

13 - Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Speaker: Kevin Winthrop, MD



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

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)

NTM Disease Clinical Manifestations

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

NTM Disease Clinical Manifestations

- | | |
|--|--|
| Skin and Soft tissue (15%) <ul style="list-style-type: none">▪ MAC, <i>M. marinum</i>, <i>M. abscessus</i>,
<i>M. chelonae</i>, <i>M. fortuitum</i>, <i>M. kansasii</i>, <i>M. ulcerans</i> | Disseminated (5%) <ul style="list-style-type: none">• MAC, <i>M. kansasii</i>, <i>M. abscessus</i>, <i>M. chelonae</i>, <i>M. haemophilum</i> |
| Lymph node disease (5%) <ul style="list-style-type: none">▪ MAC, (historically also <i>M. scrofulaceum</i>) | Hypersensitivity pneumonitis (0%) <ul style="list-style-type: none">▪ 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*
- Line-associated
 - *M. mucogenicum*
- HIV setting
 - MAC, *M. kansasii*, *M. genavense*, *M. haemophilum*
- Tropical setting
 - *M. ulcerans* (buruli ulcer)

Other Pearls Based on Species

- *M. gordonae*
 - Contaminant
- NTM are not communicable
 - Except *M. massiliense* in 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

Question #1

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

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)

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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)

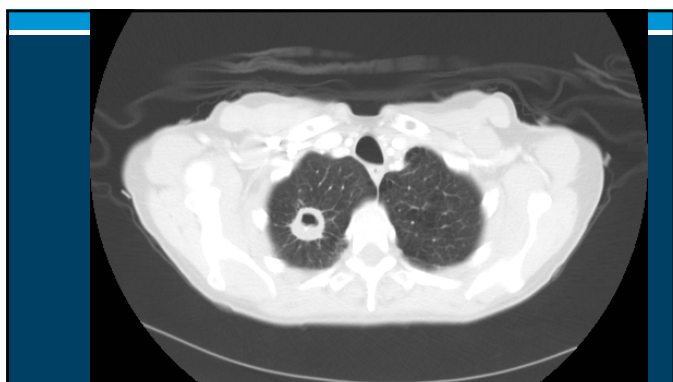
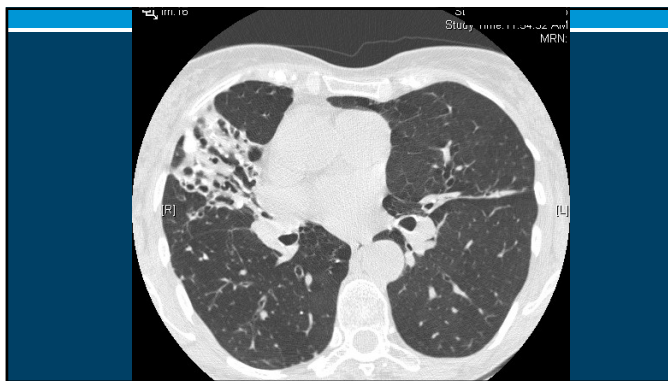
Two Types of MAC Pulmonary Diseases

- 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

*Isenman 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

NTM Pulmonary Disease Diagnosis

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

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.

Pulmonary *M. abscessus* Therapy

- *M. boletii*, *M. massiliense*, *M. abscessus*
 - Inducible macrolide resistance--erm (41) gene
- "Cure" = rare
- More rapidly progressive than MAC
- 3-4 drugs for 18-24 months
 - 4-6 months "induction" phase
 - "suppressive strategy" thereafter

M. abscessus Therapy

- Parenteral agents
 - 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)*
 - Surgical resection

EXTRAPULMONARY NTM

1. Immunocompetent settings
2. Immunocompromised settings

Immunocompetent settings

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

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

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

Nail Salon Furunculosis

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



Tattoo-associated

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



Question # 2

20 y.o. 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.

Question # 2

Based on the most likely diagnosis, which of the following do 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 (do not use!)
 - Rifabutin dose adjustment with PI
 - Immune reconstitution inflammatory syndrome (IRIS)

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

Preferred (A, B)*	Treatment	Alternative (B, B)*
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

M. chelonae in cancer patient



M. chelonae and M. fortuitum treatment

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

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

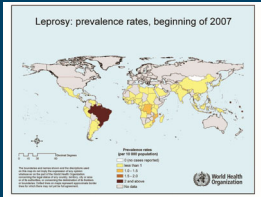
MYCOBACTERIUM CHIMAERA

- Slow growing. M. avium complex.
- Requires molecular identification
- Over 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: ???



Hansen's Disease (Leprosy)

- Rare in US (40-50 cases per year)
 - Armados 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.



Leprosy Treatment

- **PB (6 months)**
 - Dapsone 100mg daily
 - *Rifampin 600mg once monthly
- **MB (12 months)**
 - Dapsone 100mg daily
 - Clofazimine 50mg daily
 - *Rifampin 600mg once monthly OR
 - *Clofazimine 300mg once monthly

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

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