

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

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Nontuberculous Mycobacterium (NTM)

- “MOTT” or “Atypical”
- Environmental organisms
 - Soil, lakes, rivers, municipal water systems
 - Resistant to chlorine and most disinfectants
- Biofilm
 - Live within amoeba, legionella, others

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Laboratory Growth Characteristics

- “Slow” growers (>2 weeks in AFB media, liquid media more quickly)
 - *M. avium* complex (MAC), *M. kansasii*, *M. marinum*, *M. xenopi*
- “Rapid” growers (4-7 days in routine blood agar)
 - *M. abscessus*, *M. chelonae*, *M. fortuitum*
- “Need help” growing
 - *M. marinum*, *M. haemophilum*, *M. ulcerans*,
 - *M. genavense* (often molecular ID)

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NTM Disease Clinical Manifestations

- Pulmonary (75%)
 - MAC
 - *M. kansasii*
 - *M. xenopi*
 - *M. abscessus*
 - *M. malmoense*

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NTM Disease Clinical Manifestations

- Skin and Soft tissue (15%)
 - MAC, *M. marinum*, *M. abscessus*, *M. chelonae*, *M. fortuitum*, *M. kansasii*, *M. ulcerans*
- Lymph node disease (5%)
 - MAC, (historically also *M. scrofulaceum*)
- Disseminated (5%)
 - MAC, *M. kansasii*, *M. abscessus*, *M. chelonae*, *M. haemophilum*
- Hypersensitivity pneumonitis (0%)
 - MAC and hot-tubs

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Important Bug-Setting Associations

- Corneal Disease
 - *M. chelonae*
- Healthcare/hygiene associated outbreaks
 - *M. chelonae*, *M. fortuitum*, *M. abscessus*, *M. chimaera*
- Line-associated
 - *M. mucogenicum*
- HIV setting
 - MAC, *M. kansasii*, *M. genavense*, *M. haemophilum*
- Tropical setting
 - *M. ulcerans* (buruli ulcer)

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Other Pearls Based on Species

- *M. gordonae*
 - Contaminant
- NTM are not communicable
 - CF?
- *M. immunogenum*, *M. simiae*
 - Pseudo-outbreaks
- *M. szulgai*, *M. kansasii*, and *M. marinum*
 - Cross-react with IGRAs
- *M. fortuitum* lung disease
 - Aspiration
- *M. marinum*
 - Fish and fishtanks

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Question #1

72-year-old female with chronic cough, normal CXR, and 1/3 sputums grow MAC. Which one of the following do you recommend?

- A. CT scan of chest AND Additional sputum AFB cultures
- B. Empiric therapy with azithromycin, ethambutol, and rifampin
- C. Additional sputum AFB cultures
- D. Wait for in vitro susceptibility data and then treat

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Pulmonary NTM

2007 ATS/IDSA diagnostic criteria:

- Patient has both radiographic evidence of disease and pulmonary symptoms
- AND
- At least 2 sputum cultures positive, or
- One BAL or tissue specimen with positive culture, or
- Tissue with granulomatous histopathology in conjunction with positive culture (BAL or sputum)

Griffith D et al. *AJRCCM* 2007

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Pulmonary NTM

- MAC is most common etiology (60-90%)
- *M. kansasii* and *M. abscessus*
 - *M. kansasii* primarily in the South
 - Recent *M. abscessus* increase in CF
- Other organisms of importance
 - *M. xenopi* (northern US/ Canada, Europe)
 - *M. malmoense* (Europe)

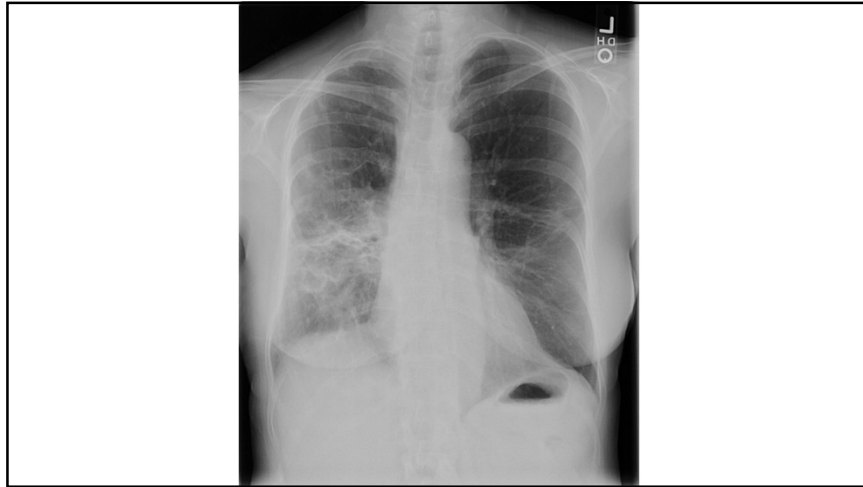
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Two Types of MAC Pulmonary Diseases

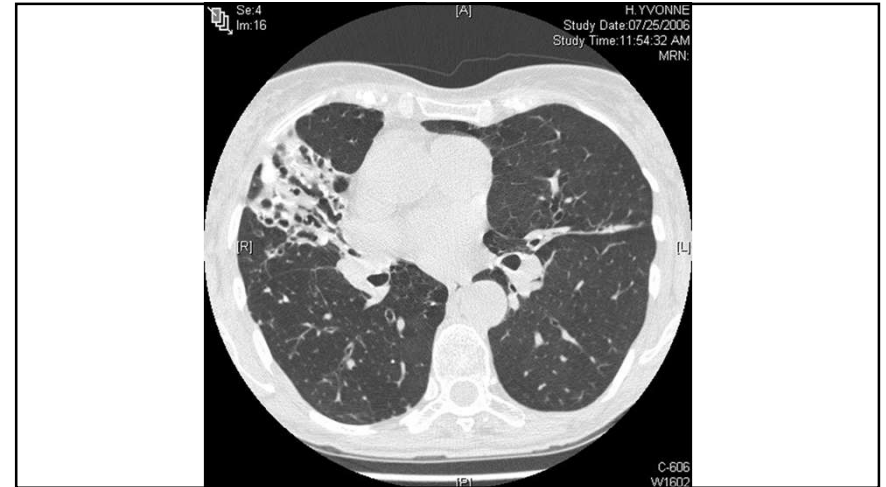
- Older male, smoker, COPD
 - Apical cavitary or fibronodular disease
 - More rapidly progressive
- Older female ("Lady-Windermere")
 - Scoliosis, thin, pectus deformities*, hypomastia
 - Nodular and interstitial nodular infiltrate
 - Bronchiectasis right middle lobe / lingula
 - Bronchiolitis ("tree and bud") on HRCT
 - Slowly progressive

*Iseman MD et al. *Am Rev Respir Dis.* 1991

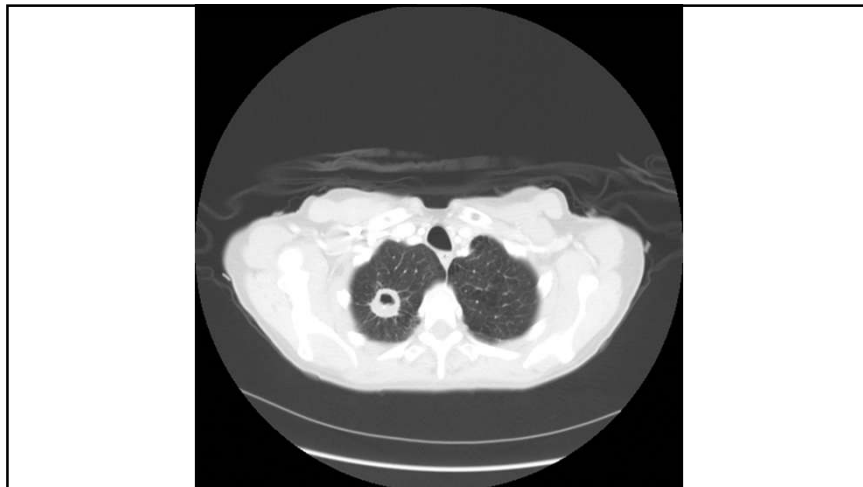
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Pulmonary NTM Risk Factors

- Underlying lung architectural abnormalities
 - Bronchiectasis, CF, α -1, emphysema
 - Prior TB, GERD/aspiration
- Exposure/transmission
 - Gardening/soil, Hot tubs
- Immunosuppressives
 - Prednisone, inhaled corticosteroids, biologics

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NTM Pulmonary Disease Diagnosis

- **Diagnosis \neq decision to treat**
 - Observation vs. suppression vs. cure

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MAC Therapeutic Options

- Treatment best defined for MAC
 - Start **Macrolide, rifampin, ethambutol**
 - Amikacin first 1-2 months for cavitary disease
 - Treatment duration 18-24 months (12-month culture negative)
 - Macrolide monotherapy is contraindicated
 - Recommended to test susceptibility for macrolide
 - **TIW okay** if non-cavitary or not re-infection

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Pulmonary *M. kansasii* Therapy

- *M. kansasii* clinically more like TB
 - Thin-walled cavities, upper lobes
 - Treatment with INH, RIF, EMB
 - TIW therapy ok
 - Treatment duration: 12 months culture negativity
 - High treatment success rates (90%+)
 - RIF is key drug.
 - FQ or Macrolide useful in RIF resistant disease

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Pulmonary *M. abscessus* ssp. Therapy

- *M. boletti*, *M. massiliense*, *M. abscessus*
 - **Inducible macrolide resistance--erm (41) gene**
- “Cure” = rare
- Can be more rapidly progressive than MAC
- 3-4 drugs for 18-24 months
 - 4-6 months “induction” phase
 - “suppressive strategy” thereafter

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***M. abscessus* Therapy**

- Parenteral agents
 - Omadacycline 100mg QD, Tigecycline 50mg QD, Cefoxitin 2gm TID, Imipenem 1000mg BID, Amikacin 10mg/kg TIW
- Oral agents
 - Clofazimine 50-100mg QD, Linezolid 600mg QD, moxifloxacin 400mg QD (rarely suscep), Azithromycin 250mg QD (if suscep), Omadacycline 300mg QD
- Surgical resection

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Extrapulmonary NTM

1. Immunocompetent settings
2. Immunocompromised settings

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Immunocompetent settings

- Nail salon, trauma, surgical or injection procedures, fish tank, hot tubs
- Rapid or slow growing NTM
- Incubation period
 - Infection usually occurs 2-8 weeks after contact with contaminated water source

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Children under 5 years NTM > TB



- Usually MAC
 - Males > females, age 1-2 years old
- Surgical resection alone is best therapy
- Adjunctive ABX rarely needed

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Post-plastic Surgery



- Usually Rapid Grower:
 - *M. chelonae*
- Remove foreign-bodies
- Therapy as per in-vitro susceptibility
- Length 4-6 months

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M. marinum---fish tank granuloma



Treatment: multiple drugs

- Macrolides, sulfonamides, doxycycline, rifampin, ethambutol
- Treat with 2 agents X 3-4 months.
- Surgical debridement if necessary

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Nail Salon Furunculosis

- Outbreaks and sporadic
- Rapid Growers most common (*M. fortuitum*)
- Oral antibiotics
 - 4 months fluoroquinolone and/or doxycycline
 - Can be self-limited



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Tattoo-associated

- *M. chelonae*
- Tattoo-ink outbreaks
- 2-3 months oral therapy
 - Based on *in-vitro* susceptibility
 - 1-2 agents
 - Macrolides almost always



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Question #2

20-year-old male complains of fever, night sweats and weight loss. Has generalized lymphadenopathy
HIV antibody positive; CD4 20 cells/ul

Node biopsy: non-caseating granuloma, AFB seen

Based on the most likely diagnosis, which of the following would you recommend?

- A. Start MAC therapy
- B. Start HAART plus MAC prophylaxis
- C. Start MAC therapy and HAART
- D. Start HAART only

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NTM in HIV

- Disseminated MAC
- GI route of infection
- Less frequent in HAART era
- Related issues
 - Clofazimine = increases mortality?
 - Rifabutin dose adjustment with PI
 - Immune reconstitution inflammatory syndrome (IRIS)

Griffith D et al. AJRCCM 2007

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISSEMINATED *MYCOBACTERIUM AVIUM* IN HIV-INFECTED PATIENTS

| Preferred (A, I)* | Alternative (B, I)* |
|--|--|
| Treatment | |
| Clarithromycin 500 mg orally twice daily | Azithromycin 500 mg daily |
| + Ethambutol 15 mg/kg orally daily | Ethambutol 15 mg/kg daily |
| ± Rifabutin [†] 300 mg orally daily | Rifabutin [†] 300–450 mg orally daily |
| Prevention [‡] | |
| Azithromycin 1,200 mg orally weekly | Clarithromycin 500 mg orally twice daily or Rifabutin [†] 300 mg orally daily |

* For evidence quality, see Table 1.

[†] Rifabutin dose may need to be modified based on drug–drug interactions (see text).

[‡] Preventive therapy indicated for persons with < 50 CD4⁺ cells/μL; may stop if > 100 cells/μL.

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Immunosuppression other than HIV

- Most frequently disseminated
 - Local inoculation versus GI route
- Risk factors and conditions
- ESRD, prednisone, biologic immunosuppressives
- Cancer, transplant, leukemia (hairy cell)
- Auto-antibody and cytokine/receptor deficiency states
 - INF-gamma, IL12-23 pathway, STAT-1
- Disease split between RGM and slow growers
 - RGM more common here than in pulmonary disease

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M. chelonae in cancer patient



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***M. chelonae* and *M. fortuitum* treatment**

- ***M. chelonae***
 - Macrolides, fluoroquinolone, linezolid
 - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline
 - **Note: tobramycin is best for *M. chelonae***
- ***M. fortuitum***
 - Macrolides, fluoroquinolone, bactrim, doxy (50%)
 - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline

Length of treatment for disseminated infection
3 drugs (including 1 IV) X 4-6 months
Depends on immunosuppression reversal

M. chimaera

- Slow growing. *M. avium* complex
 - Pulmonary disease
- Extrapulmonary disease
 - 150+ cases from open heart surgery: prosthetic valve, vascular graft, LVAD, heart transplant
- Aerosol from contaminated heater-cooler units used in operating room for cardiac by-pass.
- Time to diagnosis 1.7-3.6 years post-op, with cases reported up to 6 years postoperatively.
- Mycobacterial blood cultures
- Treatment: forever?

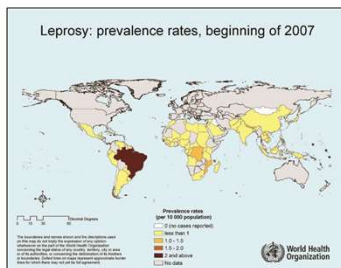


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Hansen's Disease (Leprosy)

- Rare in US (100-200 cases per year)
 - Armadillos and gulf region
 - Rest imported
- Most humans resistant
 - Household contacts at risk (low risk)
 - Nasopharyngeal transmission?
- *M. leprae* does not grow in culture



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Leprosy Disease Classification

- **Paucibacillary (PB)**
 - Most common form
 - “*Tuberculoid*”
 - Bacillary load < 1 million
 - Skin biopsy: AFB negative
 - ≤5 skin lesions
- **Multibacillary (MB)**
 - “*Lepromatous*”
 - Massive bacillary load
 - Skin biopsy: Floridly positive for AFB
 - >5 skin lesions

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Leprosy Treatment

| | |
|--|--|
| <ul style="list-style-type: none"> • PB (6-12 months) <ul style="list-style-type: none"> • Dapsone 100mg daily • Clofazimine 50mg daily • *Rifampin 600mg once monthly • (US guidelines are daily RIF and no Clofaz for 12 months) | <ul style="list-style-type: none"> • MB (12-24 months) <ul style="list-style-type: none"> • Dapsone 100mg daily • Clofazimine 50mg daily • Rifampin 600mg daily |
|--|--|

Complications: reversal reactions, erythema nodosum
 Treat with prednisone, thalidomide, other

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Top 10 or 12 NTM pearls for the Boards

- Footbaths = *M. fortuitum* or other RGM
- *Plastic Surgery* = *M. chelonae* or other RGM
- Equatorial Africa = *M. ulcerans*
- HIV disseminated MAC that doesn't grow = think of *M. genavense*
- *M. abscessus* usually has inducible macrolide resistance (erm gene)
- Macrolide, EMB, RIF for 18-24 months for pulmonary MAC
- *M. gordonae* is 99.9% a contaminant
- ATS/IDSA pulmonary case definition: need one BAL or two sputums or tissue
- Know NTM species that cross-react with TB IGRAs
- No clofazimine in HIV related MAC
- *M. kansasii* behaves like TB--- responds to TB drugs (RIF, EMB, INH)
- PZA not useful for any NTM

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