Mycobacterial Infections

An APCCMPD Ambulatory Care Curriculum Teaching Script

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Mycobacterial Infections

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.

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

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

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

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

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

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 Mycobacterium avium complex (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 clinical picture and culture data?

Scenario 2 (Continued):

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 Mycobacterium avium complex (MAC).

Question 7: What are the diagnostic criteria for MAC?

Question 8: What is the approach to treatment of MAC, and what is the success rate?

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

Question 10: How long should therapy be continued?

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.

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Post-script Questions:

1. A 32-year-old woman from the Philippines presents for a pre-employment evaluation. She is pursuing work as a caregiver in a long-term care facility, and testing for LTBI is required. She immigrated to the United States 2 years ago and received BCG vaccination as an infant. She has no symptoms and her physical examination is normal. Which of the following is the most appropriate initial test for LTBI in this patient?

    A. Tuberculin skin test (TST) because it is more sensitive than IGRA in BCG-vaccinated individuals

    B. Interferon-gamma release assay (IGRA) because it is more specific than TST in BCG-vaccinated individuals

    C. Both TST and IGRA simultaneously to maximize sensitivity

    D. No testing is indicated because she is asymptomatic

2. A 32-year-old woman presents with a 4-week history of productive cough, fevers, and 5 kg weight loss. She recently immigrated from the Philippines. Chest X-ray shows a left upper lobe infiltrate without cavitation. Sputum acid-fast bacilli smear is positive, and nucleic acid amplification testing (NAAT) is positive for *Mycobacterium tuberculosis* complex with no rifampin resistance detected. She is HIV-negative, not pregnant, has normal liver function tests, and takes no other medications. Which of the following statements about treatment options for this patient is most accurate?

    A. The 6-month regimen of isoniazid, rifampin, pyrazinamide, and ethambutol followed by isoniazid and rifampin (2HRZE/4HR) is superior in efficacy to the 4-month rifapentine-moxifloxacin regimen

    B. The 4-month regimen of isoniazid, rifapentine, pyrazinamide, and moxifloxacin followed by isoniazid, rifapentine, and moxifloxacin (2HPZM/2HPM) has been shown to be noninferior to the standard 6-month regimen and is an appropriate option for this patient

    C. The 4-month regimen of isoniazid, rifapentine, pyrazinamide, and moxifloxacin should only be used in patients with drug-resistant tuberculosis

    D. The 4-month rifapentine-moxifloxacin regimen is appropriate for all patients with tuberculosis, including those with extrapulmonary disease and HIV coinfection on antiretroviral therapy

3. A 68-year-old woman with bronchiectasis was diagnosed with *Mycobacterium avium* complex (MAC) pulmonary disease and started on azithromycin, rifampin, and ethambutol three times weekly. She has sputum cultures performed monthly for monitoring, and they continue to grow MAC after 6 months of therapy. Repeat susceptibility testing shows the isolate remains susceptible to macrolides and amikacin. She has no hearing impairment or renal dysfunction. Which of the following is the most appropriate next step in management?

    A. Continue the current 3-drug regimen of azithromycin, rifampin, and ethambutol for an additional 6 months

    B. Discontinue treatment and observe, as MAC pulmonary disease is often self-limited

    C. Add amikacin liposome inhalation suspension (ALIS) to the current regimen

    D. Switch to a fluoroquinolone-based regimen with moxifloxacin, ethambutol, and rifampin

Mycobacterial Infections

Educational Objectives:

1. Understand guidelines for interpretation of purified protein derivative (PPD) and Interferon Gamma Release Assay (IGRA) testing
2. Understand treatment options for latent tuberculosis (TB) infection (LTBI)
3. Understand routine treatment decisions for TB disease and non-tuberculous mycobacteria (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.

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

Thresholds for a positive PPD recommended by the Centers for Disease Control and Prevention (CDC) are as follows (CDC, 2025):

≥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

The thresholds reflect the risk of exposure and the risk of progression to tuberculosis disease, which is characterized by clinical manifestations (e.g. cough, fever) result from active bacterial replication, tissue damage, and inflammation (Shah & Dorman, 2021).

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

A PPD is most likely to be falsely negative in the first 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 (CDC, 2025; Sanofi Pasteur Inc., 2021).

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 Bacillus Calmette-Guérin (BCG) vaccination or in people with non-tuberculous mycobacterial infection (CDC, 2025; Sanofi Pasteur, Inc. 2021). For individuals who have been vaccinated with the BCG vaccine, an interferon gamma release assay is the preferred method of testing (CDC, 2025).

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

In most cases, IGRAs have 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 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
- Less subjective interpretation

IGRA disadvantages compared to PPD:
- Cost
- Need for phlebotomy
- Rely on lab equipment, expertise, reagents

IGRA is recommended over PPD except in the highest risk patients, where there is no preference and dual testing may be considered (Shah & Dorman, 2021; Lewinsohn et al., 2017).

Figure. Testing Recommendations for Diagnosis of LTBI

Group	Testing Strategy	Considerations
Likely infected **High** risk of progression TST ≥ 5mm	IGRA or TST Consider dual testing where either positive result considered **positive**	BCG vaccination prevalence Staff/lab expertise Test availability Patient and staff perceptions Program concerns
Likely infected **Low/intermediate** risk of progression TST≥10mm	IGRA preferred	
Unlikely infected TST≥15mm	LTBI testing NOT recommended If necessary, IGRA preferred Consider repeat or dual testing where negative result from either considered **negative**	

Adapted from: Lewinsohn et al., 2017.

Question 5: In a patient with positive PPD or IGRA (assuming no evidence of active TB disease on evaluation by both history and chest x-ray), 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.

Table 1. Recommendations for Regimens to Treat LTBI

Priority rank	**Regimen**
Preferred	3 months isoniazid + rifapentine once weekly
Preferred	4 months rifampin daily
Preferred	3 months isoniazid plus rifampin daily
Alternative	6 months isoniazid daily
Alternative	9 months isoniazid daily

Adapted from: Burgos et al., 2020

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 (Burgos et al., 2020; Shah & Dorman, 2021).

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 Mycobacterium avium complex (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 clinical picture and culture data?

Her clinical picture of subacute infectious symptoms with positive culture for TB warrants initiation of treatment for active TB disease.

For TB, the traditional initial regimen (intensive phase) was daily isoniazid/Vitamin B6

(pyridoxine), ethambutol, rifampin, and pyrazinamide for 8 weeks, followed by a maintenance phase of isoniazid and rifampin daily for 18 weeks (Nahid et al., 2016). 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, and this shorter regimen is now recommended as an alternative for the treatment of adults with drug-susceptible pulmonary TB (Dorman et al., 2021; Jereb, 2025; Saukonnen et al., 2025).

Our patient was hospitalized. Three more sputum AFB cultures were sent, and she was started on isoniazid/Vitamin B6, rifapentine, pyrazinamide, and moxifloxacin for TB.

Scenario 2 (Continued):

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 Mycobacterium avium complex (MAC).

Question 7: What are the diagnostic criteria for 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 (Daley et al., 2020):

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

Additional recommendations from the ATS/IDSA guideline (Daley et al., 2020) :
- 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 most patients once the disease is established, and especially patients with either cavitary lung disease or smear positive sputum.

Question 8: What is the approach to treatment of MAC, and what is the success rate?

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) (Daley et al., 2020).

Table 2. Dosing for Drugs that Treat Pulmonary MAC Infection

	Thrice Weekly dose:	Daily Dose:
Azithromycin	500 mg	250-500 mg
(Clarithromycin)	500 mg bid	500 mg bid
Rifampin	450-600 mg	600 mg
(Rifabutin)	300 mg	150-300 mg
Ethambutol	25 mg/kg	15 mg/kg

Adapted from: Daley et al, 2020

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 (Daley et al., 2020).

Treatment failure is defined as failure to convert cultures to negative at 6 months of guideline recommended therapy. In this setting, Amikacin Liposome Inhalation Suspension(ALIS) 590mg daily should be added to the treatment regimen to improve the likelihood of sputum conversion.

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

Patients should be monitored at routine intervals for clinical and microbiological response to therapy. Sputum samples should be obtained every 1-2 months in order to define the timepoint of culture conversion. Chest imaging may also be helpful to define radiographic

response to therapy, but findings may be variable in the setting of underlying lung disease (Daley et al., 2020).

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 ECG for QT-c, visual acuity and color discrimination testing, and audiometry is warranted (Daley et al., 2020).

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 has a sustained improvement in their symptoms and cannot produce samples for AFB culture, guidelines do not recommend surveillance bronchoscopy to monitor treatment response (Daley et al., 2020).

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 (Wallace et al., 2014).

AI Disclosure:

Generative AI was used to assist with formatting AMA to APA style and drafting post-script questions. The associate editor independently reviewed, edited, and verified all content for accuracy, relevance, and alignment with institutional standards.

Post-script Questions:

1. A 32-year-old woman from the Philippines presents for a pre-employment evaluation. She is pursuing work as a caregiver in a long-term care facility, and testing for LTBI is required. She immigrated to the United States 2 years ago and received BCG vaccination as an infant. She has no symptoms and her physical examination is normal. Which of the following is the most appropriate initial test for LTBI in this patient?

A. Tuberculin skin test (TST) because it is more sensitive than IGRA in BCG-vaccinated individuals

B. Interferon-gamma release assay (IGRA) because it is more specific than TST in BCG-vaccinated individuals

C. Both TST and IGRA simultaneously to maximize sensitivity

D. No testing is indicated because she is asymptomatic

Correct Answer: B

Explanation:

IGRA is preferred over TST in this BCG-vaccinated patient because IGRAs have superior specificity in individuals with prior BCG vaccination. The ATS/IDSA/CDC guidelines recommend performing an IGRA rather than TST in individuals ≥5 years old who are likely to be infected with *M. tuberculosis*, have a history of BCG vaccination, or are unlikely to return for TST reading.

2. A 32-year-old woman presents with a 4-week history of productive cough, fevers, and 5 kg weight loss. She recently immigrated from the Philippines. Chest X-ray shows a left upper lobe infiltrate without cavitation. Sputum acid-fast bacilli smear is positive, and nucleic acid amplification testing (NAAT) is positive for *Mycobacterium tuberculosis* complex with no rifampin resistance detected. She is HIV-negative, not pregnant, has normal liver function tests, and takes no other medications. Which of the following statements about treatment options for this patient is most accurate?

A. The 6-month regimen of isoniazid, rifampin, pyrazinamide, and ethambutol followed by isoniazid and rifampin (2HRZE/4HR) is superior in efficacy to the 4-month rifapentine-moxifloxacin regimen

B. The 4-month regimen of isoniazid, rifapentine, pyrazinamide, and moxifloxacin followed by isoniazid, rifapentine, and moxifloxacin (2HPZM/2HPM) has been shown to be noninferior to the standard 6-month regimen and is an appropriate option for this patient

C. The 4-month regimen of isoniazid, rifapentine, pyrazinamide, and moxifloxacin should only be used in patients with drug-resistant tuberculosis

D. The 4-month rifapentine-moxifloxacin regimen is appropriate for all patients with tuberculosis, including those with extrapulmonary disease and HIV coinfection on antiretroviral therapy

Correct Answer: B

Explanation:

The 4-month rifapentine-moxifloxacin regimen (2HPZM/2HPM) was demonstrated to be noninferior to the standard 6-month regimen. Based on this evidence, the 2025 ATS/CDC/ERS/IDSA guidelines provide a **conditional recommendation** for the 4-month regimen as an acceptable alternative for eligible patients ≥12 years with drug-susceptible pulmonary TB

Why other options are incorrect:

- **Option A** is incorrect because the trial demonstrated noninferiority, not superiority of the 4-month compared to the 6-month regimen. Both regimens have equivalent efficacy.

- **Option C** is incorrect because the 4-month rifapentine-moxifloxacin regimen is specifically for drug-susceptible TB; drug-resistant TB requires different regimens.

- **Option D** is incorrect because the 4-month regimen has important limitations. It is **not recommended** for patients with extrapulmonary TB (who were excluded from the trial), and significant drug-drug interactions between rifapentine and non-efavirenz-based antiretroviral therapy limit its use in many patients with HIV coinfection.[2][1]

3. A 68-year-old woman with bronchiectasis was diagnosed with *Mycobacterium avium* complex (MAC) pulmonary disease and started on azithromycin, rifampin, and ethambutol three times weekly. She has sputum cultures performed monthly for monitoring, and they continue to grow MAC after 6 months of therapy. Repeat susceptibility testing shows the isolate remains susceptible to macrolides and amikacin. She has no hearing impairment or renal dysfunction. Which of the following is the most appropriate next step in management?

A. Continue the current 3-drug regimen of azithromycin, rifampin, and ethambutol for an additional 6 months

B. Discontinue treatment and observe, as MAC pulmonary disease is often self-limited

C. Add amikacin liposome inhalation suspension (ALIS) to the current regimen

D. Switch to a fluoroquinolone-based regimen with moxifloxacin, ethambutol, and rifampin

Correct Answer: C

Explanation:

This patient has **treatment-refractory MAC pulmonary disease**, defined as remaining sputum culture positive after at least 6 months of guideline-based therapy. The 2020 ATS/ERS/ESCMID/IDSA guidelines provide a **strong recommendation** (moderate certainty in estimates of effect) that ALIS should be added to the treatment regimen in patients who have failed therapy after at least 6 months of guideline-based therapy.

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