[134]

It is recommended to make it clear to patients, families and staff from the outset that meticulous adherence to the prescribed regimen is critical to cure. Patients should be counseled to accept minor side effects in order to achieve cure and agree to remain under direct observation with each dose supervised; as well, it is recommended that patients receive in their own language clear and complete instructions before treatment begins, in addition to consistent psychological support during treatment. Traditional roles and responsibilities within families may need to be examined, and social support may need to be provided to secure adherence. Strategies for reducing treatment default in drug-resistant TB have recently been reviewed.[135]

Pregnancy may complicate the management of MDR-TB, and experience with the issues involved is necessary. The teratogenic risks of second-line drugs, the use of holding regimens, the timing of treatment initiation, the risks of vertical and lateral transmission and the role of BCG vaccination in infants have recently been reviewed.[22,49,136,137]

Table 9. Canadian Thoracic Society recommended criteria for specialized centres for the management of MDR-TB patients

- Adequate infection control environment: negative pressure rooms, adequate number of air exchanges/hour, no recirculation of air and patient access to an enclosed outdoor space.
- Expertise.
- Adequate infrastructure to deal with the needs of these patients: psychosocial support, psychiatric and psychological support,[113] nutritional needs, counseling, recreational opportunities, exercise facilities.
- Culturally sensitive environment. In Canada the majority of patients with MDR-TB are born outside of Canada.
- Reliable laboratory support.
- Reliable drug supply.
- Well-established links with public health.
- Well-structured program and follow-up in an outpatient clinic after discharge from the hospital.

Table 10. Cross-resistance and interactions among anti-TB drugs

Cross-resistance

- Resistance to amikacin induces cross-resistance to kanamycin and vice versa.[120]
- Resistance to SM does not induce cross-resistance with amikacin-kanamycin, or capreomycin.[120]
- Isolates acquiring resistance to capreomycin are usually susceptible to kanamycin and amikacin.
- Isolates acquiring resistance to amikacin and kanamycin may or may not be resistant to capreomycin.
- Resistance to one FQN induces class-effect cross-resistance to all other FQNs, though data suggest that this cross-resistance may not be complete. Some isolates resistant to ofloxacin may be susceptible to moxifloxacin.[22,97,98]
- Most isolates resistant to RMP (approximately 80%) are also resistant to RBT.[120] Resistance to RPT is universal in RMP-resistant isolates.
- Cross-resistance to ethionamide may occur when there is low-level resistance to INH.[22]

Drug interactions

- RMP has many drug interactions (see Chapter 5, Treatment of Active Tuberculosis).
- RBT does not induce catabolic enzymes or alter the pharmacokinetics of other drugs to the extent that RMP does (about 40% of that seen with RMP). Nevertheless, the potential for RBT to affect the metabolism of other drugs needs to be considered.[15] Dosage adjustment may be necessary in patients taking antiretroviral therapy.
- INH can result in increased serum concentrations of phenytoin in people taking both drugs.
- Increased risk of neurotoxicity from cycloserine has been associated with concomitant use of INH,[121] ethionamide[121] and FQNs.[122]
- *Para*-aminosalicylic acid and ethionamide have each been associated with hypothyroidism. The probability of hypothyroidism is increased when both agents are used together.[15]

SURGERY FOR MDR-TB

The option of resecting diseased lung tissue becomes more attractive as the number of drugs to which the patient's isolate is resistant increases and the likelihood of a pharmacologic cure decreases. Unfortunately for many patients the extent of disease and/or the severity of the underlying lung function abnormality preclude a surgical option. At the National Jewish Medical and Research Center patients were selected for surgery on the basis of extensive drug resistance, poor response to medical therapy and disease sufficiently localized to permit resection of the bulk of involved lung with enough remaining functioning lung to predict recovery without respiratory insufficiency.[138,139]

The selection of surgical candidates and the timing of adjunctive surgery should be performed on a case-by-case basis. It is recommended that only those patients whose organisms

demonstrate drug resistance patterns that predict a high probability of treatment failure should be considered for resection. The goal of surgery should be to remove as much diseased lung as possible, particularly cavities, while avoiding crippling respiratory impairment.[15] The optimal timing of surgical intervention is after 3 to 4 months of therapy and sputum culture conversion, though the latter may not always be possible.[15] Engaging a surgeon experienced in the performance of lung resection in TB patients is recommended. The anticipated site of the surgical stump should be evaluated bronchoscopically before surgery to establish the absence of endobronchial TB, which, if present, is associated with poor healing and a persistent broncho-pleural fistula.[112,140] Surgical outcomes are generally good.[139,141-144] Anti-TB drug treatment should be continued for 18 to 24 months after surgery.[117,139]

MONITORING OF TREATMENT OF MDR-TB PATIENTS

It is recommended that the monitoring of patients with MDR-TB include a systematic, organized approach, such as that outlined in detail by the Francis J. Curry National Tuberculosis Center.[22] Elements of such monitoring should include drug administration, weight and nutrition, drug absorption and drug interactions, substance abuse and mental health, respiratory and systemic symptoms, symptoms of drug toxicity, blood tests, visual screens, audiology and vestibular testing, bacteriology, therapeutic drug monitoring and radiology. Although the exact role of therapeutic drug monitoring in the management of MDR-TB has not been extensively studied, there are a few situations in which drug concentrations are routinely measured: aminoglycoside concentrations, especially in patients who have known renal dysfunction, cycloserine concentrations to help predict and minimize central nervous system adverse reactions and prevent seizure activity, and EMB concentrations in patient with reduced renal function.[22]

With respect to mycobacteriology, the use of sputum smear and culture results, rather than sputum smear alone, is recommended for the monitoring of patients with MDR-TB during treatment. Hospitalized patients with smear- and/or culture-positive pulmonary disease should have sputum submitted at least weekly and remain in airborne isolation until three consecutive sputum samples are culture-negative after 6 weeks of incubation in broth or 8 weeks in solid media. Otherwise, WHO criteria for culture conversion are recommended: two consecutive negative smears and cultures taken at least 30 days apart. Time to conversion is calculated as the interval between the date of MDR-TB treatment initiation and the date of sputum collection of the first of the two consecutive negative cultures.[49] Even after culture conversion specimens should be submitted at least monthly to document the stability of the mycobacteriologic response. An MDR-TB patient is not considered cured until he or she has completed treatment according to the regimen and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment.[49,145] An MDR-TB patient is considered to have failed treatment if two or more of the five cultures recorded in the final 12 months are positive, or if any one of the final three cultures is positive.[145]

Patients who have completed treatment of MDR-TB or XDR-TB should undergo clinical, radiologic and mycobacteriologic follow-up at 6-monthly intervals for a minimum of 2 years.

MANAGEMENT OF CONTACTS OF MDR-TB

Contacts of patients with MDR-TB should be rapidly identified and evaluated, especially when the index case has smear-positive pulmonary TB or laryngeal TB.[49] In settings with a high HIV prevalence, the incidence of MDR-TB among household contacts has been found to be extremely high, most secondary cases occurring shortly after the diagnosis of the source case.[146] Close contacts of an infectious case, especially those who are under the age of 5 years or are immunocompromised, are especially important to screen. After active TB has been excluded, contacts who have a tuberculin skin test (TST) result of 5 mm or more of induration or TST-negative contacts who are under the age of 5 years or are immunocompromised should be evaluated for therapy of latent TB infection (LTBI) (see also Chapter 6, Treatment of Latent Tuberculosis Infection).

There are no randomized controlled trials that have assessed the effectiveness of treatment of LTBI in people exposed to MDR-TB.[147] In a systematic review of the literature on people treated and not treated for LTBI after exposure to MDRTB there were only two observational studies that met the inclusion criteria.[148] A prospective cohort study found individualized treatment, tailored to DST, was effective in preventing active TB in children,[149] and a retrospective cohort study found INH not to be effective.[150] Since then another observational study has found that individualized treatment was effective.[151]

If the isolate from the source case is susceptible to FQNs then daily, self-administered moxifloxacin or levofloxacin for 9 months is recommended for treatment of LTBI. Thrice weekly directly observed preventive therapy may be considered. In the event of FQN resistance there is no consensus on management, although a two-drug regimen, based upon DST, for 6 to 12 months could be considered. The risks and benefits of such regimens should be discussed with the patient beforehand; when accepted, such regimens should be carefully monitored for adverse effects.[147, 152,153] Whether they are offered tailored LTBI treatment or not, close contacts of infectious MDR-TB cases should be followed clinically for 2 years.[154]

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