Mycobacterial Infections

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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 and NTM

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 TB case
- Immunosuppressed
- Evidence of prior TB infection (clinical and/or radiographic)
- Receiving TNF-αinhibitors
- Silicosis

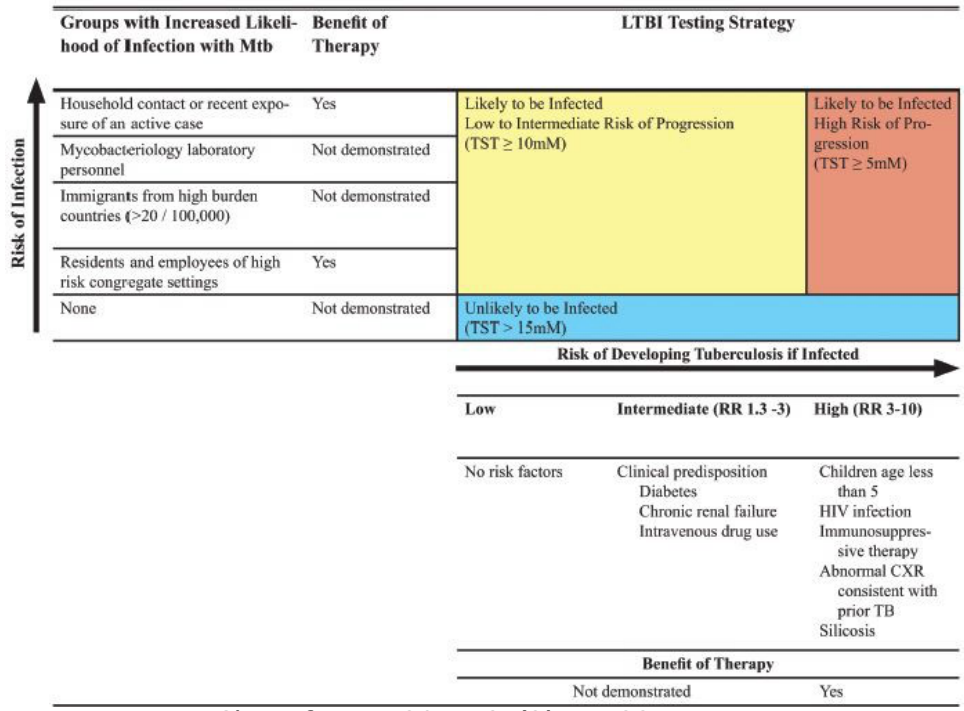
≥10 mm is positive with an increased risk of prior exposure to TB or an intermediate risk of progression to active TB:

- 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

≥15 mm:

- Everyone else

In table form:



Groups with Increased Likelihood of Infection with Mtb	Benefit of Therapy	LTBI Testing Strategy
Household contact or recent exposure of an active case	Yes	Likely to be Infected Low to Intermediate Risk of Progression (TST ≥ 10mM)
Mycobacteriology laboratory personnel	Not demonstrated	
Immigrants from high burden countries (>20 / 100,000)	Not demonstrated	
Residents and employees of high risk congregate settings	Yes	
None	Not demonstrated	Unlikely to be Infected (TST > 15mM)

Risk of Infection

Likely to be Infected
High Risk of Progression
(TST ≥ 5mM)

Risk of Developing Tuberculosis if Infected

Low	Intermediate (RR 1.3 -3)	High (RR 3-10)
No risk factors	Clinical predisposition Diabetes Chronic renal failure Intravenous drug use	Children age less than 5 HIV infection Immunosuppressive therapy Abnormal CXR consistent with prior TB Silicosis

Benefit of Therapy	
Not demonstrated	Yes

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

<u>Question 2:</u> 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.

<u>Question 3:</u> 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.

<u>Question 4:</u> How do interferon-gamma release assays (IGRA) compare to PPD testing?

In most cases, IGRAs have sensitivity equal to or greater than PPD.

IGRAs also have better specificity than PPD as IGRAs 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

Group	Testing Strategy	Considerations
Likely to be Infected **High** Risk of Progression (TST ≥ 5mM)	**Adults** **Acceptable**: IGRA OR TST Consider dual testing where a positive result from either result would be considered **positive** **Children ≤ 5 years of age** **Preferred**: TST **Acceptable**: IGRA OR TST Consider dual testing where a positive result from either would be considered **positive**[1]	Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns
Likely to be Infected **Low** to **Intermediate** Risk of Progression (TST ≥ 10mM)	**Preferred**: IGRA where available **Acceptable**: IGRA or TST	
Unlikely to be Infected (TST > 15mM)	**Testing for LTBI is not recommended** **If necessary:** **Preferred:** IGRA where available. **Acceptable**: Either IGRA OR TST **For serial testing**: **Acceptable**: Either IGRA OR TST Consider repeat or dual testing where a negative result from either would be considered **negative**[2]	

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 both 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

<u>Question 5:</u> In a patient with positive PPD or IGRA (assuming no evidence of active TB infection on evaluation), what treatment regimens are currently recommended for treatment of latent TB infection (LTBI)?

The following is from the 2018 World Health Organization guideline on Latent Tuberculosis Infection (https://apps.who.int/iris/bitstream/handle/10665/331525/9789240002906-eng.pdf). The WHO used to identify 6 months of Isoniazid as the standard regimen, with other regimens considered to be alternatives, but now lists the following regimens as equally valid:

- Isoniazid daily for 6 or 9 months
- Rifapentine and Isoniazid weekly for 3 months
- Rifampin and Isoniazid daily for 3 months

The WHO lists these as alternative options for LTBI treatment:

- Rifampin daily for 4 months
- Rifapentine and Isoniazid daily for 1 month

Rifampin daily for 4 months was shown to be noninferior to isoniazid for 9 months for treatment of LTBI, with fewer adverse events and higher completion rates, and is now typically the recommended first-line treatment regimen for LTBI (Menzies NEJM 2018). CDC guidelines from 2020 (MMWR Recomm Rep. 2020 Feb 14; 69(1): 1–11) consider these regimens to be preferred:

- Rifampin daily for 4 months
- Rifapentine and Isoniazid weekly for 3 months
- Rifampin and Isoniazid daily for 3 months

The CDC lists Isoniazid for 6 or 9 months as an alternative option. The explained preference for Rifampicin-based regimens are efficacy, favorable treatment completion rates, and relatively low hepatotoxicity rates.

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

Other alternate regimens:

- Isoniazid/B6 300 mg daily for 9 months
- Isoniazid/B6 300 mg daily for 6 months

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 in light of 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 recommended 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).

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.

<u>Question 7:</u> 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?

Diagnostic criteria for MAC (from ATS guidelines):

Clinical/Radiographic:

- Appropriate clinical picture,
  AND
- Radiographic findings consistent with MAC (bronchiectasis with small nodules, and/or cavities),
  AND
- Exclusion of other diagnoses (including TB)

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.
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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.

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)

	Thrice Weekly dose:	Daily Dose:
Azithromycin	500-600 mg	250 mg
(Clarithromycin)	1000 mg	1000 mg (or 500 mg BID)*
Rifampin	600 mg	600 mg
(Rifabutin)		150-300 mg
Ethambutol	25 mg/kg	15 mg/kg

** 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?

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 all 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, so most labs do not routinely perform susceptibility testing on MAC specimens. The guideline update in 2020 does favor using antibiotic-susceptibility testing to guide decisions about macrolides and aminoglycosides (note: this is a send-out test and we need to call the Microbiology Lab to request it specifically).

We can request that the lab send MAC isolates to National Jewish (Denver) or UT-Northeast (Tyler, TX) for susceptibility testing. UT-Northeast only tests susceptibility to Clarithomycin and Amikacin, so it can help to specify to the lab if you want susceptibility testing against a broader range of antibiotics. Even though there isn't great correlation between *in vitro* testing and clinical response, having the data might be helpful to guide which second-line or third-line agents to try.

For patients who remain culture positive after 6 months of guideline-based therapy, ALIS (Amikacin Liposome Inhalation Suspension) 590mg daily should be added to the treatment regimen. 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., need to get 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.

<u>Question 9:</u> 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) may be warranted.

For toxicity:

Macrolides -LFTs
Rifampin - LFTs
Rifabutin - LFTs, CBC (leukopenia and thrombocytopenia), visual acuity testing (uveitis)
Ethambutol - LFTs, visual acuity testing, red-green color discrimination (optic neuritis)
Amikacin - BUN/Cr, audiometry

<u>Question 10:</u> 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.

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.

<u>Question 11:</u> 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 vs. subspecies 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 massiliense), 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.

For M. abscessus disease caused by strains with macrolide resistance (typically abscessus or bolettii), an initial regimen should include at least 4 active drugs. A macrolide can be added for its immunomodulatory properties but should not count as one of the 4 active drugs.

Drugs used for M. abscessus include:

IV: Amikacin, Imipenem (or Cefoxitin), Tigecycline
Oral: Azithromycin (or Clarithromycin), Clofazimine, Linezolid
Inhaled: Amikacin

<u>Question 12:</u> 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 in patients unable to tolerate macrolides. All patients should be treated for at least 12 months.

References:
1. Lewinsohn et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children Clin Inf Dis 2017; 64 (2) e1.
2. Menzies et al, Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. NEJM 2018; 379 440.
3. Daley et al, Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline, Clin Inf Dis 2020; 71 (4): e1.