Mycobacterial Infections

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Literature review current through June 2024
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Educational Objectives:
1. Understand guidelines for interpretation of PPD and Interferon Gamma Release Assay (IGRA) testing
2. Understand treatment options for latent TB infection
3. Understand routine treatment decisions for TB disease and NTM

Scenario 1:
Scenario 1: A 54-year-old man with a history of type 2 diabetes mellitus had a PPD placed prior to starting a new job in a healthcare setting. His PPD was interpreted as having 8 mm induration and he was referred to you for further management.

NOTE: Answers to questions 1-4 from Case 1 are based on ATS/IDSA Guidelines for Diagnosis of Tuberculosis in Adults and Children: Clin Infec Dis 2017;64(2)e1-e33.

Question 1: What size induration following PPD placement would be considered positive in this patient?

Thresholds for a positive PPD (from ATS guidelines):
- ≥5 mm is considered positive in patients with a high risk of progression to active TB:
  - Close contacts of a recent active TB case
  - HIV infection
  - Immunosuppressed (TNF-alpha inhibitors, chemotherapy, organ transplant, glucocorticoid treatment)
  - Evidence of prior TB infection (clinical and/or radiographic)
- ≥10 mm is positive with an increased risk of prior exposure to TB or an intermediate risk of progression to active TB:
  - Risk of occupational exposure to TB
  - From a TB-endemic region
  - Other high risk settings: prison, homeless
  - Comorbidities that increase risk of progression to active TB: diabetes, CKD, IV drug use, silicosis
- ≥15 mm:
  - Everyone else
In table form:

<table>
<thead>
<tr>
<th>Groups with Increased Likelihood of Infection with Mtb</th>
<th>Benefit of Therapy</th>
<th>LTBI Testing Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household contact or recent exposure of an active case</td>
<td>Yes</td>
<td>Likely to be infected</td>
</tr>
<tr>
<td>Mycobacteriology laboratory personnel</td>
<td>Not demonstrated</td>
<td>Low to Intermediate Risk of Progression</td>
</tr>
<tr>
<td>Immigrants from high burden countries (&gt;20 / 100,000)</td>
<td>Not demonstrated</td>
<td>Likely to be Infected</td>
</tr>
<tr>
<td>Residents and employees of high risk congregate settings</td>
<td>Yes</td>
<td>Unlikely to be Infected</td>
</tr>
<tr>
<td>None</td>
<td>Not demonstrated</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. From Clin Infec Dis 2017;64(2)e1-e33.

**Question 2:** In which patients would we be most concerned about a possible false-negative PPD?

A PPD is most likely to be false negative in the first 6-8 weeks after infection, in immunosuppressed patients, in the setting of overwhelming disease burden (e.g., extensive, disseminated, or miliary TB), or after recent viral or bacterial infection.

**Question 3:** What circumstances are most likely to lead to a false-positive PPD?

False positives are most likely to occur in people who have received BCG vaccination or in people with non-tuberculous mycobacterial infection.

**Question 4:** How do interferon-gamma release assays (IGRA) compare to PPD testing?

In most cases, IGRA has sensitivity equal to or greater than PPD. The same circumstances that can lead to a false-negative PPD can also cause a false negative IGRA.

IGRAs also have better specificity than PPD as IGRA use responses to antigens absent from BCG vaccine and most (but not all) non-tuberculous mycobacteria.

Other IGRA advantages compared to PPD:
- Testing performed in one visit
- Much less operator dependency
IGRA disadvantages compared to PPD:
- Cost
- Need for phlebotomy
- More variability with respect to test reproducibility

IGRA is recommended over PPD except in the highest risk patients, where there is no preference and dual testing may be considered.

<table>
<thead>
<tr>
<th>Group</th>
<th>Testing Strategy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely to be Infected</td>
<td>Adults: IGRA OR TST</td>
<td>Prevalence of BCG vaccination</td>
</tr>
<tr>
<td>High Risk of Progression</td>
<td>Consider dual testing where a positive result from</td>
<td>Expertise of staff and/or laboratory</td>
</tr>
<tr>
<td>(TST ≥ 5mM)</td>
<td>either result would be considered positive</td>
<td>Test availability</td>
</tr>
<tr>
<td></td>
<td>Children ≤ 5 years of age</td>
<td>Patient perceptions</td>
</tr>
<tr>
<td></td>
<td>Preferred: TST</td>
<td>Staff perceptions</td>
</tr>
<tr>
<td></td>
<td>Acceptable: IGRA OR TST</td>
<td>Programmatic concerns</td>
</tr>
<tr>
<td></td>
<td>Consider dual testing where a positive result from</td>
<td></td>
</tr>
<tr>
<td></td>
<td>either would be considered positive¹</td>
<td></td>
</tr>
<tr>
<td>Likely to be Infected</td>
<td>Preferred: IGRA where available</td>
<td></td>
</tr>
<tr>
<td>Low to Intermediate Risk of</td>
<td>Acceptable: IGRA or TST</td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TST ≥ 10mM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely to be Infected</td>
<td>Testing for LTBI is not recommended</td>
<td></td>
</tr>
<tr>
<td>(TST &gt; 15mM)</td>
<td>If necessary:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preferred: IGRA where available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For serial testing:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider repeat or dual testing where a negative result</td>
<td></td>
</tr>
<tr>
<td></td>
<td>from either would be considered negative²</td>
<td></td>
</tr>
</tbody>
</table>

1. Performing a second diagnostic test when the initial test is negative is a strategy to increase sensitivity. This may reduce specificity, but the panel decided that this is an acceptable tradeoff in situations in which the consequences of missing LTBI (i.e., not treating individuals who may benefit from therapy) exceed the consequences of inappropriate therapy (i.e., hepatotoxicity).

2. Performing a confirmatory test following an initial positive result is based upon the evidence that false-positive results are common among individuals who are unlikely to be infected with Mtb and the committee’s presumption that performing a second test on those whose initial test was positive will help identify initial false-positive results.

Figure 2. From Clin Infec Dis 2017;64(2):e1-e33.

Question 5: In a patient with positive PPD or IGRA (assuming no evidence of active TB disease on evaluation by both history and CXR), what treatment regimens are currently recommended for treatment of latent TB infection (LTBI)?

Shorter course rifamycin based regimens are preferred over longer course isoniazid monotherapy. These rifamycin based regimens are non-inferior to isoniazid for 9 months and are preferred based on effectiveness, safety (less hepatotoxicity), and favorable treatment completion rates.

The following is from the 2020 CDC and National Tuberculosis Controllers Association Guidelines for the treatment of Latent Tuberculosis Infection (MMWR Recomm Rep. 2020 Feb 14; 69(1): 1–11).
In patients with a TB-positive contact with known resistance to one or more of the antibiotics, the established resistance pattern should inform treatment decisions.

It is important to consider potential toxicity and adherence when choosing a regimen. Patients should abstain from alcohol on isoniazid. Use of rifampin or rifapentine can be limited by drug-drug interactions. Peripheral neuropathy can occur with INH regimens and can be prevented with use of pyridoxine in higher risk patients.

**Scenario 2:**
Ms. R is a 66-year-old woman with a history of kidney transplantation (on prednisone and tacrolimus). She has been PPD positive since childhood, never treated. She has a chronic cough productive of small amounts of sputum, with mild bronchiectasis and calcified (but not enlarged) hilar lymph nodes on CT Chest. PFTs are normal. A sputum culture 5 years ago had low growth of MAC, but she was stable clinically and radiographically; she and her doctors agreed on a watchful waiting approach.

Sputum production increased over a 6-week period, followed by an episode of frank hemoptysis and pleuritic chest pain. She lost 3 lbs but had no fevers, chills, or night sweats. No known sick contacts. She was admitted to her local hospital where 3 sputum samples were AFB smear negative. Her symptoms improved and she was sent home.

The Department of Health called her 3 weeks later because 1 of the 3 sputum samples was positive for TB.

**Question 6:** What should her initial management be considering her changing clinical picture and culture data?

Given her clinical picture at this point, it is difficult to determine whether the primary pathogen is TB or MAC, although TB seems more likely given that it is the new finding in the setting of her acute presentation. With her immunosuppressed status, it is reasonable to cover both while awaiting repeat sputum AFB x3.

Discussion of MAC treatment is addressed in later questions. Treatment of multi-drug-resistant (MDR) TB or extensively drug-resistant (XDR) TB is a complicated topic that could warrant its own session, so we will limit the focus to sensitive strains of TB.

For TB, the traditional initial regimen (intensive phase) is daily isoniazid/B6, ethambutol, rifampin, and pyrazinamide daily (or 5 times per week) for 8 weeks, followed by a
maintenance phase of isoniazid and rifampin daily (or 5 times per week) for 18 weeks. Directly observed therapy (DOT, coordinated by the Department of Health) is recommended. In circumstances where it is more difficult to arrange, 3x/weekly therapy can be used, although there is a lower likelihood of treatment response if this is done. (From ATS/IDSA guideline on Treatment of Drug-Susceptible Tuberculosis: Clin Infec Dis 2016; 63(7) 853-67).

A four-month regimen for treatment of drug susceptible pulmonary TB in which rifapentine is substituted for rifampin and moxifloxacin is substituted for ethambutol was found to be non-inferior to the traditional regimen (N Engl J Med. 2021;384(18):1705). In 2022 the WHO and CDC issued interim guidance that endorsed this regimen as a treatment option for adults with drug-susceptible pulmonary TB.

Our patient was hospitalized. 3 more sputum AFB cultures were sent, and she was started on isoniazid/B6, ethambutol, pyrazinamide, azithromycin, and moxifloxacin to cover both TB and MAC. She was not given rifampin or rifabutin because cytochrome P450 interacts with tacrolimus.

**Scenario 2 Update:**
The Department of Health called 6 weeks into treatment. They discovered that the DNA probe on her sputum culture was identical to another patient. Since only 1 of her samples was positive for TB and subsequent cultures of hers have not grown TB while cultures from the other patient have repeatedly grown the same TB isolate, the DOH thinks her positive sample was a mislabeled sample from the other patient. There is no evidence that she had ever been exposed to the other patient.

Two of the three sputum AFB cultures sent when she was started on TB therapy are positive for low growth of MAC.

*NOTE: Answers to the remaining questions from Case 2 are based on ATS/ERS/ESCMID/IDSA Guidelines on Treatment of Nontuberculous Pulmonary Disease, Clin Infect Dis. 2020;71(4):e1.*

**Question 7: If we stop TB treatment, should we stop or continue MAC treatment? What are the diagnostic criteria for MAC? What standard antibiotics do we use to treat MAC?**

Members of the mycobacterium avium complex (MAC) are the most common nontuberculous mycobacteria pathogens. The three predominant species within the complex are M. Avium, M. Intracellulare, and M. chimera.

Diagnostic criteria for MAC (from ATS guidelines):

**Clinical:**
- Pulmonary or systemic symptoms **AND**

**Radiographic:**
- Radiographic findings consistent with MAC (bronchiectasis with small nodules, and/or cavities) **AND**

**Microbiologic:**
- Positive culture results from at least two expectorated samples, OR
- Positive culture results from at least one bronchial wash or BAL, OR
- Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) along with positive tissue culture for AFB
Other Comments in ATS Guidelines:
- Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination (this is becoming increasingly common as DNA testing of samples can now identify many NTM species for which there is not good clinical data).
- Patients who are suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
- Making the diagnosis of NTM does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients and is often based on the clinical presentation of the patient. “Watch and wait” may be appropriate for some patients and these patients should be closely observed with interval clinical evaluations sputum cultures, and imaging. However, the recommendation is to treat once the disease is established in patients with either cavitary lung disease or smear positive sputum.

Updated treatment guidelines for NTM were published in 2020 (Daley Clin Inf Dis 2020). The recommended treatment regimen for nodular bronchiectatic MAC is azithromycin (or clarithromycin), rifampin (or rifabutin), and ethambutol. For most patients with nodular bronchiectatic disease, dosing antibiotics 3 times weekly is recommended. Intermittent dosing has been shown to have similar sputum conversion rates as daily therapy and is better tolerated. However, in patients with severe nodular bronchiectatic disease and in patients with fibrocavitary disease, daily dosing is warranted. In addition, for fibrocavitary, severe, and/or macrolide-resistant disease, IV aminoglycoside therapy should be included in the initial treatment regimen (amikacin or streptomycin).

<table>
<thead>
<tr>
<th></th>
<th>Thrice Weekly dose:</th>
<th>Daily Dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>500-600 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>(Clarithromycin)</td>
<td>1000 mg</td>
<td>1000 mg (or 500 mg BID)*</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>(Rifabutin)</td>
<td></td>
<td>150-300 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>25 mg/kg</td>
<td>15 mg/kg</td>
</tr>
</tbody>
</table>

* May need to reduce Clarithromycin dose to 500 mg daily in older (>70) or smaller (<50 kg) patients.

**Question 8: Do I need antibiotic susceptibility testing to guide my selection of a MAC regimen?**

ATS guidelines suggest antibiotic susceptibility testing for macrolides and amikacin to guide treatment. There is some controversy with respect to antibiotic susceptibility testing, as there is not a clear correlation between *in vitro* susceptibility and clinical response for other antimycobacterial drugs.

There is evidence that *in vitro* susceptibility testing to clarithromycin does correlate with clinical response to clarithromycin or azithromycin. Wild-type MAC is almost 100% sensitive to macrolides, though most labs do not routinely perform susceptibility testing on MAC specimens, and this is a send-out test and often requires a call to the Microbiology Lab to request it specifically.)
Treatment failure is defined as failure to convert cultures to negative at 6 months of guideline recommended therapy. In this setting, ALIS (Amikacin Liposome Inhalation Suspension) 590mg daily should be added to the treatment regimen to improve the likelihood of sputum conversion. Additional second-line and third-line antibiotics that might be helpful when patients don’t tolerate first-line therapy or have inadequate treatment response:

- Moxifloxacin
- Linezolid or Tedizolid
- Clofazimine (not on the market in the U.S., can obtain it through the FDA)
- Nebulized Amikacin (using the IV form in a nebulizer; not recognized by some insurances)

If you need to change MAC therapy for lack of treatment response, remember that you need to change multiple drugs simultaneously. Changing only one drug at a time makes it easier for the bug to develop resistance to the newly added antibiotic.

For macrolide-sensitive nodular bronchiectatic MAC disease, culture conversion rates have been shown to be 85% after an average of 4 months of guideline-based treatment. However, there is also a >50% rate of microbiologic relapse or reinfection.

**Question 9: What monitoring needs to be done on MAC therapy?**

For clinical response: symptoms, monthly AFB cultures. Imaging may or may not be helpful as some of the changes associated with MAC infection will be chronic/permanent even with treatment response. With effective therapy, there should be some clinical response by the 3-6-month range and negative culture data by 6-12 months. If these are not happening, further investigation (including susceptibility testing or even drug levels) may be warranted.

Adverse reactions are common:

- GI intolerance- macrolides, ethambutol, rifampin, rifabutin, clofazimine
- Abnormal liver function tests- macrolides, rifampin, rifabutin, moxifloxacin
- Low WBC- rifampin, rifabutin
- Impaired visual acuity or color vision- ethambutol
- Decreased auditory function- aminoglycosides (systemic or inhaled) or azithromycin
- Vestibular toxicity- aminoglycosides (systemic or inhaled)
- Decreased renal function- aminoglycosides (systemic or inhaled)
- Peripheral neuropathy- ethambutol, clofazamine, aminoglycosides
- Prolonged QTc- macrolides, fluoroquinolones, clofazamine

Thus, regular monitoring of CBC and LFTs every 1-2 months as well as visual acuity and color discrimination testing, and audiometry is warranted.

**Question 10: How long should therapy be continued?**

Surveillance AFB cultures should be performed while on therapy, ideally once a month. This may not be possible in patients who cannot expectorate sputum or produce adequate induced sputum samples. ATS recommendations are to continue treatment for one year after cultures convert to negative.

In practice, many other factors play a role in deciding when to stop, including the patient’s tolerance of the medications, monitoring of toxicity, and clinical/radiographic improvement. If a patient cannot produce samples for AFB culture, guidelines do not recommend surveillance bronchoscopy to monitor treatment response.
Question 11: What approach should we use in treating *Mycobacterium abscessus* infections?

The optimal regimen for treating *M. abscessus* is not known. There is growing evidence that different subspecies within *M. abscessus* (subspecies *abscessus*, *bolletii*, and *masilliense*) have different rates of macrolide resistance. ATS/IDSA guidelines recommend:

For *M. abscessus* disease caused by strains without mutational or inducible macrolide resistance (typically *masilliense*), treatment should be with a macrolide and at least two other active drugs. However, it should be noted that strains of *M. abscessus* have an erythromycin ribosome methyltransferase (*erm*) gene that can lead to inducible macrolide resistance; i.e., the specimen will appear sensitive to macrolides initially, but will then develop macrolide resistance by day 14. Many labs know to test for this and will not report macrolide susceptibility until they confirm that there is not inducible resistance. However, not all labs know to do this so you should proceed with caution.

The following table shows recommended treatment regimens for both macrolide susceptible and resistant disease (Chest. 2022 Jan;161(1):64-75).

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**Scenario 3:**

Scenario 3: Mr. T is an 80-year-old man, former smoker with type 2 diabetes mellitus, hypertension, and hypothyroidism, who has had daily coughing productive of dark yellow sputum for more than a year. He has not had hemoptysis or dyspnea. He denies fevers, chills, or night sweats, but has lost 50 lbs over 15 months. His CT Chest shows severe emphysema and a large left upper lobe cavity. On his initial visit to pulmonary clinic, 3 sputum AFB cultures are ordered. 2 of the 3 samples are smear positive for AFB, and all 3 are growing Mycobacterium abscessus, subspecies abscessus.
Question 12: Another relatively common NTM infection is *M. kansasii*. What is a standard treatment regimen for this bug?

The suggested regimen is the same as for *Mycobacterium avium*:
- Azithromycin 250-500 mg daily (or Clarithromycin 1000 mg daily)
- Rifampin 450 mg (if <45 kg) or 600 mg (if >45 kg) daily
- Ethambutol 15 mg/kg daily

Isoniazid is an alternative option for patients unable to tolerate macrolides. All patients should be treated for at least 12 months.

References: