Managing Contacts

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

Challenges: A Lack of Data and Consensus

In 1994, the Centers for Disease Control and Prevention (CDC) convened 31 experts, and they were unable to achieve consensus on treatment recommendations for contacts to multidrug-resistant tuberculosis (MDR-TB). Consequently, the CDC guidelines have not been updated since 1992. Unfortunately, the last decade has not provided more definitive data regarding the best approach to the identification, evaluation, and treatment of contacts to patients with MDR-TB.

The management and treatment of persons exposed to and infected by patients with MDR-TB pose unique challenges because of the absence of evidence-based therapy and the lack of significant experience in these situations.

A 2006 systematic Cochrane review of the literature showed that there still have been no randomized controlled trials to address the question of the efficacy of treatment for MDR latent tuberculosis infection (LTBI) treatment. Two observational studies did meet inclusion criteria. A prospective cohort study found individualized tailored treatment to be effective for preventing TB in children, while a retrospective cohort study found isoniazid (INH) not to be effective. The authors concluded that evidence of the effects of treatment of LTBI in people exposed to MDR-TB is extremely limited in both quantity and quality.

Latent Tuberculosis Infection (LTBI)

Traditionally, LTBI is defined as a positive tuberculin skin test (TST) without clinical or radiographic evidence of tuberculosis. The TST has limitations, including false positive results in patients previously infected with nontuberculous mycobacteria (NTM) or vaccinated with bacille Calmette-Guérin (BCG), and false negatives associated with early infection or due to anergy. New blood tests called interferon gamma release assays (IGRAs) are now available which measure interferon-gamma (IFN-γ) released from a patient’s T cells after stimulation with specific TB antigens. Two commercial IGRA kits are available now in the United States: the QuantiFERON®-TB Gold (QFT-G), approved by the U.S. Food and Drug Administration (FDA) in 2005, and the QuantiFERON®-TB Gold In-Tube (QFT-GIT), a simplified variant of the QFT-G test (FDA approved in 2007). The T-SPOT.TB test is available outside the United States and was licensed by the FDA in August 2008.
As reviewed elsewhere, IGRAs have high specificity and are not affected by prior BCG vaccination. Thus, false positive results are highly unlikely. In low-incidence settings, the results of IGRAs correlate well with surrogate markers of exposure. In addition, IGRAs have several potential advantages over the TST: testing requires only one patient visit and these assays are \textit{ex vivo} tests, which reduce the risk for adverse effects and eliminate potential boosting when testing is repeated.

However, IGRAs have disadvantages, including higher material cost, need for an equipped laboratory, and a requirement to draw blood with subsequent careful handling to maintain viability of lymphocytes. Although boosting will not occur, the variability of these tests when repeated after months or years, such as in \textit{serial testing of exposed populations}, has not been well studied. In fact, serial testing studies show high rates of both conversions and reversions in exposed populations, and the prognosis of conversions and reversions is unknown. Currently, no data exist to determine the optimal timing for performing IGRAs in exposed contacts. Because a high rate of reversions has been reported in household contacts even over a short period of 3 months, a negative IGRA result does not rule out transient TB infection. Furthermore, IGRAs cannot distinguish between LTBI and TB disease, and unexplained discordances between TST and IGRAs have been reported in a variety of settings.

The greatest limitation of IGRAs is the lack of prospective data regarding the future risk for TB in persons with positive results on IGRAs. 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.

In July 2005, the CDC convened a meeting of consultants and researchers with expertise in the field to review scientific evidence and clinical experience with QFT-G. On the basis of this review and discussion, CDC recommended that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for healthcare workers). This recommendation was also reinforced in the 2005 CDC contact investigation guidelines by the National Tuberculosis Controllers Association and the CDC. \textbf{According to this guideline, QFT-G can be used in place of and not in addition to the TST while investigating contacts} (adults and children). A positive QFT-G result should prompt the same evaluation and management as a positive TST. No reason typically exists to follow a positive QFT-G with a TST. For persons with recent contact to infectious TB, negative QFT-G results typically should be confirmed with a repeat test performed 8 to 10 weeks after the end of exposure. Lastly, the guideline recommends that the timing of QFT-G testing should be similar to that used for the TST.

Given the paucity of published data regarding the sensitivity and specificity of the QFT-G in children, the CDC recommends using caution when interpreting the test in children < 17 years of age. Additionally, the CDC suggests caution in close contacts who are at particularly high risk of progression to TB disease (children < 5 years of age and immunocompromised individuals). \textbf{As with the TST, a negative IGRA does not rule out early LTBI or even TB disease}, a fact that is particularly important in these very high-risk subgroups.
With the recent FDA approval of the QFT-GIT test, and the likely impending approval of the T-SPOT.TB test, revised guidelines will be issued by CDC, the American Thoracic Society (ATS) and the Infectious Disease Society of American (IDSA). Although the QFT-G test can be used for contact investigation in the United States, some caveats are worth remembering: 1) **There are no data on the use of IGRAs for investigating contacts of MDR-TB cases;** 2) IGRAs provide no information on whether the contacts are likely to be infected with the same *M. tuberculosis* strain as the index case; 3) IGRAs provide no information on whether the contacts are likely to be infected with drug-sensitive or resistant strains (and, therefore, do not help in selecting the LTBI treatment regimen); 4) **IGRAs offer no help in distinguishing between latent infection and TB disease;** and 5) Because of concerns about suboptimal sensitivity, IGRAs should not be used alone to rule out TB disease in contacts. This is particularly relevant for high-risk subgroups such as HIV-infected and child contacts.

**The Importance of Treating LTBI**

- For the population as a whole, there is a 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, including contacts of TB cases, HIV-infected and other immunocompromised hosts, children, and recent immigrants.
- Treatment with INH, rifampin (RIF), and the combination of pyrazinamide (PZA) and RIF have been shown to decrease the risk of progressing to TB disease. (**Note:** The combination of RIF and PZA is not currently recommended for treatment of LTBI due to increased risk of hepatotoxicity.)
- Although some data suggest that MDR-TB may be less pathogenic than drug-sensitive TB, **transmission of MDR-TB to healthcare workers, children, immunocompromised persons and other close contacts is well documented,** and full evaluation of all contacts should be aggressively pursued.
- Treatment of LTBI with drug-resistant TB or MDR-TB should be considered, given the high morbidity and mortality associated with TB disease.

**General Principles of Providing Care to Contacts & Selecting Treatment Regimens**

- Evaluate exposed contacts expeditiously in order to identify any other cases of TB disease and to prevent further transmission.
- Consider the use of an IGRA for exposed contacts who are from areas where they were likely to have received BCG vaccine (especially in persons recently vaccinated).
- **Rule out TB disease prior to starting any treatment.** Amplification of resistance by use of a suboptimal regimen must be avoided.
- Immunosuppressed contacts should be treated with a multidrug MDR-LTBI or window prophylaxis regimen rather than monotherapy.
- Efficacy of any regimen depends on adherence and completion of therapy.
- Educate patients on drug side effects, importance of adherence, and TB symptoms.
- Select the most effective, best-tolerated regimen to which the isolate is likely to be sensitive.
• Window prophylaxis of very high-risk close contacts who are TST-negative should be considered when exposure is very intimate and prolonged, and transmission to other contacts has been documented.

Summary of LTBI Treatment Options

- The range of treatment options for contacts to patients with MDR-TB includes:
  - Treatment with 2 or more drugs to which the organism is sensitive
  - Monotherapy with a fluoroquinolone (this option is employed by some experts and is not included in current national guidelines)
  - Clinical monitoring for 2 years without medication if serial evaluation is feasible
  - INH alone (for patients likely to have been infected by a drug-sensitive case before exposure to the drug-resistant case)
- The recommended duration of treatment is generally 6 to 12 months.
- 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 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.
- While there are specific recommendations for the treatment of latent infection with drug-resistant TB, these recommendations are also largely empirical, and all regimens must be individualized.
- The use of BCG vaccine should be considered 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.

Variables to Consider

When designing a protocol for treatment of contacts to drug-resistant TB, consider the following variables:

- 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
- 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-sensitive TB, which can be evaluated by:
  • TST/IGRA history
  • Place of birth and history of foreign residence
  • History of prior exposures to TB disease

• Likelihood that the contact will progress to TB disease, including factors such as:
  • Immunosuppression (HIV, steroids)
  • Age (less than 5 years old, elderly)
  • Documented skin test or IGRA conversion (skin test conversion is defined as increase in reaction size by 10 mm or more within a period of 2 years)
  • Diabetes, renal failure, and certain other medical conditions

• Tolerability and toxicity of potential anti-tuberculosis drugs for treatment of LTBI

### Drug-Resistant LTBI: Treatment Options

Treatment of contacts depends on the resistance pattern of the source case’s isolate. Current national guidelines advise treatment of MDR-LTBI with 2 drugs to which the isolate is susceptible. The following are suggestions for regimens that may be used in specific situations. The actual regimen chosen will depend on the individual case.

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>LTBI treatment options</th>
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| INH (rifampin-susceptible)                             | Adults: RIF 4 months  
Children: RIF 6 months                             |
| INH and RIF                                            | PZA/Ethambutol (EMB) or Fluoroquinolone +/- EMB or PZA |
| INH, RIF, EMB                                          | Fluoroquinolone +/- PZA                             |
| INH, RIF, PZA                                          | Fluoroquinolone +/- EMB                             |
| INH, RIF, PZA, EMB                                     | Fluoroquinolone +/- Ethionamide*                    |
| INH, RIF, PZA, EMB, injectable                         | Fluoroquinolone +/- Ethionamide*                    |
| INH, RIF, PZA, EMB, injectable, Ethionamide            | Fluoroquinolone +/- Cycloserine                     |
| INH, RIF, PZA, EMB, and fluoroquinolone                | Cycloserine/PAS or PAS/Ethionamide* or Ethionamide/Cycloserine |

* Better tolerated in children than in adults.
Duration of Therapy

- National guidelines suggest treatment of MDR-LTBI for 6 to 12 months.
- HIV-infected, children, and other individuals with medical risks should receive 12 months of treatment (cases of children with MDR-TB have been seen following 9 months of MDR-LTBI treatment).
- Lower-risk individuals should receive at least 6 months of treatment.

MDR-LTBI Treatment Options

**Pyrazinamide and Ethambutol**

- Follows CDC/ATS 1992 recommendations of using 2 drugs to which isolate is sensitive
- No data on efficacy in preventing progression to disease
- May be better tolerated than a fluoroquinolone-containing regimen

**Levofloxacin or Moxifloxacin and a Second Drug (First-Line Agent Preferable) to Which Isolate Is Likely to Be Susceptible (e.g., PZA, EMB, Ethionamide, PAS)**

- Follows CDC/ATS 1992 recommendations of using 2 drugs to which isolate is sensitive
- Frequently poorly tolerated due to increased side effect profile
- Side effects may deter patient from completing this regimen
- Potential toxicity in children must be balanced against unproven 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
- Avoid fluoroquinolones in pregnant or breast-feeding women (See Chapter 5: “Special Situations” for more information)
- Levofloxacin/EMB may be better tolerated than Levofloxacin/PZA
- No data on efficacy in preventing progression to TB disease

Consider use in TST/IGRA converters, immunocompromised individuals, and those in whom recent transmission with MDR-TB is highly suspected.

Experience in Texas, New York City, Orange County, California, and Geneva, Switzerland indicates high risk for hepatitis and intolerance to a fluoroquinolone and PZA.

**Levofloxacin or Moxifloxacin Alone**

- Better tolerated than 2-drug combination, and therefore more likely to complete regimen
- Demonstrated bactericidal activity against TB
- No evidence of efficacy in preventing progression to TB disease
- Recommended by some TB experts because of the higher likelihood of completion and known in vitro anti-tuberculosis activity; this option is not included in current national guidelines
Some experts are reluctant to use fluoroquinolone monotherapy because of the possibility of developing resistance.

Potential toxicity in children must be balanced against unproven 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.

Avoid fluoroquinolones in pregnant or breast-feeding women (See Chapter 5, “Special Situations” for more information).

Consider use in TST/IGRA converters and those with newly documented positive TST/QFT, but who may have intermediate exposure to index case so that likelihood of exposure to MDR-TB is less certain.

**INH Alone**

- Proven to decrease likelihood of progression to TB disease if infected with a drug-susceptible strain.
- Use for contacts with history of previously untreated LTBI.
- Use for contacts with lower likelihood of infection with MDR-TB.
- Consider for contacts to cases with low-level INH resistance. Can be used twice weekly by directly observed therapy (DOT) and/or with a second drug in these cases. Ask the lab what the level of INH resistance is (percent resistance with proportion method, minimum inhibitory concentration [MIC], or concentrations studied).
- No efficacy for treatment of MDR-TB LTBI.

**Other Possible Regimens Include**:

- INH, Levofloxacin or moxifloxacin, and a third drug.
- INH and Levofloxacin or moxifloxacin.

**No Treatment: Clinical Monitoring**

- This is a reasonable alternative to treatment, given the lack of proven efficacy of treatment regimens in this situation and likely side effects of regimens.
- Evaluate with chest radiograph and symptom review every 3 to 6 months for 2 years.
- Educate the patient about symptoms of TB disease.

**Consider especially when**:

- Contact is not HIV-infected.
- Contact is over 5 years of age.
- Contact is not a documented converter or otherwise at risk for progression to TB disease.
- An LTBI regimen is not tolerated despite best efforts.
Adherence and Monitoring

- Contacts to TB cases should receive treatment by DOT if local resources permit, 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 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.

Treatment of Children Exposed to Drug-Resistant TB

While good data are available for treatment of LTBI for drug-susceptible TB, scant data are available for treatment of drug-resistant LTBI:

- Children exposed to INH-resistant, RIF-susceptible TB should be treated with 6 months of RIF. A study of 157 adolescents receiving RIF for 6 months after exposure to INH-resistant TB reported no cases of TB (at least 56% protection).
- The 2-month regimen of RIF and PZA has not been studied in children, is associated with unacceptable hepatotoxicity in adults, and should not be used.
- In an unpublished series on MDR-LTBI in children, 14 children (age 4 months to 13 years) in New York City were treated with 2 to 3 drugs (without fluoroquinolones) and none developed TB. Regimens included PZA, EMB, cycloserine, and ethionamide.
- In a South African series, 2 of 41 (5%) children who received 2 to 3 drug treatment (without fluoroquinolones) of MDR-LTBI developed TB, compared to 13 of 64 (20%), who did not receive treatment. The MDR-LTBI regimens consisted of some combination of the following drugs: high-dose INH (probably not effective), EMB, PZA, ofloxacin and ethionamide. The cohort consisted of 125 children contacts to MDR-TB, the median age was 27.5 months and 14 of 125 (12%) had TB disease at time of presentation, suggesting a setting of significant transmission of TB.

Fluoroquinolone Use in Children

- Fluoroquinolones are used reluctantly in children due to the observation that puppies receiving fluoroquinolones have developed arthropathy and the reports of tendon rupture in adults.
- Thousands of children have received shorter courses of fluoroquinolones without report of arthropathy.
- Ciprofloxacin has recently been licensed for treatment of urinary tract infection in children. Liquid suspensions are available for ciprofloxacin and levofloxacin.
- Thirty-two children in the South African report received ofloxacin for treatment of MDR-TB for 6 to 12 months without development of arthropathy (age 7 to 36 months).
Young children with presumed MDR-LTBI should be treated with a 2 to 3 drug regimen for 12 months, including a fluoroquinolone if appropriate. If a fluoroquinolone is used, informed consent of the parents should be obtained. Families should be counseled regarding the puppy model risks and advised to watch closely for any joint pain, swelling, or decreased range of motion.

Window Prophylaxis

Window prophylaxis is the practice of treating TST-negative contacts to TB cases with anti-tuberculosis therapy during the early phase when the TST may not yet have become positive.

- **Window prophylaxis prevents rapid progression to TB soon after infection.**
- Individuals at very high risk of progressing to TB if infected (very young children, immunocompromised contacts, close contacts to very contagious individuals) are targeted for window prophylaxis.
- Contacts should be screened by history, physical exam, 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 is repeated. If the skin test has become positive, treatment for LTBI is completed. If the skin 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).
- 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: very young children, and HIV-infected individuals with very intimate and prolonged contact with individuals likely to be contagious (smear-positive, cavitary disease, coughing source case, and TST conversions among other contacts indicating transmission of TB).

Follow-Up of MDR Contacts

- It is essential to carefully educate 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.
- Patients who have not received treatment for MDR-LTBI should be screened with symptom review, physical examination, chest radiograph and sputa, if indicated, every 3 to 6 months for 2 years.
- Given the lack of efficacy data on MDR-LTBI treatment, some experts recommend evaluation/symptom review, with or without chest radiographs, every 3 to 6 months for 2 years for contacts who have completed treatment. Special emphasis should be placed on high-risk contacts: HIV and other immunocompromised individuals, children under age 5, and TST converters.
Summary

- IGRAs may be used instead of TST in contact investigations, but the significance of conversions and reversions observed following recent exposure is unknown.

- While it is highly desirable to prevent MDR-TB cases by treatment of LTBI and use of window prophylaxis, there are limited efficacy data and a lack of expert consensus to guide clinicians.

- Treatment of LTBI should be considered particularly for patients at highest risk for progression to TB.

- Careful contact investigation is required to determine timing of infection. Patients who were previously TST positive were more likely infected with a susceptible strain and should be treated with INH.

- Recommended treatment regimens include 2 drugs to which the source case isolate is susceptible for 6 to 12 months. Some experts now recommend monotherapy with a fluoroquinolone drug to which the isolate is susceptible for select cases.

- Young children and patients who are immunocompromised should be treated with 2-drug regimens for at least 12 months.

- For some patients, clinical monitoring without treatment can be considered.

- All exposed patients should be monitored for symptoms and radiographically for at least 2 years for evidence of TB.

References


