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Chapter 8: Drug-resistant tuberculosis

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KEY POINTS

- Prior to choosing an initial tuberculosis (TB) treatment regimen, clinicians should assess all patients for risk factors for drug-resistant TB.
- Rapid molecular tests to predict rifampin resistance (and, ideally, isoniazid resistance) should be performed for every patient, with results used to guide treatment. Rapid molecular tests are especially important for patients with risk factors for drug-resistant TB.
- For the optimal management of drug-resistant TB, particularly multidrug-resistant (MDR-TB), providers should have access to: (i) state-of-the-art drug susceptibility testing for all drugs that will be used; (ii) an uninterrupted supply of quality-assured first- and second-line anti-TB drugs; (iii) directly observed therapy and other components of a patient-centered comprehensive management program; and (iv) a team experienced in the management of drug-resistant TB that includes physicians, nurses and pharmacists.
- Isolates from all TB patients diagnosed with rifampin resistance or multidrug resistance should undergo phenotypic drug susceptibility testing for all anti-TB medicines currently recommended to treat MDR-TB.
- Federal and provincial government agencies, and pharmaceutical companies operating in Canada, should facilitate timely access to second-line drugs for MDR and extensively drug-resistant (XDR)-TB.
- In patients with mono-isoniazid resistance, a treatment regimen including a later generation fluoroquinolone (levofloxacin is preferred), rifampin, ethambutol and pyrazinamide should be given for 6 months.
- For the treatment of isoniazid-resistant TB, in patients with less extensive disease (eg, noncavitary), and especially if there is increased risk of liver toxicity, pyrazinamide should be given for the first 2 months only; in the final 4 months, rifampin, ethambutol and the fluoroquinolone should be given.
- For the treatment of MDR-TB, treatment should include:
  - use of regimens that include bedaquiline, for all patients;
  - use of regimens that include linezolid, for all patients; and
  - use of regimens that include either levofloxacin or moxifloxacin, for all patients.
- For the treatment of MDR-TB, drugs that the infecting strain has proven resistance to through drug susceptibility testing should not be used.
- For the treatment of MDR-TB, the initial regimen should include levofloxacin or moxifloxacin AND bedaquiline AND linezolid AND clofazimine AND cycloserine.
- For the treatment of MDR-TB, 5 to 7 months after culture conversion occurs, the total number of drugs in the regimen can be reduced to 4.
- For the treatment of MDR-TB, a total treatment duration of 18 to 20 months, modified based on response to therapy, is appropriate.
- For the treatment of pre-extensively drug-resistant or extensively drug-resistant TB, or in situations where one or more of the Group A and B drugs cannot be used due to side effects, contra-indications, unavailability or resistance, one or more Group C drugs can be added, to ensure at least 5 drugs are in the regimen. The order of preference for the addition of Group C drugs is (from most to least preferred): ethambutol, pyrazinamide, delamanid, amikacin, imipenem-cilastatin or meropenem (plus clavulanic acid), ethionamide and *p*-aminosalicylic acid.
- In patients with MDR-TB, partial lung resection (lobectomy, segmentectomy or wedge resection) in carefully selected patients can be an adjunct to optimized medical therapy. The optimal timing of surgical resection appears to be after culture conversion is achieved.

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1. Introduction

People with TB are said to have drug-resistant disease if their strain of Mycobacterium tuberculosis *(M. 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, the isolate is resistant to, and reflects the different, but complementary, role each drug plays in the treatment of TB.[1]

At the level of the individual patient who begins with TB disease due to drug-susceptible *M. tuberculosis* organisms, it is commonly believed that drug resistance occurs due to one or more of the following: improper prescription of anti-TB drugs (including drug selection and dosing), their proper prescription but unavailability, the malabsorption of these drugs, treatment interruptions or inadequate treatment supervision. Recent studies suggest that low anti-TB drug concentration exposures, caused by inter-individual pharmacokinetic variability, poor quality drugs, suboptimal drug dosing and/or poor drug penetration into tissues, could be a major cause of acquired drug resistance.[2]

At the population level, it is likely that the resource-driven use of standardized regimens in the absence of pretreatment drug susceptibility testing (DST) has resulted in a steadily rising global prevalence of drug resistance.[3] 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% 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.[4] In some geographic locations, transmission of organisms that are already drug-resistant in congregate institutions—notably hospitals and prisons—amplifies the problem of drug-resistant TB.

1.1. Definitions

- Mono-resistant TB is defined as resistance to only 1 of the 4 first-line drugs.
- Polydrug-resistant TB is defined as resistance to at least two first-line drugs without resistance to RMP.
- MDR-TB is defined as TB due to bacteria resistant to isoniazid and rifampin with or without resistance to other first line anti-TB drugs.
- Extensively-drug-resistant TB (XDR-TB) is now, after being updated,[5] divided into: Pre-XDR-TB, which is now defined as MDR-TB with additional resistance to any fluoroquinolone; and XDR-TB, which is defined as pre-XDR-TB with additional resistance to bedaquiline or linezolid.

1.2. Epidemiology

The 2020 Global Tuberculosis Report[6] produced by the World Health Organization (WHO) includes reported resistance patterns in 198 countries and territories accounting for more than 99% of estimated global TB cases. The WHO, together with other international guidelines, groups RMP-resistant TB with MDR-TB because mono-resistant TB that is resistant to RMP requires similar treatment as MDR-TB. (Thus, all further reference to MDR-TB can be read as including RMP-resistant TB.) The global mean of MDR-TB has remained at 3-4% of all new cases, and 14-18% of previously treated cases. In 2019, an estimated 465,000 cases of MDR-TB emerged globally, with India, China and the Russian Federation accounting for almost 50% of the world's total cases. In addition, 20.1% of these were found to have pre-XDR-TB.

The most recent report from the WHO indicated the population-weighted mean of resistance to any of INH, RMP, EMB or streptomycin 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.[6]

The overall pattern of TB drug resistance in Canada from 2011-2015 is shown in Table 1.[7] In 2018, the most recent year reported, 10.1% of 1,459 *M. tuberculosis* isolates in Canada were resistant to one or more drugs. The majority were mono-resistant (81.8%, n = 121), with INH, PZA and RMP mono-resistance at 60.1% (n = 89), 17.6% (n = 26) and 4% (n = 6), respectively.[7] Poly-resistance was found only in 5 isolates; which were all resistant to both INH and PZA. MDR-TB was found in 1.4% (n = 21), with both fluoroquinolone and second-line injectable resistance in one isolate. Most TB cases (69.5%) and most MDR-TB cases (78.4%) in Canada were reported from 3 provinces: BC, Ontario and Quebec.[7] While prevalence of drug resistance stratified by prior TB treatment status has not been reported in recent years, between 2006 and 2010, drugresistant TB was reported most commonly in people with a past history of TB ("re-treatment cases," previously called "relapse" cases). About 83% of drug-resistant TB from 2006-2016 were reported in the foreign-born population.[7]

1.3. Drug resistance theory

Traditionally, drug resistance in TB has been classified into 3 types.[8]

1. Primary drug resistance: When previously untreated patients are found to have drug-resistant organisms,

Table 1. Drug resistance on initial and follow-up isolates of *M. tuberculosis* complex, in Canada, 2011-2015.[7]

	Number	%
All isolates (Total)	6,819	100.00
Fully susceptible isolate to first-line drugs	6,159	90.32
Any resistance to INH	543	7.96
Any resistance to RMP	96	1.41
Any resistance to EMB	39	0.57
Any resistance to PZA	155	2.27
Resistant to ≥1 first line drug	**660**	**9.68**
Mono-resistant	562	8.24
Polydrug-resistant	14	0.21
MDR	80	1.17
MDR with FQN-R and SLI-R	4	0.06

Abbreviations: INH, isoniazid; RMP, rifampin; EMB, ethambutol; PZA, pyrazinamide; MDR, multidrug-resistant; FQN-R, fluoroquinolone-resistant; SLI-R, second line injectable-resistant.

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 traveled abroad to a country with a high prevalence of drug-resistant TB.

2. Acquired drug resistance: When patients who initially have drug-susceptible TB bacteria that later become drug-resistant during treatment. Acquired drug resistance is uncommon in Canadian-born people.[9]
3. Initial drug resistance: When drug resistance occurs in patients who deny previous treatment but whose lack of prior TB drug use cannot be verified. In reality it consists of true primary resistance and an unknown amount of undisclosed acquired 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.[10,11] Random mutations that confer resistance to each of the major anti-TB drugs occur at predictable frequencies in *nontreated* populations of TB bacteria (Table 2). A 2-cm diameter TB cavity harboring 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, and so forth. 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.[10,12,13]

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: "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."[14] Because PZA accelerates bacterial killing in the initial phase and shortens the duration of treatment, and because bacterial loads may occasionally be very large, it is usually added to INH and RMP; to prevent acquired resistance to RMP in the event the initial isolate of *M. tuberculosis* is resistant to INH, EMB is usually added to INH, RMP and PZA.[1,15] Thus, the standard short-course therapy recommended includes these 4 drugs. If the initial isolate is determined to be fully drug-susceptible, EMB may be discontinued (see Chapter 5: Treatment of Tuberculosis Disease).

Table 2. 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.[12]

Drug	Mutation rate	Average mutant frequencies
INH (0.2 µg/mL)	1.84×10^{-8}	3.5×10^{-6}
RMP (1.0 µg/mL)	2.20×10^{-10}	1.2×10^{-8}
EMB (5.0 g/mL)	1.00×10^{-7}	3.1×10^{-5}
SM (2.0 µg/mL)	2.90×10^{-8}	3.8×10^{-6}

Abbreviations: INH, isoniazid; RMP, rifampin; EMB, ethambutol; SM, streptomycin.

If latent TB infection (LTBI) is present, then it is reasonably safe to assume the bacterial load is small, and treatment need only include a single drug, usually RMP or INH.[15]

The emergence of drug resistance is due to the selection of preexisting resistant mutants in the original bacterial population by "drug pressure." 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 or 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 as a tool to the practitioner. 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.[16] If RMP alone is now added to the regimen, then by the same mechanism, an MDR strain (ie, resistant to both drugs) 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.[12,14]

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.[1,12,17] 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 favoring 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.

1.3.1. Acquired drug resistance

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

- when the treatment regimen is inadequate;[12,14]
- when there is intermittent or erratic ingestion of the prescribed anti-TB drugs; [12,14]
- when suboptimal drug doses, or poor-quality drugs are used;[2]

- when the patient is malabsorbing 1 or more of the drugs in the treatment regimen;[12]
- when the patient has cavitary pulmonary TB, with cavities containing large numbers of bacteria with correspondingly large numbers of drug-resistant mutants[10], and differential penetration of anti-TB drugs into cavities has been shown; and [18]
- when the patient's disease is sequestered, for example, pericardial TB, meningeal TB, or TB empyema, which also may lead to differential drug penetration.[19–21]

1.3.2. Heteroresistance

Heteroresistance, either due to infection with a mixture of drug-susceptible and drug-resistant organisms arising from a single strain, or infection with mixed strains, has also been described, and may lead to selection of a drug-resistant subpopulations during treatment.[22–26] Instances of infection with a drug-resistant strain during treatment of disease that is due to a drug-susceptible strain have also been reported.[27]

2. Risk factors for drug-resistant TB

The possibility of drug-resistant TB should be considered at the time of TB diagnosis and selection of the initial treatment regimen. Failure to consider the possibility of drug-resistant TB until conventional 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 for TB disease

Previous treatment (of at least 1 month of 1 or more anti-TB drugs) has been consistently shown to be a strong risk factor for drug-resistant TB, especially MDR-TB.[2] This association may be explained by the acquisition of drug resistance during the prior treatment episode or, alternatively, reemergence of an already drug-resistant strain that was undiagnosed and/or inadequately treated. A detailed history of prior TB treatment and prior drug-susceptibility test results (if available) are essential. Patients previously treated in Canada may have records of previous treatment through the provincial/territorial TB program. If active TB disease is not adequately excluded beforehand, treatment of presumed LTBI, even if only for a month, can result in drug resistance.

2. Origin from, history of residence in or frequent or extended travel to a country with higher rates of drug resistance

Drug-resistant TB is more common in the foreign-born population than other population groups in Canada.[7] Published prevalence estimates for drug-resistant TB from a foreign-born patient's country of origin, such as those from the WHO, can be helpful to estimate an individual patient's risk. However, it is important to keep in mind that some discordance between WHO estimates and actual rates of drug-resistant TB by country of origin in foreign-born patients may exist, as has been shown in the U.S.[28] Table 3 shows the total TB disease incidence, and the prevalence of isoniazid resistance and MDR/rifampin resistance among new and previously treated TB cases by country, for the most common countries of birth among patients with TB in Canada. Fortunately, transmission of drug-resistant TB from the foreign-born population to the Canadian-born population is relatively uncommon.[9,29]

3. Exposure to an individual with confirmed (or highly suspected) infectious drug-resistant TB

While some data suggest that drug-resistant bacteria are less transmissible or less pathogenic once transmitted than drug-susceptible bacteria[31–39], other data indicate that this may not be so[40] and the transmission risk is offset by longer periods of infectiousness in drug-resistant cases[41,42] or compensatory mutations in drug-resistant bacteria.[43–45] Clinical evidence of the transmissibility of drug-resistant strains is compelling.[46–49] For clinical purposes, such as treatment regimens or contact tracing, drug-resistant bacteria should

Table 3. Total TB incidence, prevalence of isoniazid resistance, and prevalence of MDR/RMP resistance among new and previously treated TB cases; reported by the country to WHO, for the most common countries of birth among foreign-born patients diagnosed with TB in Canada.

Country	Total TB incidence per 100,000[a]	INH-R New[b]	INH-R Previously treated[b]	MDR/RR New[a]	MDR/RR Previously treated[a]
India	193 (132-266)	8.3%	13.5%	2.8% (2.3-3.5)	14% (14-14)
Philippines	554 (311-866)	12.1%	14.9%	1.8% (1.3-2.6)	28% (27-29)
China	58 (50-67)	7.5%	8.2%	7.1% (5.6-8.7)	23% (23-24)
Viet Nam	176 (112-255)	14.3%	9.9%	3.6% (3.4-3.8)	17% (17-18)
Pakistan	263 (187-353)	7.9%	6.6%	4.2% (3.2-5.3)	7.3% (6.8-7.8)
Ethiopia	140 (98-188)	6.1%	13.2%	0.71% (0.62-0.8)	12% (11-13)
Somalia	258 (167-368)	6.0%	8.3%	8.7% (6.1-12)	88% (73-96)
Haiti	170 (130-215)	N/A	N/A	2.1% (0.78-4.1)	12% (7.4-17)
China, Hong Kong SAR	63 (54-72)	5.2%	7.2%	0.81% (0.49-1.3)	2.8% (0.93-6.5)
Afghanistan	189 (122-270)	N/A	N/A	2.6% (1.1-4.7)	24% (21-27)

Abbreviations: TB, tuberculosis; INH-R, isoniazid resistance without rifampin resistance; MDR/RR, multidrug resistance or rifampin resistance without confirmed INH resistance; WHO, World Health Organisation; N/A, data not available; Hong Kong SAR, Hong Kong Special Administrative Region.

[a]Total TB incidence estimates and MDR/RR estimates are all for 2019, produced by WHO in consultation with countries; ranges represent uncertainty intervals.[6] See https://www.who.int/teams/global-tuberculosis-programme/data. . . for other country estimates.

[b]INH-R estimates are for the following years: India 2016, Philippines 2012, China 2013, Viet Nam 2012, Pakistan 2013, Ethiopia 2005, Somalia 2011, China, Hong Kong SAR 2017. Source Dean et al.[30]

be considered just as transmissible and just as pathogenic as drug-susceptible bacteria.

In addition to exposure to documented drug-resistant TB, patients who report a history of exposure to a person with TB disease who had treatment resulting in treatment failure or relapse and whose DST results are not known should be considered at increased risk for drug-resistant TB.

4. HIV infection

Two meta-analyses have shown an association between HIV infection and MDR-TB, although the association is more significant for primary MDR-TB[50,51] and may have more to do with shared risk factors, such as substance abuse or transmission in congregate settings, than biological factors.[51,52]

5. Other risk factors for drug-resistant TB

Other risk factors for drug-resistant TB include younger age[2,53,54] and more recent arrival in Canada (among foreign-born patients).[53,54]

3. What to do when drug-resistant TB is suspected

It is important to consider drug-resistant TB early on, as TB treatment recommendations are based on the assumption that the pattern of drug resistance will not change between the time the specimen was collected and the time the phenotypic DST results are reported. Unfortunately, this gap can last several weeks, during which the patient is receiving standard or empiric therapy. If the initial isolate of the TB bacterium 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 may have induced resistance to other drugs included in the initial regimen ("amplified" resistance).

There are really only two ways to avoid the aforementioned scenario: (i) make certain (within reason) that the empiric regimen is strong enough to cover the possibility that the pretreatment isolate is resistant; or (ii) use one of the newer molecular DST methods that target resistance-conferring mutations and provide an indication, early on, of the existence of resistance to INH and/or RMP (see the following section). Ideally, rapid molecular tests to predict RMP resistance (and, ideally, INH resistance) should be performed for every patient newly diagnosed with TB disease (based upon a positive nucleic acid amplification test or a positive culture), with results used to guide treatment. In locations that do not perform rapid molecular DST on all new positive samples/cultures, rapid molecular tests to detect rifampin resistance (and, ideally, INH resistance) should be performed for patients with risk factors for drug-resistant TB. See the Diagnostic Considerations section, Section 3.1, for additional guidance.

The aforementioned comments pertain to the consideration of resistance at the time of initial diagnosis and treatment initiation. During the course of treatment, certain factors should make clinicians consider the possibility that drug resistance has been acquired (among patients with initially susceptible TB) or amplified (in patients starting with a form of drug-resistant TB). Progressive clinical and/or radiographic deterioration, failure of smears or cultures to convert in a timely fashion or reversion of smears or cultures from negative to positive should lead to suspicion of TB treatment failure (defined in Canada and the United States as continued or recurrent positive cultures after 4 or more months of treatment),[55] which should trigger a review of prior DST results and performance of repeat DST on the most recently collected, on-treatment, culture-positive sample. Self-administered treatment, if used, should be abandoned in favor of directly observed therapy (DOT) and, in the event of possible drug malabsorption, serum drug concentrations should be measured.[55] 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 suggested — it is inadvisable to add a single drug to a failing regimen. It is also 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.[56]

Good practice statements

- **Prior to choosing an initial TB treatment regimen, clinicians should assess all patients for risk factors for drug-resistant TB.**
- **While awaiting rapid molecular drug susceptibility testing (DST) results, an empiric 4-drug (first-line) regimen can be initiated, with the regimen modified when rapid molecular DST results return (typically <48 hours later). If rapid molecular DST cannot be performed or will be delayed, and conventional culture-based DST results are not expected imminently, consultation with a drug-resistant TB expert is advised regarding the optimal empiric regimen in patients considered at high risk for drug-resistant TB.**

3.1. Diagnostic considerations

Conventional, culture-based (phenotypic) DST, while still considered the gold standard, takes weeks before a result is reported. Rapid molecular DST assays detect mutations in mycobacterial DNA that are associated with resistance to specific drugs. These assays can be performed on patient samples or on positive cultures, with results available within hours to days. Current molecular DST assays are reviewed in Chapter 3: Diagnosis of Tuberculosis Disease and Drug-resistant Tuberculosis.

Rapid molecular tests to predict rifampin resistance (and, ideally, INH resistance) should be performed for every patient newly diagnosed with TB disease. In locations that do not perform rapid molecular DST on all new positive samples/cultures, rapid molecular testing for rifampin resistance should be requested by clinicians at the time of TB diagnosis in patients considered at increased risk for MDR/rifampin resistant TB, including patients who have been treated for TB in the past, patients who have lived for at

least one year in a country with a high primary MDR-TB prevalence (≥2%) or moderate total TB incidence (≥20/100,000), patients who have a history of contact with a person with infectious drug-resistant TB and patients with HIV infection.[57] Clinicians should communicate with their laboratory to request this testing and ensure that the laboratory has the specimens needed; generally, multiple samples from potentially involved organs should be collected, in order to increase the likelihood of obtaining good samples/isolates for molecular and phenotypic DST.

Use of rapid molecular DST also reduces the delay to the start of appropriate second-line therapy.[58,59] It is assumed that this will, in turn, benefit the patient by increasing cure, decreasing mortality, reducing development of additional resistance and reducing the likelihood of failure and relapse, although data supporting benefits in these patient-important outcomes are limited to lower-resource settings.[58] Additional assumed benefits of early initiation of appropriate therapy include reduced risk of transmission and shorted duration of airborne isolation.

It is important to note that the positive predictive value of rapid molecular DST for the detection of rifampin resistance is low in populations with a very low prevalence of drug resistance (for example, most Canadian-born TB patients). Clinicians should consider the possibility of a false positive result in patients with a low risk for rifampin resistance, and liaise with the laboratory regarding confirmatory testing (sequencing-based methods, or conventional DST). While awaiting confirmatory testing when a rapid molecular test demonstrates rifampin resistance, the patient's individual risk for rifampin resistance should be considered before deciding on the initial treatment regimen. Patients considered at increased risk for rifampin resistance should be initiated on an MDR-TB treatment regimen. However, patients considered at low risk for rifampin resistance could receive the standard first-line regimen plus additional second-line drugs. Consultation with a drug-resistant TB expert is strongly advised in these circumstances.

Use of rapid tests does not eliminate the need for culture and phenotypic DST. These are important to confirm the molecular results, and for susceptibility testing for other first- and second-line drugs. Individual patient data meta-analyses have demonstrated worse outcomes in the treatment of MDR-TB when drugs are used despite demonstrated *in vitro* resistance.[60] Currently (2021), phenotypic drug susceptibility testing is available in Canada for all first-line drugs, but only some second-line drugs. Importantly, at the time of writing, phenotypic DST for 2 key drugs now recommended for first-line treatment of MDR-TB (bedaquiline, clofazimine) are not available anywhere in Canada, even though lab standards have been established for these drugs.[61] Until testing for bedaquiline and clofazimine susceptibility becomes available in Canada, isolates should be sent to reference laboratories in the United States for this testing.

Cross-resistance occurs among certain anti-TB drugs; this should be considered when constructing a treatment regimen.

Cross-resistance among anti-TB drugs

- Resistance to amikacin induces cross-resistance to kanamycin and vice versa.[62]
- Resistance to streptomycin does not induce cross-resistance with amikacin-kanamycin, or capreomycin.[62]
- Isolates acquiring resistance to capreomycin are usually susceptible to kanamycin and amikacin.[62]
- Isolates acquiring resistance to amikacin and kanamycin may or may not be resistant to capreomycin.[62]
- Resistance to one fluoroquinolone induces class-effect cross-resistance to all other fluoroquinolones, though data suggest that this cross-resistance may not be complete. Some isolates resistant to ofloxacin may be susceptible to moxifloxacin.[56,63,64]
- Most isolates resistant to rifampin (approximately 80%) are also resistant to rifabutin.[62] Resistance to rifapentine is universal in rifampin-resistant isolates.
- Cross-resistance to ethionamide may occur when there is low-level resistance to INH.[56]
- There have been a few reports of cross-resistance between bedaquiline and clofazimine.[65,66]

Recommendation

- **We strongly recommend that isolates from all TB patients diagnosed with rifampin resistance/multidrug resistance undergo phenotypic drug susceptibility testing for all anti-TB medicines currently recommended to treat MDR-TB** (*good evidence*).

4. Management of drug-resistant TB

Since the last edition of the Canadian TB Standards, the evidence base for the treatment of drug-resistant TB has improved, but not for all types of resistance. Important advances have been made toward strengthening the evidence for treating INH mono-resistant TB and MDR-TB, with randomized trials and individual patient data-level meta-analyses published.[60,67] With few exceptions, the treatment regimens for drug-resistant extra-pulmonary TB are the same as those for pulmonary TB.

Good practice statement

- **For the optimal management of drug-resistant TB, particularly MDR-TB, providers should have access to: (i) state-of-the-art drug susceptibility testing for all drugs that will be used (performed either at their center or outsourced if necessary); (ii) an uninterrupted supply of quality-assured first- and second-line anti-TB drugs; (iii) directly observed therapy and other components of a patient-centred comprehensive management program; and (iv) a team experienced in the management of drug-resistant TB that includes physicians, nurses and pharmacists. 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.**

4.1. Isolated resistance to isoniazid

In Canada, resistance to INH is the most common pattern of first-line drug resistance (see Table 1). Resistance to INH is usually due to a mutation in either the *katG* or *inhA* gene.[68,69] Less commonly, it is due to one or more mutations in other genes, such as the *ahpC* gene.[13]

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 *M. tuberculosis*. 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]).[13] 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.[70] 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).

INH is considered one of the two most effective anti-TB drugs and has particularly potent early bactericidal activity. INH resistance is the most common form of drug-resistant TB, with prevalence among previously untreated patients ranging from 1% to 20% in different countries and averaging approximately 8% globally.[30,71] A systematic review and meta-analysis of patients who received standardized regimens of INH, RMP, PZA and EMB, followed by INH and RMP, found that patients with INH mono-resistance had failure, relapse and acquired MDR rates of 11, 10 and 8%, respectively, compared to rates of 1, 5 and 0.3%, respectively, in patients with fully drug-susceptible TB.[72] Hence, it is clear that effective therapy is necessary to reduce the risk of failure, relapse and acquired MDR in patients with isolates that are resistant to INH.

In 2017, an individual patient database (IPD) was assembled of 33 datasets. In a meta-analysis of this IPD, 3,923 patients in 33 datasets were analyzed to inform WHO[73] and ATS/CDC/ERS/IDSA/ERS/IDSA (American Thoracic Society, Centers for Disease Control and Prevention, European Respiratory Society and the Infectious Diseases Society of America) guidelines.[55] Briefly, a fluoroquinolone added for at least 1 month to a regimen of 6 months of RMP, EMB and PZA had significantly improved treatment success compared to 6 months of those 3 drugs alone (adjusted odds ratio (aOR): 2.8; [95% confidence intervals (CI): 1.1 to 7.3]) and significant reduction in acquired drug resistance (aOR 0.1: [0.0 to 1.2]).[67] The addition of fluoroquinolone was also associated with lower mortality, but this was not significant (aOR: 0.7 [0.4 to 1.1]). Findings were similar when analyses were restricted to patients who received later-generation fluoroquinolones, such as levofloxacin or moxifloxacin. A subset of 118 patients received only 2 months of PZA together with 6 months or more of a fluoroquinolone plus RMP and EMB. In this subset, 117 had treatment success, a much higher rate than with 6 months of INH, RMP and PZA alone (aOR: 5.2; [0.6 to 47]). The wide confidence intervals reflect the smaller number who received this regimen, and that only 1 person failed or relapsed with the 2-month PZA regimen. In the IPD dataset, almost all studies considered persons whose isolates had "low-level" or "high-level" INH resistance as having INH resistance. Hence, the benefits of adding a fluoroquinolone can be expected for persons with disease due to isolates with either level of resistance. There was insufficient information in the IPD datasets to analyze relative frequency of serious adverse events with the different regimens. Therefore, an important consideration that remains unresolved is the tradeoff between risk of adverse events and improvement of end-of-treatment outcomes with addition of a fluoroquinolone, and/or dropping PZA after 2 months. The preferred fluoroquinolone is Levofloxacin, due to lower hepatotoxicity and less effect on QT interval.

In practice, many patients are started on empiric therapy with INH, RMP, PZA and EMB, and the INH resistance is detected 1-to-2 months later. In these patients, 6 months of fluoroquinoline therapy is counted from the day the fluoroquinolone is added. In other words, the initial therapy of 1-to-2 months empiric regimen is not considered part of the total recommended therapy. RMP, EMB and PZA alone for 6 months (counting as previously outlined) can be an option if there is fluoroquinolone resistance or the fluoroquinolone is not tolerated.

Recommendations

- **We strongly recommend, in patients with mono-isoniazid resistance, a treatment regimen including a later-generation fluoroquinolone (levofloxacin is preferred), rifampin, ethambutol and pyrazinamide, given for 6 months** (*Good evidence*).
- **We conditionally recommend that, in patients with less extensive disease (eg, noncavitary), and especially if there is increased risk of liver toxicity, pyrazinamide be given for the first 2 months only; in the final 4 months, rifampin, ethambutol and the fluoroquinolone should be given** (*Poor evidence*).

4.2. Isolated resistance to rifampin

Resistance to RMP, in 95% of cases,[74] is due to point mutations in the *rpo* gene in the beta subunit of DNA-dependent RNA polymerase. Resistance to RMP results in cross-resistance to rifabutin in most (~80%) cases and to rifapentine in all (100%) cases. With one exception, RMP mono-resistance is uncommon, and intolerance and/or allergic reactions to it are more common clinical scenarios. RMP mono-resistance has been seen in patients with advanced HIV disease (CD4 counts in cases of acquired RMP resistance have all been <200 cells × 10^6/L and usually <50 cells × 10^6/L) who were taking rifabutin as prophylaxis against *M. avium* complex, or received an intermittent anti-TB regimen during the initial phase of treatment. [75–81] Treatment options for patients determined to be RMP mono-resistant are given in Table 4.[56,82,83]

In 2013, the WHO simplified definitions and reporting requirements to include RMP-resistant TB cases with MDR-TB. Currently, neither the WHO or ATS/CDC/ERS/IDSA guidelines address management of RMP resistance in the absence of INH resistance.

Recommendation

- **We conditionally recommend, in patients with isolated resistance (or intolerance) to rifampin, either: 1) isoniazid, ethambutol and a fluoroquinolone daily for 12 to 18 months, supplemented with pyrazinamide for at least 2 months during the intensive phase; 2) isoniazid and ethambutol for 18 months, supplemented with pyrazinamide for at least 2 months during the intensive phase; or 3) treatment as MDR-TB** (*poor evidence*).

4.3. Isolated resistance to pyrazinamide and ethambutol

Isolated resistance to PZA or EMB is rare. Isolated PZA resistance occurs genotypically in *M. bovis*.[12] In 2003, PZA mono-resistance was reported in isolates of *M. tuberculosis* from Quebec.[84] Patients with these strains had worse clinical outcomes than those with fully susceptible strains.[85] In patients with disease due to PZA-resistant isolates, the total duration of treatment should be 9 months or more. EMB mono-resistance will not change the efficacy or duration of treatment with standard regimens (see Table 4).[56,86]

4.4. Resistance to two or more first-line drugs (polydrug-resistant TB) not including MDR-TB

Polydrug-resistant TB is uncommon in Canada (see Table 1); the range of possible resistance patterns and treatment options are outlined in Table 4.[56,86,87]

5. MDR-TB

Several case series describing Canadian experience with MDR-TB management have been published.[54,88–92] In these series, the majority of cases (83-96%) were among foreign-born populations and few patients were HIV-positive (0-24%). The proportion of re-treatment cases varied considerably, from 33-67%. The mean number of first-line drugs to which the patients' isolates were resistant ranged from 3.2-4.7.

It is important to avoid amplification of drug resistance, as there are few highly effective second-line drugs and one or more drugs are commonly stopped or held during the course of MDR and XDR-TB treatment. Preventing amplification of resistance requires that, if a medication is stopped, it must be replaced by an alternative drug. 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 patient.[121] The most common errors were addition of a single drug to a failing regimen, failure to identify preexisting or acquired resistance and administration of an initial regimen inadequate in number of drugs or duration of therapy, or both — all errors that open the door for amplification of resistance.

5.1. Treatment regimens for people with a presumptive or established diagnosis of MDR-TB

Since the 7th edition of the Canadian TB Standards was published, there have been a number of major changes in MDR-TB treatment recommendations. The WHO recommends two options: a standardized, all-oral shorter regimen; and an individualized longer regimen.[93] In their combined guidelines, the ATS/CDC/ERS/IDSA recommend a regimen that is similar in composition and duration to the WHO longer regimen.[94] The following recommendations are largely based on the evidence reviews performed for the WHO and/or ATS/CDC/ERS/IDSA.

Table 4. Treatment regimens for the management of mono or polydrug-resistant TB.

Resistance to which first-line drugs:	Drugs to drop	Drugs to add	Regimen	Total duration
Mono-resistance				
INH	INH	FQN	6 months daily RMP + EMB + PZA + FQN	6 months from date FQN started
	INH	FQN	2 months daily RMP + EMB + PZA + FQN/4 months daily RMP + EMB + FQN	6 months from date FQN started
RMP	RMP	FQN	2 months daily INH + EMB + PZA + FQN /10-16 months daily INH + EMB + FQN	18 months from date FQN started
	RMP	None	2 months daily INH + EMB + PZA / 16 months INH + EMB daily or thrice weekly	18 months from start of therapy
EMB	EMB	None	2 months daily INH + RMP + PZA /4 months INH + RMP daily or thrice weekly	6 months from start of therapy
PZA	PZA	None	2 months daily INH + RMP + EMB /7 months INH + RMP daily or thrice weekly	9 months from start of therapy
Polydrug-resistance				
INH + EMB	INH + EMB	FQN	6 months daily RMP + PZA + FQN	6 months from date FQN started
INH + PZA	INH + PZA	FQN	9 months daily RMP + EMB + FQN	9 months from date FQN started
INH + EMB + PZA	INH + EMB + PZA	FQN + injectable	2 months daily RMP + FQN + injectable /7 months daily RMP + FQN	9 months from date FQN started

Abbreviations: TB, tuberculosis; INH, isoniazid; FQN, fluoroquinolone (moxifloxacin or levofloxacin); RMP, rifampin; EMB, ethambutol; PZA, pyrazinamide.

5.1.1. Standardized versus individualized approaches

Whether to use a standardized or an individualized approach when constructing regimens for MDR and XDR-TB has been a matter of debate for a number of years. Standardized regimens always use the same combination of drugs for all patients, under the assumption that the regimens will be effective even in the face of resistance to some of the component medications. By contrast, individualized regimens are designed based on results of first- and second-line DST, and avoid administration of medications which show resistance on DST. A large IPD meta-analysis found consistently worse outcomes with regimens that included medications to which the infecting organism was resistant, as compared to regimens that did not use those medications.[60] Other IPD meta-analyses have shown that when standardized shorter regimens are used in the presence of baseline resistance to component medications, outcomes are worse compared to the absence of such resistance,[95] and also compared to using individualized longer regimens.[96] In Canada, all jurisdictions should have access to first- and second-line DST, and patients with MDR and XDR-TB should not be treated with medications for which there is DST-demonstrated resistance (with the exception of high-dose INH in the all-oral standardized shorter regimen, described in the following section).

5.1.2. Choice of medications

Table 5 summarizes the new classification system used by the WHO for grouping medicines recommended in the treatment of MDR and XDR-TB.[93] Group A consists of drugs found to be highly effective at reducing risks of treatment failure/relapse and death in an IPD meta-analysis that informed the 2018 WHO guidelines:[60] levofloxacin and moxifloxacin (later-generation FQN), bedaquiline (a diarylquinoline) and linezolid (an oxazolidinone). Group B consists of drugs that can be orally ingested and that reduce risks of treatment failure or relapse, but whose effectiveness for lowering the risk of death was less certain: clofazimine and cycloserine (or terizidone). Group C consists of anti-TB drugs, as well as repurposed medications, with less certainty on their effectiveness for MDR-TB or that require parenteral administration.

The IPD meta-analysis included 12,030 patients from 25 countries in 50 studies**,** and reported the likelihood of treatment success and death associated with the use of individual drugs in the management of MDR-TB**.** [60] In this study:

- use of levofloxacin was associated with 15% greater treatment success, compared with failure or relapse (adjusted risk difference 15%; 95% CI 13 to 18%), and moxifloxacin was associated with 11% greater success (95% CI 8 to 14%); use of levofloxacin or moxifloxacin was also associated with 6-7% lower mortality (adjusted risk difference -6%, 95% CI −9 to −4% for levofloxacin and −7%, 95%CI −10 to −4% for moxifloxacin);
- bedaquiline use also resulted in 10% greater treatment success (adjusted risk difference 10%, 95% CI 5 to 14%), and a significant reduction in death (−14%, 95% CI −19 to −10%);
- linezolid use was also associated with significantly greater treatment success (adjusted risk difference 15%, 95% CI 11 to 18%) and lower mortality (−20%, 95% CI −23 to −16%);
- clofazimine use was associated with significantly greater treatment success (6%, 95% CI 1 to 10%), but had no impact on mortality (95% CI −8 to 0);
- cycloserine use was associated with significantly greater treatment success (5%, 95% CI 3 to 6%) and lower mortality among patients with susceptible isolates, but was not beneficial in patients with resistant isolates; and
- aside from carbapenems, which were significantly associated with treatment success (14%, 95% CI 6 to 21%), but not with mortality, all other drugs studied were associated with only slight or no improvements in outcomes.

In 2018, the WHO removed the second-line injectable agents from first line MDR-TB treatment regimens.[93,94] This is because of evidence demonstrating the greater effectiveness, and better tolerability, of newer and repurposed drugs for treating MDR-TB. Additionally, the IPD meta-analysis described above found that patients treated with certain second-line injectable drugs (kanamycin and capreomycin) had worse outcomes when compared to patients who did not receive any injectable anti-TB drugs. The only second-line injectable currently recommended for use is amikacin, which was associated with greater chance of success (adjusted risk difference 6%, 95% CI 4 to 8%), but had no effect on death.[60]

Based on the aforementioned considerations, the WHO currently recommends that MDR-TB regimens consist of the following 4 drugs: levofloxacin *or* moxifloxacin, bedaquiline, linezolid and clofazimine *or* cycloserine (an alternative WHO-recommended regimen is discussed later in this section). ATS/CDC/ERS/IDSA recommends an initial 5-drug regimen consisting of a quinolone (either levofloxacin or moxifloxacin) plus bedaquiline, linezolid, clofazimine *and* cycloserine. These combinations are based on the effectiveness of each individual drug; there are few data, and no randomized trials that have evaluated the recommended combinations. We favor an approach similar to ATS/CDC/ERS/IDSA; an initial five-drug regimen for most patients, with the option to use an initial four-drug regimen for those patients with less extensive TB disease.

In the absence of prior treatment, resistance to bedaquiline, linezolid, clofazimine and cycloserine is expected to be rare. Hence the MDR-TB regimens recommended by the WHO and ATS/CDC/ERS/IDSA could be initiated even in the absence of second-line DST, as soon as RMP resistance has been detected. Even if fluoroquinolone (levofloxacin or moxifloxacin) resistance (which is more common) is later detected, the initial regimen is likely sufficiently strong to prevent amplified resistance.

In situations where one or more of the drugs in the preferred initial regimen cannot be used due to intolerance, contra-indications, unavailability or resistance, such as in pre-XDR or XDR, then one or more of the following Group C drugs (see also Table 5) should be included in the regimen in order to ensure the provision of at least five effective (or likely effective) drugs: EMB, PZA, delamanid, amikacin,

Table 5. Grouping and doses for anti-TB drugs used for the treatment of MDR-TB.

GROUP[a]	MEDICINE		Adults	Children (<15 years old)[99–102]
Group A	Levofloxacin OR Moxifloxacin	LFX MFX	750-1000 mg PO or IV daily 400 mg PO or IV daily	15–20 mg/kg/day (max 750 mg) PO or IV 10-15 mg/kg/day (max 400 mg) PO or IV
	Bedaquiline	BDQ	400 mg PO daily x 14 days then 200 mg PO 3 times/ week	Use only in patients > 6 years AND > 15 kg; 6-month duration Weight Band: 16-30 kg: 200 mg PO daily x 14 days, 100 mg PO thrice weekly >30 kg: 400 mg PO daily x 14 days, 100 mg PO thrice weekly; 6 mg/kg PO x 14 days followed by 3-4 mg/kg/day PO thrice weekly (max 400 mg)
	Linezolid	LZD	600 mg PO or IV daily	<16kg: 15mg/kg/day PO or IV ≥16kg: 10-12mg/kg/day PO or IV (max 600mg)
Group B	Clofazimine	CFZ	100 mg PO daily	2-5 mg/kg/day PO (max 100 mg) Often given on alternate days or thrice weekly due to formulation (see references for specific weight banded dosing)
	Cycloserine OR Terizidone	CS TRD	250–750 mg PO daily to achieve serum levels of 20-35 mg/L	15-20 mg/kg/day PO divided BID (max 1 gram)
Group C	Ethambutol	EMB	15 mg/kg PO daily	15-25 mg/kg/day PO (max 800 mg)
	Pyrazinamide	PZA	25-40 mg/kg PO daily	30-40 mg/kg/day PO (max 2000 mg)
	Delamanid	DLM	100 mg PO twice daily	Use only in patients >2 years; use with caution if splitting dose or crushing; use up to 6 months Weight-band: 7-23 kg: 25 mg PO BID 23-34 kg: 50 mg PO BID >34 kg: 100 mg PO BID; 3-4 mg/kg/day PO (max 200 mg)
	Amikacin (OR Streptomycin)	AM S	15mg/kg IV daily or 25mg/kg IV three times weekly[b]	15-20 mg/kg/day IV or IM (max 1 gram) [b] 20-40 mg/kg/day IV or IM (max 1 gram) [b]
	Imipenem-cilastatin OR Meropenem[c]	IPM-CLN MPM	1,000 mg IV BID – QID 1,000 mg IV 3 times daily	IPM-CLN not used in <15 years old MPM: 20-40 mg/kg IV q8h (max 6 grams)
	Ethionamide	ETO	15–20 mg/kg PO daily divided BID (usually 250–500 mg PO once or twice daily)	15-20 mg/kg/day PO (max 1 gram)
	p-aminosalicylic acid	PAS	4 g PO 2–3 times daily (total 8 to 12 grams per day)	200 mg/kg/day PO once daily OR divided BID (see references for weight-banded dosing)

Abbreviations: TB, tuberculosis; MDR-TB, multidrug-resistant tuberculosis; PO, per oral; IV, intravenous; IM, intramuscular; BID, twice a day; QID, four times a day; q8h, every 8 hours.

[a]Group A consists of drugs found to be highly effective at reducing risks of treatment failure/relapse and death; Group B consists of drugs that can be orally ingested and that reduce risks of treatment failure or relapse, but whose effectiveness for lowering the risk of death is less certain; Group C consists of anti-TB drugs, as well as repurposed medications, with less certainty on their effectiveness for MDR-TB or that require parenteral administration.[93]

[b]Some centers utilize lower doses of amikacin with therapeutic drug monitoring, to minimize ototoxicity. Amikacin/streptomycin should only be used where hearing can be formally monitored.[103,104]

[c]Every dose of imipenem-cilastatin or meropenem should be administered with oral clavulanic acid, which is only available in formulations combined with amoxicillin, dosed at 125-250 mg clavulanic acid (BID-QID). Amoxicillin-clavulanic acid is not counted as an additional effective anti-TB drug.

Pyridoxine should be given to patients receiving linezolid or cycloserine.

Cycloserine doses are often divided twice daily to improve tolerance. See *The Curry International TB Center Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*[56] for suggestions on how to ramp up to full-dose Cycloserine to improve tolerance. Some experts suggest pyridoxine 50 mg for each 250 mg of cycloserine.

Ethionamide administration at bedtime may help to reduce nausea. See *The Curry International TB Center Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*[56] for suggestions on how to ramp up to full-dose ethionamide.

imipenem-cilastatin or meropenem (plus clavulanic acid), ethionamide or *p*-aminosalicylic acid, chosen in that order. Clinicians may feel uncomfortable including cycloserine in the initial treatment regimen due to the risk of neuropsychiatric adverse events; in this circumstance, a Group C drug can be used in place of cycloserine.

The WHO currently recommends that its guidance on longer treatment regimens also applies to drug-resistant extra-pulmonary TB.[93] Data on the use of bedaquiline in extra-pulmonary TB is limited to small numbers of cases included in case series.[97,98] Bedaquiline is not available in Canada for extra-pulmonary TB; while we suggest its use for extra-pulmonary TB, if it cannot be obtained then we suggest adding a Group C drug to replace it, using the approach previously described.

Unfortunately, in Canada, bedaquiline, cycloserine, and clofazimine are often only available several days to weeks after the indication to use them has become evident. This is due to the lengthy process needed to obtain these medicines, which involves applications to Health Canada's Special Access Program and to the pharmaceutical companies that hold proprietary claims on them. As such, while waiting to gain access

to bedaquiline, cycloserine and clofazimine, it is reasonable to initiate (or continue) other drugs used to treat MDR-TB (see Table 5) for which there is DST-proven susceptibility or the likelihood of resistance is judged to be very low.

We encourage federal and provincial government agencies and pharmaceutical companies operating in Canada to facilitate timely access to second-line drugs for MDR and XDR-TB by eliminating existing administrative obstacles, such as the requirement for Special Access Program approval for drugs recommended by WHO for drug-resistant TB treatment, and the current (2021) limitations on the use of bedaquiline for extra-pulmonary TB.

5.1.2.1. Initial and continuation phases of treatment. In prior MDR-TB guidelines, treatment was divided into two phases: the initial phase was defined as the period when an injectable was used, and the continuation phase was the period when only oral medications were utilized. In its most recent guidance, because longer regimens may now be all oral, WHO no longer divides treatment into initial and continuation phases. By contrast, ATS/CDC/ERS/IDSA suggest an initial phase during which a greater number of drugs are used, followed by a continuation phase during which fewer drugs are used. Clinical, microbiologic, and radiologic responses to treatment should be assessed before deciding to reduce the number of drugs in a regimen. We favor an approach that includes an initial phase with more drugs and reduces the number of drugs once there is evidence of a good response to treatment.

Bedaquiline is marketed as a medication that is to be used for only 6 months, based on the initial randomized controlled trials, in which it was used only for 6 months. Most patients will have shown substantial improvement, and some may have experienced culture conversion by the time bedaquiline has been given for 6 months, hence it is a reasonable time to stop. In its most recent guidance, WHO judged that there is sufficient evidence to support the safe use of bedaquiline beyond 6 months as long as appropriate follow-up monitoring is pursued, but also that there is insufficient evidence of bedaquiline's efficacy beyond 6 months.[93] If clinicians judge the benefits of extending bedaquiline use beyond 6 months outweigh the benefits of stopping bedaquiline, and an informed patient prefers to continue bedaquiline beyond 6 months over alternative treatment modifications, it would be reasonable to extend the use of bedaquiline as long as best practices for off-label use are followed.

5.1.2.2. Duration of treatment. For its longer regimen, the WHO recommends a total duration of 18-20 months. ATS/CDC/ERS/IDSA recommends an intensive phase of between 5 and 7 months *after* culture conversion, and a total treatment duration between 15 and 21 months *after* culture conversion. In other words, the 2 guidelines are quite similar in their recommendations for total treatment duration for the longer regimen. In patients with smear-positive or cavitary disease or who were severely ill at the time treatment was initiated, we suggest switching to the continuation phase 5-to-7 months after culture conversion, provided there are other signs of improvement.

Recommendations

- **We strongly recommend, for the treatment of MDR-TB:**
  a. **use of regimens that include bedaquiline, for all patients;**
  b. **use of regimens that include linezolid, for all patients; and**
  c. **use of regimens that include either levofloxacin or moxifloxacin, for all patients** (*good evidence*).
- **We strongly recommend, for the treatment of MDR-TB, against use of drugs to which the infecting strain has drug susceptibility testing-proven resistance (with the exception of high-dose isoniazid in the all-oral standardized shorter regimen)** (*good evidence*).
- **We conditionally recommend, for the treatment of MDR-TB, the following five drugs as the initial regimen in the absence of drug susceptibility testing-proven resistance or contraindications: (levofloxacin or moxifloxacin) AND bedaquiline AND linezolid AND clofazimine AND cycloserine** (*poor evidence*).
- **We conditionally recommend, for patients with less extensive MDR-TB disease (smear negative, without cavitary lesions) that is solely pulmonary or occurring at a site where TB is usually paucibacillary, that the initial regimen could include only 4 drugs, consisting of (levofloxacin OR moxifloxacin) AND bedaquiline AND linezolid AND (clofazimine OR cycloserine)** (*poor evidence*).
- **We conditionally recommend, for the treatment of MDR-TB, that 5-to-7 months after culture conversion occurs, any one of the drugs in the regimen could be dropped, continuing the other 4; for patients whose initial phase consisted of (levofloxacin OR moxifloxacin) AND bedaquiline AND linezolid AND (clofazimine OR cycloserine), any one of the drugs can be dropped so that the continuation phase consists of three drugs** (*poor evidence*).
- **We conditionally recommend, for the treatment of MDR-TB, a total treatment duration of 18 to 20 months, although this can be modified based on response to therapy** *(poor evidence).*
- **We conditionally recommend, for the treatment of pre-extensively drug-resistant or extensively drug-resistant TB, or in situations where one or more of the Group A and B drugs cannot be used due to side-effects, contra-indications, unavailability or resistance, adding 1 or more Group C drugs to ensure at least 5 drugs are in the regimen. The order of preference for the addition of Group C drugs is (from most to least preferred): ethambutol, pyrazinamide, delamanid, amikacin, imipenem-cilastatin or meropenem (plus clavulanic acid) ethionamide or p-aminosalicylic acid** (*poor evidence*).
- **We conditionally recommend, unless explicitly stated otherwise, that for the treatment of extra-pulmonary MDR-, pre-extensively drug-resistant and extensively drug-resistant TB, the same treatment approach be utilized as for pulmonary TB** (*poor evidence*).

Good practice statement

- **In designing a treatment regimen for MDR-TB, the potential cross-resistances, drug interactions and toxicities should be taken into account.**

5.1.3. All-oral standardized shorter regimen. Since 2016, WHO guidelines have included a standardized shorter regimen as a potential option for treating MDR-TB. The initial shorter regimen that the WHO recommended in those guidelines had an intensive phase with a second-line injectable, but in the 2020 update of its guidelines, WHO changed this recommended shorter regimen to an all-oral regimen, with bedaquiline being used instead of the second-line injectable.[93] The change was based on data from South Africa's National TB Programme, in which the outcomes of 891 patients who received the shorter all-oral regimen was compared to 987 patients treated with that based on injectable medication use.[93] In that analysis, it was found that use of the all-oral shorter regimen was associated with higher treatment success rates (73% versus 60%), adjusted odds ratio 2.1 (95% CI 1.1–4.0) for the treatment outcomes of success versus failure/recurrence. Rates of loss to follow-up were also lower among the group who received the all-oral regimen (9.9% vs 17.3%; aOR 0.5, 95% CI 0.4–0.7).

The outcomes of the 891 patients who were treated with the all-oral shorter regimen were also compared to those of 1,437 patients treated with longer regimens without any new drugs (such as bedaquiline, delamanid, linezolid or carbapenems) and 474 patients treated with longer regimens including bedaquiline.[93] The all-oral shorter regimen performed significantly better than the longer regimen without any new drugs, across all outcomes and all subgroups. When the shorter regimen was compared to the longer regimen with bedaquiline, there were no marked differences in the outcomes observed. However, the shorter regimen performed slightly better; aOR: 3.9; 95% CI: 1.7–9.1 for success versus failure/recurrence; aOR: 1.6; 95% CI: 1.2–2.2 for success versus all unfavorable outcomes; aOR: 0.5; 95% CI: 0.4–0.8 for loss to follow-up.

Per the WHO, eligibility for treatment with the all-oral shorter standardized regimen requires that resistance to any component medications (with the exception of INH) be excluded by DST (or considered very unlikely); that patients have not previously been treated with second-line drugs for more than one month; and that patients do not have extensive disease or severe extra-pulmonary TB. Pregnant women and children under six-years-old are excluded.

The all-oral shorter regimen for MDR-TB treatment that is recommended by the WHO consists of an initial 4-to-6 month phase with bedaquiline, levofloxacin, clofazimine high-dose INH, ethionamide, PZA and EMB; and a 5-month continuation phase of levofloxacin, clofazimine, PZA and EMB. Eligibility requirements are strict because the shorter regimen is standardized and the effectiveness of alternative drug combinations is unknown. If used, the all-oral standardized regimen must be prescribed and monitored according to WHO recommendations; this means that no modifications to the regimen are permitted. If a patient is started on the all-oral shorter standardized regimen and subsequently needs the regimen altered, they should be switched to a longer regimen rather than making modifications to the shorter one.[93] Note that this regimen utilizes high-dose INH even in the presence of INH resistance; it is the only exception to our prior recommendation against using drugs when there is demonstrated resistance to them.

The decision to choose the all-oral standardized shorter regimen over the longer regimen among eligible patients should be made jointly between patient and provider. While the shorter duration is an advantage, the shorter regimen requires a greater number of drugs to be taken (7 drugs initially vs 5). This results in a greater risk of adverse drug reactions. It is important to note that premature discontinuation of any drugs in the short regimen will necessitate switching to a longer regimen.

Recommendation

- **We conditionally recommend, for the treatment of MDR-TB, the all-oral standardized shorter regimen recommended by the World Health Organization as an alternative to the preferred longer regimen, for patients who meet all eligibility requirements and for whom routine treatment monitoring can be assured** (*poor evidence*).

5.2. Special situations in the management of MDR-TB

5.2.1. HIV infection

An IPD meta-analysis that included 11,920 patients with MDR-TB found that HIV-positive patients not on antiretroviral therapy have 4-fold higher odds of death when compared to HIV-negative patients.[105] The same study reported that among HIV-positive people with MDR-TB, odds of death were significantly lower with use of at least 1 Group A medication and with antiretrovirals. Hence, the aforementioned recommendations and best practice statements should be followed regardless of HIV status and antiretroviral therapy should be used for all HIV-positive patients with MDR-TB (or other circumstances requiring second-line anti-TB drugs), irrespective of CD4 cell count, and following the same timeline with respect to initiation as for drug-susceptible TB[93] (see Chapter 10: Treatment of Active Tuberculosis in Special Populations). It is important to carefully consider how to manage drug-drug interactions between antiretrovirals and anti-TB medications to ensure that both HIV and MDR-TB are optimally treated. Such strategies could include measuring therapeutic drug levels or increasing the frequency of monitoring for adverse events. In addition to drug-drug interactions, other challenging issues that arise with the treatment of HIV and MDR-TB co-infection include: overlapping adverse effects (eg, neuropathy);[56] paradoxical reactions related to immune reconstitutions; a high pill burden;[56] malabsorption of medications;[56] and heightened negative psychosocial factors (eg, stigmatization, isolation).[106]

Good practice statement

- **For the treatment of MDR-TB in HIV-positive people, TB treatment providers should consult with patients' HIV providers and with pharmacists with expertise in HIV and TB in order to identify, and determine how to manage, potential drug-drug interactions that could compromise the effectiveness or increase the toxicity of HIV and/or MDR-TB treatment. Given the strong evidence supporting the effectiveness of bedaquiline, moxifloxacin or levofloxacin, and linezolid, treating teams should strive to identify strategies to ensure the safe and effective use of Group A anti-TB drugs even in the presence of drug-drug interactions with antiretrovirals.**

5.2.2. Pregnancy

MDR-TB management is very complex in pregnancy, and these patients should be co-managed by clinicians with expertise in both drug-resistant TB and high-risk pregnancy. The ATS/CDC/ERS/IDSA writing group conducted a systematic literature review on pregnant women with MDR-TB.[94] They found several observational case reviews that included a total of 65 women. Among them, 69% had a successful treatment outcome. Regarding pregnancy outcomes:

- 78.5% of women had healthy births;
- 12% of women had premature or low birthweight babies;
- 12% of women had medical abortions;
- 3% of women had spontaneous abortions;
- 1.5% of women had a stillbirth;
- 3% of babies were born with HIV; and
- 1.5% of babies were born with HIV/TB coinfection.

A more recent review of 108 pregnant women treated for MDR-TB in South Africa found similar MDR-TB treatment outcomes (including 67% success).[107] In that study, 91% of the babies were born alive, but 28% were pre-term and 35% low birthweight; this high proportion of unfavorable pregnancy outcomes was felt likely to be due to the high prevalence of HIV infection (81%). Fetal exposure to bedaquiline in utero was associated with low birthweight in that study; otherwise, there were no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in the infants until 1 year of age. MDR-TB should be treated promptly in pregnant women and should not be deferred, as the benefits of treatment outweigh the harms. The regimen may need modification and the woman will need concurrent care by a TB expert and an obstetrician with expertise in high-risk pregnancies. There are no data to support a particular regimen, however aminoglycosides and ethionamide are generally avoided because of potential teratogenicity.

5.2.3. Central nervous system MDR-TB

Treatment of central nervous system (CNS) MDR-TB should be guided by DST results and by whether the medications cross the blood-brain barrier. Immediate consultation with an expert in MDR-TB management is strongly advised. Levofloxacin/moxifloxacin, ethionamide, cycloserine, linezolid, imipenem-cilastatin, high-dose INH and PZA penetrate the CNS well,[93] while *p*-aminosalicylic acid and EMB do not. Amikacin and streptomycin penetrate the CNS only in the presence of meningeal inflammation. There are sparse data on the CNS penetration of clofazimine, bedaquiline and delamanid.[108–110]

5.2.4. Pediatrics

Any child being considered for treatment of drug-resistant TB should be managed by a clinician with experience with such cases. The signs, symptoms and radiographic findings of TB disease in children are outlined in Chapter 9: Pediatric Tuberculosis, and are the same in both drug-susceptible and drug-resistant TB. Drug-resistant TB in children is confirmed using the same microbiologic criteria as those outlined for adults. High-quality sputum specimens, and other specimens appropriate to the site of disease, should always be collected with considerations about optimal collection method guided by age (Chapter 9: Pediatric Tuberculosis).

The challenges of confirming the microbiologic diagnosis in infants and young children are the same for both drug-resistant and drug-susceptible TB. The bacillary burden is much lower in infants and young children with primary TB disease, than in teens and adults, and the majority of these children will not have a positive nucleic acid amplification test or culture. The choice to initiate therapy for drug-resistant TB must thus be guided by other considerations. A child who has clinical and radiographic diagnosis of TB disease and who has been exposed to an infectious drug-resistant TB source case is considered to have probable drug-resistant TB.[99] A child who has clinical and radiographic diagnosis of TB disease and who has not responded to first-line TB treatment after 2 to 3 months, or who has been exposed to an infectious source case who has died, failed treatment or is a retreatment case is also considered to have possible drug-resistant TB disease.[99]

The regimen design for children should ideally be based on the child's own isolate, but if none is available, then the infectious source case's isolate serves as a surrogate. Generally, the same regimen designs that are outlined for adult drug-resistant TB treatment can be used in children, with the exceptions of bedaquiline and delamanid, which have lower recommended age limits (Table 5). Aminoglycosides should be avoided as much as possible, to avoid the risk of permanent hearing loss, which has a profound impact on child development.[93]

Prescribing second-line agents in age- and weight-appropriate doses is challenging. Many of the dosing recommendations for children are extrapolated from adult strategies.[93] This is further complicated by the lack of child-friendly formulations, which means some drugs cannot be given at a precise amount of drug per kilogram. General guidance is given on dosing of second-line agents in Table 5; please review the weight-banded dosing strategies from the primary references

cited for more specific guidance. Several pharmacokinetic and safety studies are underway for fluoroquinolones, linezolid, bedaquiline and delamanid.[101]

5.3. Follow-up and monitoring during MDR-TB treatment

Patient-centered care principles should be applied when treating individuals for MDR or extensively drug-resistant TB. Patients should be educated about the disease and treatment, and engaged in their care through shared decision making with their health care providers. Multidisciplinary support (physiotherapy, occupational therapy, nutritionists, social workers, TB nurses and medical specialist services) should be easily accessible to address patients' physical, psychosocial, material and legal (eg, immigration-related) needs. At minimum, patients should be followed by a dedicated team consisting of 1 or more physicians with expertise in TB, as well as 1 or more nurses with such expertise.

Treatment should be directly observed at the initiation of MDR and extensively drug-resistant TB treatment. DOT, including virtual DOT, for 5 days per week with self-medication on weekends is acceptable if there are no problems with adherence. A switch to fully self-administered treatment can be considered once patients are no longer contagious, *and* there is confidence on the part of patients as well as the treating team that the risk of missing doses is sufficiently low.

To the extent that it is possible, outpatient (ambulatory) care is encouraged.[93] The role of hospitalization should be limited to situations where there is a need for: 1) close medical monitoring due to acute illness or unstable condition, and/or while introducing treatment in a patient with significant prior or anticipated drug adverse events; and/or 2) preventing transmission to household members when a person with MDR or extensively drug-resistant TB is contagious. Ideally, patients who require hospitalization should be admitted to specialized centers able to provide the suggested multidisciplinary support.

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[56] and the WHO companion handbook.[111] The specific elements necessary to monitor for treatment response and drug toxicity will be dependent upon the patient's TB disease manifestations and treatment regimen.

With respect to treatment response, monitoring includes regular evaluation of symptoms, weight, radiography and mycobacteriology. Early in therapy, clinicians should assess inpatients daily, and outpatients weekly, until treatment is well tolerated, and then monthly thereafter, asking about symptoms of TB disease, drug toxicity and adherence. Treatment adherence should also be assessed more often by the DOT worker. Weight should be measured at least monthly. Patients with pulmonary MDR-TB should have chest x-rays done at baseline, every 3-to-6 months during treatment, and at end of treatment. Radiographs (x-rays, CT scans, or MRIs) are useful in monitoring response to treatment for patients with extra-pulmonary TB.

Regarding 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. Patients with smear- and/or culture-positive pulmonary disease should have 3 sputum samples submitted at baseline, 2-to-3 sputum samples submitted at least every 1-to-2 weeks until smear conversion, and then at least monthly until culture conversion. If cultures remain positive after 3-to-4 months of treatment, drug-susceptibility tests should be repeated. Even after culture conversion, at least one sputum specimen should be submitted at least monthly to document the stability of the mycobacteriologic response.

Patients with infectious pulmonary MDR-TB should remain in airborne isolation until drug-susceptibility testing results for second line drugs are available, and until the patient is established on an effective regimen consisting of at least 3 drugs for which the isolate is susceptible (or expected to be susceptible). (For further details see Appendix B - De-isolation Review and Recommendations).

Monitoring for drug toxicity will vary depending upon the regimen composition. See the section later in this chapter on adverse drug events, and Table 6 for a summary of common drug adverse events and suggested monitoring for each drug used to treat MDR-TB.

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.[56] Monitoring of linezolid to minimize toxicity and maintain efficacy has been utilized by some specialized American centers[112] but this approach has not been systematically evaluated. Other reasons to consider therapeutic drug monitoring include known or suspected malabsorption; patients who are not responding to treatment or failing treatment; patients with few effective drugs in their regimen; and patients with potentially significant drug-drug interactions.

Patients who have completed treatment of MDR-TB or XDR-TB should undergo clinical, radiologic and mycobacteriologic follow-up at 6-month intervals for a minimum of 2 years.[56]

5.4. MDR-TB treatment outcomes

The WHO recently updated its TB treatment definitions, which are now uniform for both drug-susceptible and drug-resistant TB.[5] Culture conversion is now defined as two consecutive negative cultures taken at least 7 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 2 consecutive negative cultures.

Table 6. Adverse events and monitoring recommendations for anti-TB drugs used for the treatment of MDR-TB.

Medicine	Incidence of adverse events resulting in drug discontinuation (95%CI)[a]	Common adverse events[b]	Recommended routine monitoring
Levofloxacin	1.3% (0.3–5.0)	MSK (64%), peripheral neuropathy (14%), rash (14%), hypoglycemia (7%), GI disturbance, headache, anxiety, tremulousness, prolonged QT interval	EKG when used in combination with other QT-prolonging drugs
Moxifloxacin	2.9% (1.6–5.0)	Cardiovascular[d] (21%), hepatotoxicity (17%), GI disturbance (13%), peripheral neuropathy (11%), MSK (8%), headache, anxiety, tremulousness	EKG when used in combination with other QT-prolonging drugs
Bedaquiline	1.3% (0.3–5.0)	Cardiovascular[d] (56%), hepatoxicity (22%), CNS toxicity (11%), MSK (11%), GI disturbance	EKG at baseline and weeks 2, 12, 24. Baseline potassium, magnesium, calcium. Baseline and monthly liver tests
Linezolid	14.1% (9.9–19.6)	Peripheral neuropathy (64%), myelosuppression (22%), optic neuropathy (5%), GI disturbance (2%), rash (2%)	Regular (initially weekly, then at least monthly) complete blood counts Clinical assessment for peripheral neuropathy Visual acuity and color vision monthly
Clofazimine	1.3% (0.3–5.0)	Skin hyperpigmentation (42%), cardiovascular[d] (33%), rash (17%), GI disturbance (8%), discoloration of conjunctiva, cornea and body fluids, photosensitivity	EKG when used in combination with other QT-prolonging drugs
Cycloserine, Terizidone	5.7% (4.1–7.8)	Psychiatric (66%) (depression, psychosis, suicidal ideation), CNS toxicity (25%) (seizures, lethargy), GI disturbance (4%), peripheral neuropathy (1%), rash (1%), optic neuritis	Peak concentrations after 1-2 weeks of starting, then intermittently throughout treatment; Screen for psychiatric symptoms
Ethambutol	1.8% (1.0–3.3)	Visual impairment (including optic neuritis) (70%), GI disturbance (17%), MSK (3%), rash (3%), hepatotoxicity (2%)	Baseline and monthly visual acuity and color discrimination
Pyrazinamide	5.1% (3.1–8.4)	MSK (33%), GI disturbance (23%), hepatotoxicity (20%), rash (13%), hyperuricemia (6%)	Monthly liver tests
Delamanid[c]	N/A	GI disturbance, dizziness, insomnia, QT prolongation	EKG at baseline and monthly. Baseline potassium, magnesium, calcium, albumin; monthly if risk factors for electrolyte disturbance or QT prolongation
Amikacin	10.2% (6.3–16.0)	Ototoxicity (87%), nephrotoxicity (10%), GI disturbance (1%), MSK (1%), vestibular toxicity, hypokalemia, hypomagnesemia, hypocalcemia	Baseline and monthly assessment of hearing and vestibular system (symptoms, physical exam, audiology) Baseline and regular (at least monthly)
Streptomycin	2.9% (1.3–6.2)	Ototoxicity (83%), peripheral neuropathy (17%), vestibular toxicity, hypokalemia, hypomagnesemia, hypocalcemia	Renal function and electrolytes. Peak and trough concentration at least at baseline if impaired renal function; some monitor routinely
Imipenem-cilastatin, Meropenem	5.1% (3.1–8.4)	Hepatotoxicity (50%), rash (17%), fatigue (17%), pneumonia (7%), GI disturbance, seizure (in CNS infection)	
Ethionamide	6.5% (4.1–10.1)	GI disturbance (48%), hepatotoxicity (22%), psychiatric (6%), gynecomastia (5%), MSK (5%), hypothyroidism, neurotoxicity	Monthly liver tests TSH at least every 3 months
p-aminosalicylic acid	11.6% (7.1–18.3)	GI disturbance (79%), hypothyroidism (5%), hepatic dysfunction (4%), rash (4%), nephrotoxicity (3%). Avoid if allergic to aspirin.	CBC, electrolytes Monthly liver tests TSH at least every 3 months

Abbreviations: MDR-TB, multidrug-resistant tuberculosis; MSK, musculoskeletal; EKG, electrocardiogram; GI, gastrointestinal; CNS, central nervous sytem; TSH, thyroid stimulating hormone; CBC, complete blood count.

Note: The complete list of possible adverse events and monitoring parameters is not provided. Please refer to The Curry International TB Center Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd Edition.[56]

[a]Incidence of adverse events taken from an Individual Patient Data Meta-analysis (IPD-MA) including 9178 patients from 35 studies; adverse events as defined here were those that resulted in permanent discontinuation of the drug.[115]

[b]Estimates of frequencies of adverse events taken from an IPD-MA[115] and include only those that resulted in permanent discontinuation of the drug, therefore the frequency of occurrence of adverse events that can be managed without drug discontinuation may differ from those reported here. Adverse events shown in the table without associated frequencies are from,[56,93] not the IPD-MA.

[c]Adverse events associated with delamanid were not reported in the IPD-MA.

[d]Further details regarding the type of cardiovascular adverse event were not provided in the IPD-MA;[115] however these drugs are known to cause QT prolongation.

5.5. Drug interactions and adverse drug events in MDR-TB treatment

Table 6 summarizes the incidence of the most common adverse events associated with the medications used to treat MDR-TB, as well as the recommended monitoring. Table 7 describes important drug interactions to consider when prescribing MDR-TB treatment.

Most patients experience side effects to at least 1 drug used to treat MDR-TB. Patients should be educated about

Table 7. Drug-drug interactions with second-line anti-TB drugs.

Drug interactions
• Increased risk of neurotoxicity from cycloserine has been associated with concomitant use of isoniazid, ethionamide and fluoroquinolones.[113,114]
• *P*-aminosalicylic acid and ethionamide have each been associated with hypothyroidism. The probability of hypothyroidism is increased when both agents are used together.[12]
• Linezolid should generally not be administered to patients taking serotonergic agents, such as monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, as the combination could result in serious reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions.
• Bedaquiline is metabolized by the cytochrome P450 system enzymes in the liver. Drugs that induce or inhibit this system of enzymes will result in drug–drug interactions that can affect the blood levels of bedaquiline. Cytochrome P450 inducers decrease blood levels of bedaquiline, resulting in the possibility of inadequate serum levels of bedaquiline. Conversely, cytochrome P450 inhibitors increase blood levels of bedaquiline, resulting in the possibility of an increased risk of toxicity.[93]

adverse effects, and clinicians should attempt to investigate and treat all adverse effects quickly. Some adverse effects are difficult to tolerate but do not pose any risk of organ damage (eg, nausea and vomiting without evidence of hepatotoxicity); attempts should be made to manage these symptoms with supportive care and ancillary medication, before discontinuing the culprit anti-TB medication. Other adverse effects do put patients at risk for serious organ damage and necessitate discontinuing the culprit medication in a timely manner. When an anti-TB drug is discontinued due to adverse effects, that medication should be replaced by another drug used for the treatment of MDR-TB, in order to continue with the recommended number of effective drugs in the regimen. However, the strength of the regimen should be kept in mind; if many of the drugs in the preferred initial regimen (ie, moxifloxacin/levofloxacin, bedaquiline, linezolid, cycloserine, clofazimine) cannot be used or are discontinued because of adverse events, clinicians should consider using more than 5 drugs in the intensive phase and/or extending the treatment duration beyond 18 months. See the WHO Operational Handbook for examples of regimens that can be used in these circumstances.[93]

5.6. Surgery for MDR-TB

Surgical resection of lungs affected with active TB disease predates the antibiotic era. With the advent of effective antibiotic therapy, use of surgery declined and was reserved only for emergencies, such as hemoptysis. However, there has been renewed interest in surgical resection as an adjunct to medical therapy in patients with MDR-TB, given the limitations of medical therapy in these patients. Many case series have reported good success rates and some reported better outcomes in surgically treated patients than patients treated with medical therapy alone.

An IPD meta-analysis, published in 2016[116] reported on the results of 478 patients who underwent surgical resection out of a total of 6,431 patients from 26 studies. Partial lung resection (lobectomy, segmentectomy or wedge resection) was associated with an improved odds of treatment success (aOR: 3.0; [95% CI: 1.5 to 5.9]). Total lung resection, or pneumonectomy, was not associated with improved success (aOR: 1.1; [0.6 to 2.3]). Mortality during medical therapy following surgery occurred in 13% of those undergoing pneumonectomy, compared to 3% of those who underwent partial lung resection and 13% of those receiving medical therapy alone. Treatment success was greater if surgery was performed after sputum culture conversion (aOR: 2.6; 0.9 to 7.1). There were a number of limitations of this analysis, in particular that no patients with HIV, nor children who underwent resection surgery, were included in the analysis. The most important limitation is the confounding of surgical resection with better clinical and functional status, which was partially controlled through sophisticated matching analyses, but some residual confounding likely remained. In addition, this analysis was based on studies published up to 2008, so there was limited use of linezolid or bedaquiline; even later generation fluoroquinolones were given only to a minority of patients. With the introduction of these more effective drugs into routine MDR-TB treatment, the benefits of surgery may be less. Analysis of a more recent IPD, which included patients who had received these newer drugs, revealed that the benefits of partial lung resection was still seen, but the effect was more modest, while total lung resection (pneumonectomy) was of no benefit, as in the earlier analysis.[117]

Recommendations

- **We conditionally recommend, in carefully selected patients with MDR-TB, partial lung resection (lobectomy, segmentectomy or wedge resection) as an adjunct to optimized medical therapy. The optimal timing of surgical resection appears to be after culture conversion is achieved** (*poor evidence*).
- **We conditionally recommend, in patients with MDR-TB who have more extensive disease that could only be addressed by pneumonectomy, against resection surgery, as such patients do not appear to benefit from it. Surgery in these patients should be reserved for treatment of major complications, such as massive hemoptysis** (*poor evidence*).

5.7. New drugs and new regimens for MDR-TB

In 2020, an open-label, single-group study reported on the efficacy and safety of a new drug regimen (bedaquiline, pretomanid and linezolid – BPaL) taken for 6-to-9 months, in the management of 109 patients with XDR-TB or difficult-to-treat MDR-TB.[118] The study found that 98 patients (90%) had a favorable treatment outcome. Adverse events, however, were frequent; all patients had at least one adverse event and 17% had a serious adverse event. Linezolid was started at 1200 mg daily, with dose adjustment for adverse

events, and linezolid-related adverse events were very common; peripheral neuropathy occurred in 81% of patients, and myelosuppression in 48%. The 2020 WHO guidelines recommend use of this regimen only in operational research conditions, in MDR-TB patients with TB that is resistant to fluoroquinolones, and in those who have had no previous exposure (≤2 weeks) to bedaquiline or linezolid. Other eligibility criteria, drug dosing and monitoring are found in the WHO Operational Handbook.[93] Some expert centers in other countries are using BPaL with lower doses of linezolid, guided by therapeutic drug monitoring.[112] An ongoing clinical trial (ZeNix) is evaluating the BPaL regimen with a lower dose and shorter duration of linezolid.[119]

In addition to the ongoing studies of the BPaL regimen, there are multiple other ongoing studies of shorter treatment regimens for MDR-TB, most of which include bedaquiline.[120] Numerous new anti-TB drugs are also under development.[120] Only one new drug, however, is currently in use outside of clinical trials for MDR-TB management, a drug called pretomanid, which was studied as part of the BPaL regimen. Given there is no experience with pretomanid in other combinations, it is not recommended by WHO for use outside the context of the BPaL regimen.

The high number of ongoing trials of new anti-TB drugs and new regimens suggests that the optimal management of MDR-TB will continue to evolve in the near future.

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