Contacts

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The rise in TB resistance rates worldwide and outbreaks of MDR-TB have brought attention to the treatment of contacts to drug-resistant TB cases.

Challenges: Limited data and consensus

The Centers for Disease Control and Prevention (CDC) guidelines for treatment of contacts exposed to multidrug-resistant tuberculosis (MDR-TB) were last updated in 1992. The national guidelines for the investigation of contacts to infectious TB cases were last updated in 2005 when limited data were available for newer methods for diagnosing latent TB infection (LTBI). Over the past two decades, several publications on the tolerability and toxicity of regimens used for treatment of LTBI among contacts to MDR-TB cases, and more extensive publications on the application of newer LTBI diagnostics, have appeared. These reports can inform the approach to the identification, evaluation, and treatment of contacts to patients with MDR-TB.

The management and treatment of persons exposed to and presum-ably infected by patients with MDR-TB pose unique challenges because:

- the evidence base remains of low quality for selecting a safe and effective regimen; and
- the growing body of evidence indicates that the multidrug regimens recommended in 1992 are poorly tolerated and some have unacceptable toxicity.

A systematic review conducted in 2012 reached the same conclusion as the 2006 Cochrane review of the literature that there is insufficient data to address the question of the efficacy of MDR-LTBI treatment. However, a number of studies have documented high rates of discontinuation of treatment, particularly with combination regimens including pyrazinamide (PZA). In addition, patients treated with PZA and rifampin (RIF) for LTBI after exposure to pan-susceptible TB have been reported to have 0.9% fatality and 2.8% hospitalization rates. These observations should lead to avoidance or extreme caution in using combination LTBI regimens containing PZA.
Contact investigation

Recent studies have demonstrated a wide variation in the concentration of infectious particles in sputum specimens from patients with smear-positive TB. Transmission to contacts was more strongly associated with concentration of infectious particles than with the grade of the acid-fast bacilli (AFB) smear. These findings may provide an explanation for years of observation that some sputum AFB smear-positive TB patients seem not to transmit at all, and some with the same clinical features are associated with high rates of transmission and secondary TB cases. Until new tools are developed to gauge the risk of infectiousness, public health staff must continue to use the results of the contact investigation to determine if, and how extensively, transmission has occurred. One of the primary responsibilities of the case manager or disease investigator is to identify, locate, and evaluate contacts. **Contact investigation for cases of MDR-TB is important for detection of prevalent TB cases as well as identification of contacts with LTBI who were likely infected by the MDR-TB strain of the index case.**

Results from a number of studies show that zero to 8% of contacts to MDR-TB cases were found to have active TB at the initial evaluation or during follow-up. Half or more of the cases among contacts are prevalent active TB cases detected at the initial evaluation, and the majority of the subsequent incident cases are detected within the first year after the diagnosis of the index case. The majority of culture-confirmed cases among contacts are also due to MDR-TB but some may have isolates with other drug-susceptibility findings.

In general, the process of performing a TB contact investigation is the same whether a case is drug-resistant or not, and includes:

- Review of the index case’s medical history and history of present illness
- Interview of the case to identify locations where transmission could have occurred
- Interview of the case to identify contacts exposed at one or more locations
- Performance of a field investigation
- Risk assessment for TB transmission
- Prioritization of contacts for evaluation
- Evaluation of initial contacts
- Review of the data on baseline results of initial contacts to assess the likelihood that transmission has occurred and whether expanded contact investigation may be indicated
- Provision of treatment for LTBI and follow-up of contacts
- Evaluation of contact investigation outcomes

This assessment of whether transmission of *Mycobacterium tuberculosis* has occurred due to exposure to MDR-TB is critical to reaching the conclusion that individual contacts have been infected with MDR-TB. Since many of the contacts to infectious TB cases may have been exposed previously, it can be challenging to determine whether TB infection among contacts represents exposure to the recent drug-resistant TB case or exposure to a previous and likely drug-susceptible case. **This assessment should be based on the transmission risk assessment findings, the individual contact's TB exposure and LTBI history, and an evaluation of the results of the contact investigation.**
TB transmission risk assessment

The risk of TB transmission is contingent on 4 main factors:

1. **Infectiousness of the TB patient**: Symptoms, sputum smear status, site of TB, presence of cavitary disease

2. **Environment where transmission likely occurred**: Size of room, amount of ventilation, presence of air cleaning systems

3. **Characteristics of the contact's exposure**: Frequency of contact, proximity and cumulative duration of the exposure

4. **Host susceptibility**: Very young children and immunocompromised patients may or may not be at increased risk of infection, but are certainly at increased risk of progression to TB if infected

**Indications of transmission include:**

- Identification of a secondary case
- High infection rate among contacts, especially those born in the United States or other TB low-burden countries
- Infection in a young child
- Presence of converters

A “close contact” is described by the CDC as, “A person who had prolonged, frequent, or intense contact with a person with TB while he or she was infectious.”

According to the American Thoracic Society and CDC, a skin test “converter” is someone who has an increase in reaction size of 10 mm or more within a period of 2 years. An interferon-gamma release assay (IGRA) converter is a person who changes from negative to positive within a 2-year period.

Contact TB exposure history

A very thorough TB history of contacts with LTBI will help to assess the likelihood of recent infection and assist in treatment decisions.

Include these essential factors in the assessment:

- Prior tuberculin skin test (TST) or IGRA history and baseline TST (or IGRA if done). Taking the time to find documented prior TST history is time well spent in a drug-resistant TB contact investigation. Sources of this information include:
  - Employment or immigration/refugee health record
  - Primary care provider medical record
  - School/immunization health record
  - Military health/immunization records
• History of incarceration (a situation in which TST or IGRA is often performed)
• Other programs that the patient may have accessed, such as CureTB, TBNet, or programs such as foster care that have a health screening component on entry into the program
• History of previous exposure to TB—was it a pan-sensitive case? Was previous treatment for LTBI or active disease prescribed and completed? If so, what medications were used?
• Information on the contact’s country of birth, year of arrival (if foreign-born), and travel history is helpful and may give clues to prior exposure potential

Latent tuberculosis infection (LTBI)

Traditionally, LTBI is defined as a positive TST without clinical or radiographic evidence of TB disease.

Two commercial IGRAs are now available for the diagnosis of LTBI: the QuantiFERON®-TB Gold In-Tube (QFT-GIT) and the T-SPOT.TB (T-SPOT). It is important to remember that these blood assays (as well as the TST) are not direct measures of LTBI but are immunologic assays that measure cell-mediated immunity to protein (PPD for the TST) or more specific peptides (ESAT and CFP-10 for both IGRAs, with TB-7 added for QFT-GIT).

The 2010 CDC recommendations stated that IGRAs could be used instead of TST, and noted the specific advantages of these tests among populations likely to have received prior bacille Calmette–Guérin (BCG) vaccination or who were less likely to return for the TST interpretation. At that time, caution was advised for the use of IGRA in young children and individuals with impaired immunity, primarily due to limited data. Since then, numerous studies have been published, including systematic reviews, and the overall conclusions are 1) IGRAs appear to perform at least as well as TST in adults, children 5 years of age and older, and immunocompromised populations, having equal or better sensitivity for active TB than TST; and 2) IGRAs have improved specificity over TST, particularly in BCG-vaccinated persons. The 2015 American Academy of Pediatrics Redbook® notes that some experts use IGRAs for children as young as 3 years of age.

IGRAs have a lower frequency of positive results compared to TST among individuals with prior BCG vaccination, a finding best interpreted as higher specificity rather than lower sensitivity. Thus, positive IGRA results at baseline testing are less likely than a positive TST to be falsely positive among high-risk foreign-born populations. Repeat TST has the potential for immunological boosting. Although the IGRAs avoid the potential for boosting, false-positive conversions at the 8-week follow-up testing may occur due to test variability. False-positive rates of up to 4% have been reported during repeat IGRA testing in low-risk populations, such as U.S.-born health care workers, and this phenomenon is likely to occur among baseline-negative contacts when retested at 8-10 weeks, at least among adults.

According to the 2010 CDC guidelines, testing for LTBI with more than one test is not recommended in most situations, and one should not do a second test without specific plans for how the results will be used. An IGRA can help to decide whether a positive TST
is due to prior BCG vaccination or true TB infection (but if the IGRA is negative, it should be interpreted with caution in the setting of high-risk exposures, especially to MDR-TB). Among adolescent and young adult contacts likely to have received BCG at birth and previously diagnosed with LTBI based on TST done during routine screening, there is up to a 50% chance that the prior TST was a false-positive. If a patient has been more recently exposed to MDR-TB, IGRA testing is still indicated even if the patient was previously treated for LTBI. This is based on a randomized trial that demonstrated that LTBI treatment does not result in reversion of a positive IGRA to negative. Contacts with a negative baseline IGRA likely represent individuals previously treated for a false-positive TST who require an 8-10 week follow-up IGRA.

Currently, no data exist to determine the optimal timing for performing IGRAs in exposed contacts, but it is reasonable to assume that the tests perform similar to the TST for which the assumption has been accepted that a test 8-10 weeks after the last exposure is adequate for detection of new TB infection.

The greatest limitation of IGRAs is the more limited prospective data on the predictive value of a positive IGRA for future TB disease. This has been established for different-sized TST reactions in many large-scale cohort and experimental studies, which permits the estimation of risk for disease and benefit of therapy.

As with the TST, a negative IGRA does not rule out early LTBI or even TB disease. This fact is particularly important in subgroups at high-risk for progression to TB disease, such as young children, and adults with HIV or other medical conditions associated with defects in cell-mediated immunity. When the risk of progression is high and validity of TST and/or IGRA questionable, clinicians may treat in the face of discordant results or in the absence of positive test results.

The importance of treating LTBI

- For the population as a whole, there is a 5-10% lifetime risk of developing TB disease following infection, half of the risk occurring within 1 to 2 years after infection.

- Treatment of LTBI is widely recommended for individuals at increased risk of developing TB disease, including, but not limited to, contacts to infectious TB cases, HIV-positive and other immunocompromised hosts, children, and recent immigrants.

- Treatment with isoniazid (INH), either daily or intermittently, has been shown to decrease the risk of progressing to TB disease among contacts, and a more recent study showed similar effectiveness using 12 once-weekly, directly-observed doses of INH plus rifapentine (RPT). RIF for 4 months and the combination of INH plus RIF for 4 months are also options for treating LTBI based on less extensive data. The combination of PZA and RIF was also shown to be as effective as INH in preventing progression to TB disease among HIV-positive patients, but significant hepatotoxicity led to the withdrawal of this regimen as a recommendation for treatment of LTBI.
• Transmission of MDR-TB is well documented to healthcare workers, immunocompromised persons, children in homes or at school, and other close contacts such as family members and those at work sites. Aggressively pursue a full evaluation of all close contacts, and carefully consider expanding the contact investigation when high rates of transmission are documented in the initial evaluation.

• Given the high morbidity and mortality associated with drug-resistant TB disease, consider treatment of LTBI thought to be due to infection with drug-resistant TB, but weigh the risks and benefits to lessen the risk of toxicity from unnecessary treatment with toxic medications.

General principles of evaluating and managing contacts

• Evaluate exposed contacts expeditiously in order to identify any other cases of TB disease and to prevent further transmission.

• IGRAs are the preferred test for exposed contacts who originate from areas where they were likely to have received BCG vaccine, even among adolescents and young adults who were vaccinated only at birth.

• Rule out TB disease prior to starting any treatment. Before starting a patient on treatment for LTBI, exclude TB disease to avoid amplification of resistance by use of a LTBI regimen when active MDR-TB is present.
  • Contact screening for active TB in the United States is most often done with a two-stage screening process of testing individuals with a TST or IGRA test and performing chest radiography only among those with either a positive TST or IGRA test or symptoms of TB. This approach is limited by the possibility of false negative TST or IGRA, and radiography of only those with a positive TST or IGRA will miss 10-15% of TB cases. Therefore, it is important to evaluate those contacts with symptoms both clinically and radiographically for TB.
  • Children under 5 years of age and those with HIV infection or significant immunosuppression are routinely evaluated by chest radiography even if the TST or IGRA tests are negative.
  • Some patients with normal chest radiographs should have sputum and other specimens collected if there are clinical signs or symptoms of TB.

• Some general principles for treating LTBI due to MDR-TB are as follows:
  • Efficacy of any regimen depends on adherence to and completion of therapy.
  • Educate patients on drug resistance, drug side effects, importance of adherence, and TB symptoms.
  • Select the most effective, best-tolerated regimen to which the presumed source case isolate is susceptible. Despite the emphasis on two-drug regimens in the 1992 CDC guidelines, recent reports indicate that fluoroquinolone single-drug therapy can be used and may be preferable due to fewer side effects and, as a result, greater tolerability.
  • For immunosuppressed contacts with a positive TST or IGRA test, consider treatment with a two-drug MDR-LTBI regimen rather than monotherapy.
  • In children under age 5 and in HIV-positive close contacts with initial negative LTBI tests, consider window prophylaxis when exposure was very intimate.
and prolonged, and when transmission to other contacts has been documented. See section on Window prophylaxis later in this chapter.

- In children under age 6 months and in HIV-positive close contacts, consider treating for presumed MDR-LTBI even in the absence of positive test for LTBI, especially in the setting of documented transmission (converters, secondary cases).
- Take into account the patient’s wishes, as there is limited evidence to guide treatment of presumed MDR-LTBI.

Summary of management options of LTBI in contacts exposed to MDR-TB

- Experts agree that, regardless of the decision to treat or the treatment option selected, it is important to: 1) Follow those with presumed latent MDR-TB infection at regular intervals for a minimum of 2 years following exposure; and 2) Educate patients about the signs and symptoms of TB in case they progress to TB disease.
- The range of treatment options for contacts to patients with MDR-TB includes:
  - Monotherapy with a fluoroquinolone. This option has increasingly been employed although not included in 1992 CDC guidelines.
  - Treatment with 2 drugs to which the organism is sensitive and the toxicity profile is acceptable. This would most likely be a fluoroquinolone plus ethambutol (EMB).
- The recommended duration of treatment is generally 6 to 12 months.
- Since there are limited observational data supporting specific recommendations for the treatment of MDR-LTBI, treatment recommendations must take into account the well-documented toxicity of PZA-containing regimens, and the poor tolerability of most of the second-line anti-TB drugs. Recommendations are based on expert opinion, and the risk versus benefit must be considered.
- A 2014 observational study by Bamrah et al., showed a treatment completion rate of 89% and no secondary MDR-TB cases among contacts treated with a fluoroquinolone as monotherapy or combined with EMB or ethionamide (ETA) in an MDR-TB outbreak in Micronesia and the Marshall Islands. Of 15 contacts not treated, 3 developed TB disease.
- Other regimens such as INH alone, RIF, or INH plus RPT may be considered for patients likely to have been infected by a drug-susceptible case before exposure to the drug-resistant case.
- Consider the BCG vaccine for infants and children with a negative TST who are continually exposed to a case of MDR-TB and who cannot be removed from this exposure. (See Resources at the end of this chapter for information on how to obtain and administer the BCG vaccine.)
- No treatment with clinical monitoring may be appropriate. (See section, No Treatment: Clinical Monitoring.)
Selecting a treatment regimen for contacts to drug-resistant TB

Variables to consider:

- Drug-susceptibility pattern of the *M. tuberculosis* isolate of the presumed source case
- Infectiousness of the source MDR-TB case, which can be evaluated by:
  - Smear and culture status
  - The presence or absence of cavitary disease
  - The site of TB involvement (pulmonary or laryngeal vs. other sites)
  - The evidence of transmission to other contacts based upon higher than expected prevalence of 8-week conversions by TST or IGRA tests
- Closeness and intensity of MDR-TB exposure, which can be evaluated by documenting hours of cumulative exposure and setting of exposure (i.e., indoor vs. outdoor, ventilation, etc.)
- Contact’s likelihood of prior exposure to drug-susceptible TB, which can be evaluated by:
  - Place of birth and history of foreign residence or travel
  - History of prior exposures to TB disease
  - TST/IGRA history must be interpreted cautiously – prior positive TST during routine screening in younger immigrants may have been false-positive TST due to BCG cross-reaction. IGRA testing of such contacts may be recommended since some may have negative IGRA results at baseline and be candidates for 8-week post-exposure testing. For those with a positive baseline IGRA, one cannot distinguish between those previously infected or more recently infected with MDR-TB.
- Likelihood that the contact will progress to TB disease, including factors such as:
  - Immunosuppression (HIV, steroids, tumor necrosis factor [TNF] alpha agents, other immune-suppressing drugs)
  - Age (less than 5 years old)
  - Documented TST or IGRA conversion
  - Diabetes, renal failure, and certain other medical conditions
- Tolerability and toxicity of potential anti-TB drugs for treatment of LTBI

Drug-resistant LTBI treatment options

Table 1 includes suggestions for regimens that are fluoroquinolone-based, due to the significant activity of levofloxacin (LFX) or moxifloxacin (MFX) for TB disease and lower anticipated toxicity. EMB, if likely to be effective, may be a reasonable second drug. Other second-line drugs for LTBI treatment may be less acceptable due to toxicity. The actual regimen chosen will depend on the individual case; consultation with an expert in drug-resistant TB is recommended.
**TABLE 1.**

Specific treatment options dependent on susceptibility of source case isolate

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>LTBI treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (RIF-susceptible)</td>
<td>RIF 4 months (Adults and children)</td>
</tr>
<tr>
<td>INH and RIF</td>
<td>Fluoroquinolone or Fluoroquinolone + EMB</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>Fluoroquinolone or Fluoroquinolone + ETA</td>
</tr>
<tr>
<td>INH, RIF, PZA</td>
<td>Fluoroquinolone or Fluoroquinolone + EMB</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, +/--injectable</td>
<td>Fluoroquinolone or Fluoroquinolone + ETA</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, injectable, ETA</td>
<td>Fluoroquinolone or Fluoroquinolone + cycloserine (CS)</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, and fluoroquinolone</td>
<td>No treatment, clinical monitoring*</td>
</tr>
<tr>
<td></td>
<td>(In select cases, CS + para-aminosalicylic acid [PAS] or PAS + ETA* or ETA* + CS may be considered)</td>
</tr>
</tbody>
</table>

* See section, No treatment: Clinical monitoring

**Considerations when choosing MDR-LTBI treatment options**

**LFX or MFX alone**

- Better tolerated than 2-drug combination, and therefore more likely to complete regimen.
- Demonstrated bactericidal activity against *M. tuberculosis*.
- Only limited observational data on efficacy in preventing progression to TB disease.
- Due to the potential risk of tendon rupture (a few case reports), advise patients to avoid vigorous exercise and to report any symptoms of calf pain or tenderness.
- Use of fluoroquinolones for pediatric MDR-LTBI has been well-tolerated, despite concerns for potential arthropathy seen in animal studies. (See Chapter 6, Pediatrics).
- Consider the risks versus benefits regarding the use of fluoroquinolones in pregnant or breastfeeding women. (See Chapter 7, Co-morbidities and Special Situations, for more information.)
• Consider use in TST or IGRA converters and those with newly documented positive TST or IGRA, but who may have intermediate exposure to index case (exposure to MDR-TB was less certain).

LFX or MFX and a second drug (EMB preferable) to which isolate is likely to be susceptible (e.g., EMB, ETA, PAS, CS)

• Follows CDC/ATS 1992 recommendations of using 2 drugs to which isolate is susceptible.
• Consider use in immunocompromised individuals and children under age 5.
• Frequently poorly tolerated due to increased side effect profile.
• Side effects may deter patient from completing this regimen.
• Potential toxicity must be balanced against benefits.
• Due to the potential risk of tendon rupture, advise patients to avoid vigorous exercise and to report any symptoms of calf pain or tenderness.
• Consider the risks versus benefits regarding the use of fluoroquinolones in pregnant or breast-feeding women. See Chapter 7, Co-morbidities and Special Situations, for more information.
• Limited observational data on efficacy in preventing progression to TB disease.

Published experience in Texas, New York City, Orange County, California, and Geneva, Switzerland indicates high risk for hepatitis and/or intolerance to a fluoroquinolone and PZA combination, and it should generally be avoided.

No treatment: Clinical monitoring

• This may be a reasonable alternative to treatment, particularly when the source resistance pattern limits options to toxic combinations, given the limited data on efficacy of treatment regimens for MDR-LTBI and side effects.
• Evaluate with clinical exam, symptom review every 3 to 6 months for 2 years (with chest radiographs and/or sputum collection as clinically indicated).
• Educate the patient about symptoms of TB disease.

Clinical monitoring without treatment, especially when there is evidence of significant transmission, is not advised when:

• Contact is HIV-positive or otherwise significantly immunocompromised.
• Contact is under age 5.
• Contact is someone with a documented recent conversion or otherwise at high risk for progression to TB disease.
Treatment of children exposed to drug-resistant TB

Many providers treat children for MDR-LTBI, although efficacy data from randomized controlled trials are lacking. In general, MDR-LTBI regimens have been found to be better tolerated in children than adults. Fluoroquinolone monotherapy is sometimes used, especially in older children. See Chapter 6, Pediatrics, for more information.

Duration of therapy

- National guidelines from 1992 suggest treatment of MDR-LTBI for 6 to 12 months.
- Consideration of 12 months of treatment should be made for HIV-positive patients, children, and other individuals with medical risk factors.
- Lower-risk individuals should receive at least 6 months of treatment.

Adherence and monitoring

- If local resources permit, consider directly observed therapy (DOT) for treatment of contacts with presumed MDR-LTBI especially those at higher risk for progression and nonadherence.
- Individuals receiving treatment for drug-resistant LTBI should be monitored closely and supported through side effects.
- Side effects should be treated symptomatically and with great encouragement, as few alternate treatment options are available.
- Arthralgias and myalgias are common in patients receiving fluoroquinolones for prolonged periods of time. Expert opinion suggests that giving patients short drug holidays may decrease these symptoms and allow for treatment completion.

Children under age 5 are at increased risk of developing TB if infected and deserve aggressive evaluation and treatment if exposed to an individual with TB.

Window prophylaxis

Window prophylaxis is the practice of treating a patient who has been exposed to a potentially infectious source case, but has no current evidence of TB disease or infection.

- Since it can take weeks to months for the immune system to recognize a TB infection (and therefore to produce a positive TST or IGRA test), window prophylaxis can potentially abort an early infection or prevent rapid progression from early TB infection to TB disease in vulnerable hosts.
- Individuals at very high risk of progressing to TB if infected (very young children, HIV-positive patients and other significantly immunocompromised contacts) are targeted for window prophylaxis.
• Contacts should be screened by history, physical exam, symptom review and chest radiograph to rule out early TB disease before initiating window prophylaxis.

• Contacts are typically treated for 8 to 10 weeks from the end of risk of transmission, and then the TST or IGRA is repeated. If the test has become positive, treatment for LTBI is continued to complete a full course. If the test remains negative, window prophylaxis is stopped, unless the contact is at risk for anergy (immunosuppressed or an infant younger than 6 months of age). In the case of suspected anergy, a full course of LTBI treatment may be warranted.

• Window prophylaxis for MDR-TB is problematic due to lack of efficacy data and toxicity of potential regimens.

• Window prophylaxis for MDR-TB should be considered in consultation with TB experts for the following two groups: children under age 5, and HIV-positive individuals or others with significant immunocompromise. This is especially true if there has been intimate and prolonged contact with individuals likely to be infectious (smear-positive, cavitary disease, coughing source case, and TST/IGRA conversions among other contacts or secondary cases indicating transmission of TB).

Follow-up of MDR-TB contacts

• It is essential to carefully educate infected contacts who have not received treatment and those finishing MDR-LTBI treatment about the signs and symptoms of TB, stressing the need for prompt medical evaluation if symptoms occur.

• Given the limited efficacy data on MDR-LTBI treatment, some experts recommend evaluation/symptom review every 3-6 months for 2 years, even for contacts who have completed treatment. Chest radiographs and sputum should be done as clinically indicated. Special emphasis should be placed on high-risk contacts: HIV-positive and other immunocompromised individuals; children under age 5; and persons with documented TST/IGRA conversion.
**Summary**

- IGRAs may be used instead of TST in contact investigations, and these are preferred in foreign-born persons who have a history of BCG vaccination, even if previously TST-positive. Conversions need to be interpreted cautiously given the boosting with TST and false-positive rate of up to 4% with repeat testing using IGRAs in adults.

- While it is highly desirable to prevent MDR-TB cases by treatment of LTBI and use of window prophylaxis, there are limited data on efficacy, and more extensive data on poor tolerability, especially for PZA-containing regimens.

- Treatment of LTBI should be considered in most circumstances, and particularly for patients at highest risk for progression to TB.

- Careful contact investigation is required to determine likely timing of infection. Patients who were previously TST or IGRA positive are more likely infected with a susceptible strain and may be treated with regimens for drug-susceptible TB. However, when there has been evidence of significant transmission and prolonged exposure, re-infection with a MDR-TB strain may occur and MDR-LTBI treatment warranted.

- Given the lack of data on efficacy and the documented poor tolerability/toxicity of the previously recommended 2-drugs regimens, most patients should receive fluoroquinolone monotherapy (for contacts to fluoroquinolone-susceptible cases), after active TB is excluded.

- In children under age 5 and patients who are immunocompromised, consider treatment with 2 drugs to which the presumed source case isolate is susceptible for 12 months.

- For some patients, clinical monitoring without treatment may be an appropriate option.

- High-risk contacts with MDR-LTBI should be monitored for 2 years for evidence of progression to active TB disease.
Resources

Contact Investigation: Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis: Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR 2005; 54 (No. RR-15, 1-37).
www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a1.htm
Accessibility verified November 1, 2015.

Instructions for BCG application.
Accessibility verified November 1, 2015.

Information about how to obtain BCG.
BCG can be ordered from any wholesaler that distributes Merck vaccines. You may also contact Merck (800-672-6372) directly to determine if the product is available as shortages may occur. It is important to clarify your request for BCG vaccine for percutaneous use (not the BCG live for intravesical administration for bladder cancer).

The Online TST/IGRA Interpreter. An online tool that estimates the risk of active TB for an individual with a TST reaction of ≥5mm, based on his/her clinical profile. Intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial IGRA.
http://www.tstin3d.com
Accessibility verified November 1, 2015.

The BCG World Atlas. An interactive website providing detailed information on current and past BCG policies and practices for over 180 countries. A useful resource to assist clinicians with interpretation of TB diagnostics.
http://www.bcgatlas.org
Accessibility verified November 1, 2015.
References


