

Mycobacterial Infections in HIV

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Learning Objectives

- List the most common mycobacterial infections -- including, in particular, non-tuberculous (non-TB) mycobacterial infections -- occurring among persons with HIV infection.
- Describe the clinical manifestations of mycobacterial infections (especially those due to non-TB mycobacteria) among persons with HIV infection, including clinical manifestations associated with immune reconstitution inflammatory syndrome (IRIS).
- List the recommended treatment regimens for mycobacterial infections (especially non-TB mycobacterial infections) among HIV-infected persons, with particular emphasis on drug-drug interactions between antimycobacterial and antiretroviral medications, respectively.

Classification of mycobacterial species causing human disease

M. tuberculosis complex	Slowly growing nontuberculous mycobacteria
M. tuberculosis	Photochromogens
M. bovis	M. kansasii
M. africanum	M. marinum
M. microti	Scotochromogens
M. canetti	M. goodii
M. leprae	M. gordonae
Rapidly growing nontuberculous mycobacteria	M. scrofulaceum
M. fortuitum complex	Nonchromogens
M. fortuitum	M. avium complex
M. peregrinum	M. avium
M. porcinum	M. intracellulare
M. chelonae	M. terrae complex
M. abscessus	M. ulcerans
M. abscessus	M. xenopi
M. bolletii (previously M. massiliense)	M. simiae
M. smegmatis	M. malmoense
M. mucogenicum	M. szulgai
	M. asiaticum
	M. haemophilum

NONTUBERCULOUS MYCOBACTERIA (NTM)

Definition

Mycobacterial species other than those belonging to:

The Mycobacterium tuberculosis (Mtb) complex:

- M. tuberculosis

- M. bovis: pyrazinamide- (PZA-) resistant

- M. africanum

- M. microti

- M. canetti

- M. leprae

NONTUBERCULOUS MYCOBACTERIA (NTM)

General Characteristics

Generally free-living organisms that are ubiquitous in the environment, e.g., *M. gordonae* (“the tap-water bacillus”)

>140 NTM species identified

NONTUBERCULOUS MYCOBACTERIA (NTM)

Clinical Syndromes in Humans (1)

1. Pulmonary disease: chronic lung infections account for $\leq 90\%$ of patient encounters due to NTM

- Especially in:
 - older persons with or without underlying lung disease
 - patients with cystic fibrosis
- Caused mostly by:
 - *M. avium* complex (MAC): **MAC pulmonary disease uncommon in persons with HIV/AIDS**
 - *M. kansasii*
- Other species that cause lung disease include:
 - *M. abscessus*
 - *M. fortuitum*
 - *M. xenopi*: more common in Europe, Great Britain, and eastern Canada
 - *M. malmoense*: more common in Scandinavia and Northern Europe
 - *M. szulgai*
 - *M. simiae*

Clinical and microbiologic criteria for diagnosing nontuberculous mycobacterial (NTM) lung disease

Clinical (both required)
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules
and
2. Appropriate exclusion of other diagnoses
Microbiologic
1. Positive culture results from at least two separate expectorated sputum samples. If the results from the initial sputum samples are nondiagnostic, consider repeat sputum AFB smears and cultures.
or
2. Positive culture result from at least one bronchial wash or lavage
or
3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM
Additional considerations
<ul style="list-style-type: none">• Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination• Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded• Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients

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NONTUBERCULOUS MYCOBACTERIA (NTM)

Clinical Syndromes in Humans (2)

2. Superficial lymphadenitis, especially cervical lymphadenitis (scrofula), in children

- Caused mostly by:
 - MAC
 - *M. scrofulaceum*
 - In northern Europe:
 - *M. malmoense*
 - *M. haemophilum*

NONTUBERCULOUS MYCOBACTERIA (NTM)

Clinical Syndromes in Humans (3)

3. Disseminated disease in severely immunocompromised patients

- Most commonly caused by MAC
- Less commonly caused by the rapidly growing mycobacteria (RGM), e.g.,
 - *M. abscessus*
 - *M. fortuitum*
 - *M. chelonae*

NONTUBERCULOUS MYCOBACTERIA (NTM)

Clinical Syndromes in Humans (4)

4. Skin and soft tissue infection

- Usually as a consequence of direct inoculation
 - Caused primarily by:
 - *M. marinum*, cause of “fish-tank granuloma”
 - *M. ulcerans*, cause of “Buruli ulcer”
 - The rapidly growing mycobacterial (RGM) species:
 - *M. abscessus*
 - *M. fortuitum*
 - *M. chelonae*
- RGM infections in this category may be nosocomial, including surgical-site infections

Disseminated *Mycobacterium avium* Complex (MAC) Disease

- Epidemiology
- Prevention
- Diagnosis
- Treatment
- Clinical Manifestations
- Considerations in Pregnancy

Disseminated MAC: Epidemiology

- Multiple related species of non-TB mycobacteria: *M avium*, *M intracellulare*, others
- *M avium* is the causative agent in >95% of AIDS patients with disseminated MAC disease
- MAC organisms are ubiquitous in the environment
- Transmission believed to be via inhalation, ingestion, inoculation via respiratory or GI tract; person-to-person transmission unlikely
- Not associated with specific environmental exposures or behaviors

Disseminated MAC: Epidemiology (2)

- Usually occurs in people with CD4 count <50 cells/ μ L
- Incidence: 20-40% in patients with advanced AIDS who are not on effective ART or MAC prophylaxis
- Other risk factors: plasma HIV RNA >100,000 copies/mL, previous opportunistic infections, previous colonization with MAC
- 10-fold decrease in incidence in areas with effective ART

Disseminated MAC: Clinical Manifestations

- Usually a disseminated multiorgan infection
 - Symptoms: fever, night sweats, weight loss, fatigue, diarrhea, abdominal pain
- Localized manifestations most common in persons on ART: lymphadenitis (cervical or mesenteric), pneumonitis, pericarditis, osteomyelitis, skin or soft tissue abscesses, genital ulcers, CNS infection
 - These also may be manifestations of IRIS

Disseminated MAC: Clinical Manifestations (2)

- Physical exam or imaging: hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, paraaortic, less commonly peripheral)
- Laboratory abnormalities: anemia, elevated liver alkaline phosphatase

Disseminated MAC: Clinical Manifestations (3)

■ IRIS

- Focal lymphadenitis, fever; may have systemic syndrome that is clinically indistinguishable from active MAC infection
- No bacteremia
- Occurs in patients with low CD4 count and subclinical or known MAC who begin ART and have rapid increase in CD4 (≥ 100 cells/ μ L)
- May be benign and self-limited or may be severe and require systemic antiinflammatory therapy

Disseminated MAC: Diagnosis

- Confirmed diagnosis: compatible signs and symptoms plus isolation of MAC from blood, bone marrow, lymph node, or other normally sterile tissue or fluid
- Species identification with specific DNA probes is essential for differentiating MAC and TB
- Other studies may support diagnosis (eg, AFB smear and culture of stool or tissue biopsy, radiographic imaging)

Disseminated MAC: Prevention

- Preventing exposure
 - No recommendations; MAC organisms are common in the environment
- Preventing disease
 - Recommended for all with CD4 count <50 cells/μL
 - Before prophylaxis, rule out disseminated MAC disease (clinical assessment +/- blood culture)
- Stopping prophylaxis
 - Discontinue in patient on ART with increase in CD4 count to >100 cells/μL for ≥3 months
- Restart prophylaxis if CD4 count decreases to <50 cells/μL

Disseminated MAC: Prevention (2)

- Primary prophylaxis
- Recommended
 - Azithromycin 1,200 mg PO Q week
 - Clarithromycin 500 mg PO BID
 - Azithromycin 600 mg PO TIW
- Alternative
 - RFB 300 mg PO QD (adjust dosage based on interactions with ARVs)
 - Rule out active TB before use
 - Significant interactions with PIs and NNRTIs

Disseminated MAC: Prevention (3)

- Clarithromycin + RFB not more effective than clarithromycin alone; should not be used
- Azithromycin + RFB more effective than azithromycin alone but higher cost, adverse effects, risk of drug interactions, and no demonstrated survival benefit: not recommended

Disseminated MAC: Treatment

- Initial treatment (≥ 12 months)
 - At least 2 drugs, to prevent resistance
 - Preferred
 - Clarithromycin 500 mg PO BID + ethambutol 15 mg/kg PO QD
 - Azithromycin 500-600 mg PO QD + ethambutol 15 mg/kg PO QD (when drug interactions or intolerance precludes use of clarithromycin)
 - Test MAC isolates for susceptibility to macrolides

Disseminated MAC: Treatment (2)

- Consider adding 3rd or 4th drug, if CD4 count <50 cells/ μ L, high mycobacterial load, in absence of effective ART, or if drug resistance likely
- Clarithromycin + ethambutol + rifabutin improved survival and reduced emergence of resistance in earlier studies; no data in context of effective ART
- Alternatives to rifabutin, or possible 4th agents: amikacin, streptomycin, levofloxacin, moxifloxacin
- Rifabutin interacts with many ARVs: some combinations are contraindicated; some require dosage adjustment
- Efavirenz may decrease clarithromycin levels (and increase level of active metabolite); clinical significance is unknown

Disseminated MAC: Starting ART

- ART and immune reconstitution are important aspects of MAC treatment
- ART generally should be started (or optimized) as soon as possible after the first 2 weeks of antimycobacterial therapy
 - 2-week delay may decrease risk of IRIS

Disseminated MAC: Monitoring

- Clinical improvement and decrease in quantity of MAC in blood or tissue are expected within 2-4 weeks after start of appropriate therapy; may be delayed if extensive disease or advanced immunosuppression
- If little or no clinical response to therapy: repeat MAC blood culture 4-8 weeks after initiation of therapy

Disseminated MAC: Adverse Events

- Clarithromycin, azithromycin: nausea, vomiting, abdominal pain, abnormal taste, transaminase elevations, hypersensitivity
 - Clarithromycin doses >1 g per day for MAC treatment are associated with increased mortality, should not be used
- Rifabutin doses ≥ 450 mg/day: higher risk of adverse interactions with clarithromycin or other inhibitors of cytochrome P450 3A4; possible higher risk of uveitis, neutropenia, other adverse effects

Disseminated MAC: Adverse Events (2)

- IRIS: if moderate-severe symptoms of immune reconstitution reaction, consider NSAIDs; if no improvement, short-term corticosteroids (eg, prednisone 20-40 mg QD for 4-8 weeks)

Disseminated MAC: Treatment Failure

- Absence of clinical response and persistence of mycobacteremia after 4-8 weeks of treatment
- Test MAC isolates for drug susceptibility
- Regimen of ≥ 2 new, active drugs, based on susceptibility testing
- Optimize ART

Disseminated MAC: Treatment Failure (2)

- Second-line agents:
 - If macrolide resistance, include ethambutol, rifabutin, amikacin, streptomycin, or a fluoroquinolone
 - Consider use of an injectable agent (eg, amikacin, streptomycin)
 - Unknown whether clarithromycin or azithromycin offer benefit if resistance is present
 - Clofazimine: should not be used; increased mortality and limited efficacy
 - Other agents: limited data

Disseminated MAC: Preventing Recurrence

- Secondary prophylaxis: chronic maintenance therapy should be continued unless immune reconstitution on ART
 - Therapies same as treatment regimens
- Stopping secondary prophylaxis:
 - Completed ≥ 12 months of MAC treatment, asymptomatic, CD4 count > 100 cells/ μ L for > 6 months, on ART
- Restart secondary prophylaxis if CD4 count decreases to < 100 cells/ μ L

Disseminated MAC: Considerations in Pregnancy

- Prophylaxis, diagnosis, and treatment as in nonpregnant adults
- Clarithromycin not recommended as first-line agent: increased risk of birth defects in animal studies
- Azithromycin recommended for primary prophylaxis; azithromycin + EMB recommended for treatment and for chronic maintenance therapy
 - Limited data on azithromycin in 1st trimester

Case #1

- A 45-year-old African-American male with AIDS (CD4 37 cells/cu mm) has no known drug allergies and has not yet started antiretroviral therapy (ART). At his first office visit with you, he complains of chronic diarrhea and weight loss, as well as chills, but denies dyspnea on exertion (DOE). He's found to be febrile (102 degrees F) and tachycardic (97 bpm). Laboratory evaluation reveals anemia (hemoglobin 8.5 g/dL) and an elevated serum alkaline phosphatase (352 U/L).

Case #1 (cont'd)

- Your initial plan for this patient should include all of the following EXCEPT:
- Obtain blood samples for performance of HIV-1 viral load testing and HIV-1 genotype testing
- Start sulfamethoxazole-trimethoprim (SMX-TMP) for *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis
- Obtain a blood culture for acid-fast bacilli (AFB)
- Start azithromycin 1200 mg po weekly for prophylaxis against disseminated *Mycobacterium avium* complex (MAC) infection

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Case #2

- A 26-year-old Hispanic male was diagnosed with AIDS (CD4 33 cells/cu mm; HIV-1 viral load 573,000 copies/mL) 6 weeks ago. One month ago he started antiretroviral therapy (ART) with abacavir/dolutegravir/lamivudine; today his CD4 count and HIV-1 viral load are 325 cells/cu mm and 10,500 copies/mL, respectively. He complains of fever and swelling in the right side of his neck. Physical exam is remarkable only for fever (101.3 degrees F) and a swollen, slightly tender right anterior cervical lymph node.

Case #2 (cont'd)

Which of the following procedures is most likely to yield the correct diagnosis?

- A. Bronchoscopy
- B. Blood culture for acid-fast bacilli (AFB)
- C. Aspiration of right anterior cervical lymph node (LN) with AFB staining and AFB culture of LN aspirate
- D. Blood cultures for aerobic and anaerobic bacteria

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Infections due to Non-MAC Nontuberculous Mycobacteria (NTM) in HIV

- MYCOBACTERIUM KANSASII
- M. XENOPI
- M. HAEMOPHILUM
- M. SIMIAE
- M. MALMOENSE
- M. FORTUITUM AND M. CHELONAE
- M. GENAVENSE
- M. SZULGAI

MYCOBACTERIUM KANSASII

HIV-Positive Persons (1)

- 2nd most common cause of nontuberculous mycobacterial (NTM) disease in HIV/AIDS pts in USA (after MAC).
- Usually causes lung disease, but disseminated disease also occurs.
- In HIV+ pts, single + Cx may indicate disease.
- Dx: mycobacterial Cx from infected site.
- 2007 ATS diagnostic criteria for non-HIV
- (these criteria may be too strict for HIV+ patients):
 - Compatible Sx or parenchymal lung abnormalities on imaging,
 - 2+ positive sputa or 1+ from BAL, and
 - Exclusion of other diseases
- On AFB microscopy may appear longer and wider than M. tuberculosis, but this feature not reliable enough for Dx
- No FDA-approved rapid tests for species-specific Dx from primary clinical specimen

MYCOBACTERIUM KANSASII

HIV-Positive Persons (2)

- Disease typically with CD4 < 200 (most often < 50)
 - Typical clinical presentation: fever, cough, pulmonary infiltrates and/or cavities.
 - CXR: >50% bilateral disease with consolidation of nodules or effusion. Cavitation < 10%. Normal < 10%.
- Clinical features similar to TB.
- Primarily pulmonary disease, but can also disseminate.
- DDx: TB, other nontuberculous mycobacterial (NTM) diseases; pneumocystosis (*Pneumocystis jiroveci* pneumonia, PJP); lymphoma; nocardiosis; histoplasmosis; coccidioidomycosis; bacterial pneumonia
- Standard treatment: rifampin, isoniazid, ethambutol
- (“RIE, not RIPE”)

MYCOBACTERIUM XENOPI

- Has been found in institutional hot-water systems
- Contaminated bronchoscopes have been associated with pseudoinfections
- Authentic cases of infection mostly reported from Europe and eastern Canada
- Not uncommonly isolated from respiratory secretions of HIV/AIDS patients in U.S.
- Pulmonary *M. xenopi* disease (most common site of infection) may radiographically resemble TB or MAC (upper-lobe cavitory lesions) or manifest as nodules or diffuse infiltrates
- Disseminated *M. xenopi* disease is rare but may be seen in patients with AIDS or those receiving TNF inhibitors

MYCOBACTERIUM SIMIAE

- Often thought to be a commensal in respiratory isolates
- Possible sites of infection:
 - Pulmonary infection
 - Disseminated disease with isolation from blood (presenting in AIDS patients in a manner similar to disseminated MAC, with fever, night sweats, weight loss, and lymphadenopathy)
 - Osteomyelitis
 - Renal infection in AIDS patients

MYCOBACTERIUM FORTUITUM

MYCOBACTERIUM CHELONAE

- a cause of cutaneous infection, especially following trauma or surgery
- in immunocompromised patients, reports of disease include disseminated disease with pustular and nodular cutaneous lesions, localized pulmonary disease with lymphadenopathy, multifocal osteomyelitis, and lymphadenitis
- morphologic appearance of the sometimes irregularly staining mycobacteria has resulted in misdiagnosis of *Nocardia* infection
- nosocomial pseudo-outbreak of *M. fortuitum*, linked to a contaminated ice machine on an HIV inpatient ward, was reported in 2002

MYCOBACTERIUM SZULGAI

- can be found in water sources
- usually associated with pulmonary disease in a presentation similar to that of *M. tuberculosis*
- extrapulmonary presentations have been described in patients with HIV infection, including:
 - cutaneous disease
 - osteomyelitis
 - septic arthritis

OTHER NONTUBERCULOUS MYCOBACTERIA (NTM) Microbiology

- *M. celatum*: slow growing (3-8 wks to culture). May cause false positive *M. tuberculosis* direct (MTD) test.
- *M. genavense*: very slow grower; difficult to grow; alert lab if *M. genavense* suspected.
- *M. haemophilum*: slow growing; alert lab if suspected since requires hemin or iron to grow in culture and grows best at 28-30°C (low temperature).
- *M. malmoense*: slow growing; most clinical isolates/reports from northern Europe.
- *M. mucogenicum*: rapidly grows (< 7 days in culture); sporadic contaminant in respiratory samples; water is environmental reservoir. Previously known as *M. chelonae*-like organism.

OTHER NONTUBERCULOUS MYCOBACTERIA (NTM) Clinical

- *M. haemophilum*: suspect if AFB-smear positive, but no growth on routine AFB media.
- *M. malmoense*: second most common NTM recovered from sputa or LN in children (after MAC). Most commonly reported in Northern Europe and Japan. U.S. cases described in Florida, Georgia and Texas.
- *M. mucogenicum*: if isolated from respiratory specimen, most likely a contaminant. As true pathogen, mostly described as rare cause of catheter-related infection.

OTHER NONTUBERCULOUS MYCOBACTERIA (NTM) Sites of Infection (1)

- *M. celatum*: pulmonary disease in AIDS; clinical presentation similar to TB.
- *M. genavense*: disseminated infection in advanced AIDS; similar presentation to disseminated MAC. Nodular skin lesions may occur. Dx made by AFB blood culture, or culture of liver or bone marrow biopsy.
- *M. haemophilum*: typically occurs in severely immunocompromised - solid organ or bone marrow transplant, chronic steroids, AIDS. Skin lesions, lymphadenitis, septic arthritis most common manifestations.

OTHER ATYPICAL MYCOBACTERIA

Sites of Infection (2)

- *M. malmoense*: pulmonary disease in adults (especially in COPD pts), cervical lymphadenitis in children most common.
- *M. mucogenicum*: peritonitis associated with peritoneal dialysis, central venous catheter infections most commonly. Respiratory disease unusual and typically associated with multiple positive cultures.

References

(listed alphabetically)

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- UpToDate:
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<https://aidsinfo.nih.gov/>
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