Non-Tuberculosis Mycobacterium (NTM) in Cystic Fibrosis

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Cystic Fibrosis (CF)

- Defect in the CFTR gene
  - Sinuses
  - Lungs
  - Pancreas (Endocrine/Exocrine)
  - Liver
  - Absorption/Nutrition
  - Bowel health/digestive transit
  - Reproductive System
  - Bones/Joints

CF Epidemiology

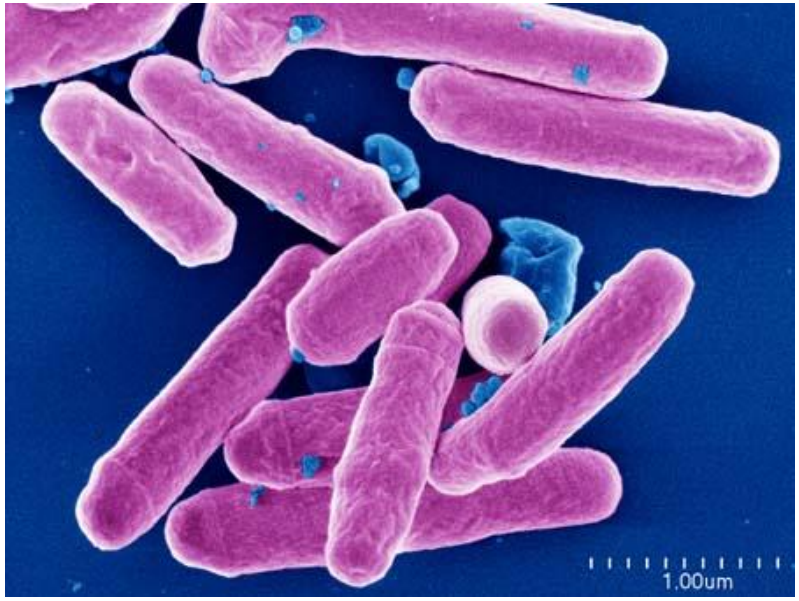
- One of the most common genetic diseases
  - ~30,000 US (~70,000 worldwide)
  - ~1,000 new cases per year
  - >70% of patients are diagnosed by age two.
  - >45% of the patient population is >18 years old!
- Dramatic improvement in survival over the past 50 years
  - Predicted median age early 40s.

Cystic Fibrosis Foundation, 2014

Other Pathogenic organisms

- *Burkholderia cepacia*
- *Stenotrophomonas maltophilia*
- *Achromobacter (Alcaligenes xyloxidans)*
- Nontuberculousis mycobacteria (NTM)

What are mycobacteria?

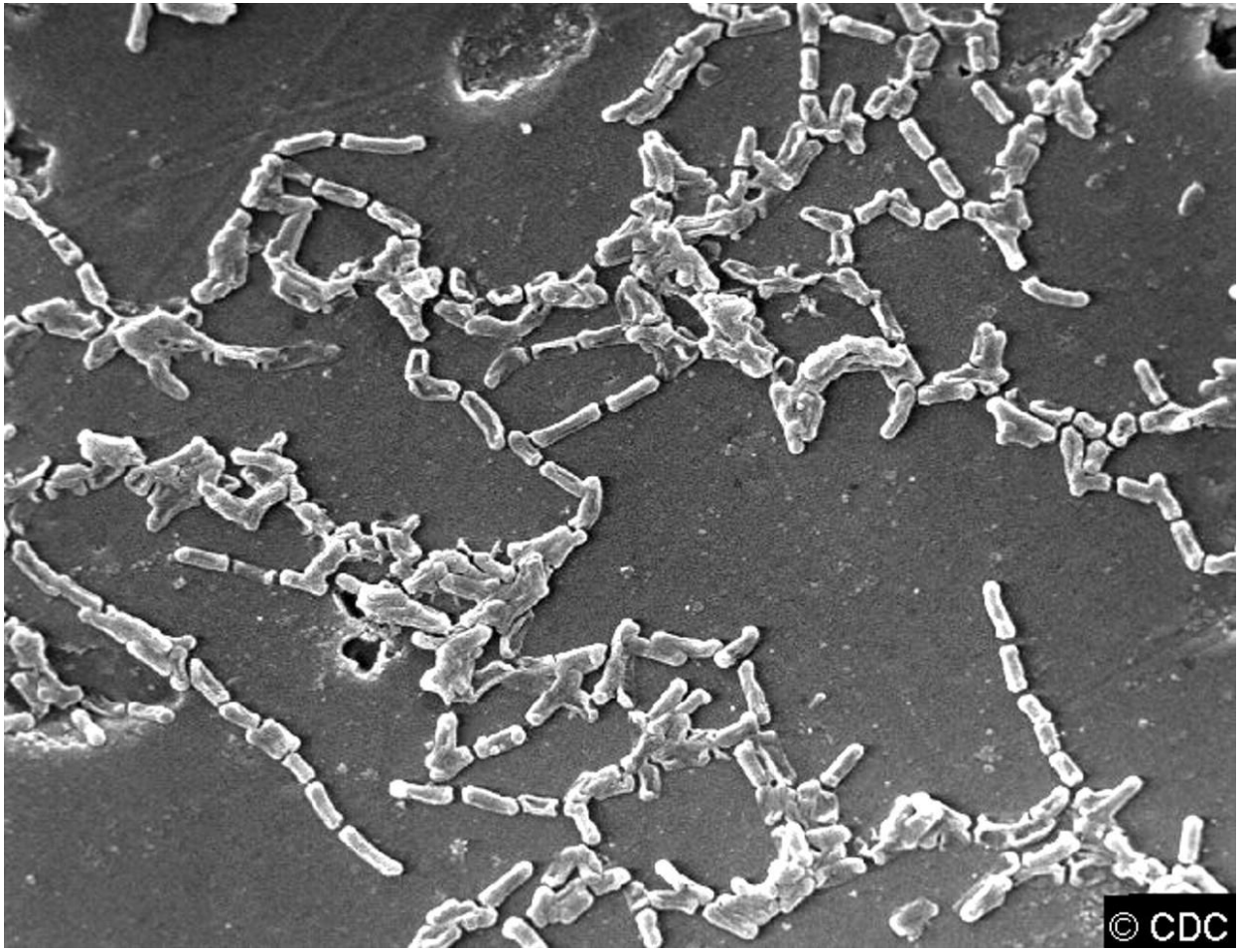


- *M. tuberculosis* complex
  - TB
- *M. leprae* and *M. lepromatosis*
  - Hansen's disease or leprosy
- NTM – also known as:
  - **Environmental mycobacteria** (Water and soil)
  - **Atypical mycobacteria**
  - **Mycobacteria other than tuberculosis** (MOTT)

www.waterscan.rs

en.wikipedia.org/wiki/Nontuberculous_mycobacteria

NTM – Microscopic



aapredbook.aappublications.org

NTM – Acid Fast Bacilli (AFB)

http://canadian-familypharmacy.com/

NTM Species

- M. avium Complex
- M. kansasii
- M. abscesus
- M. haemophilium
- M. immunogenum
- M. malmoense
- M. smegmatis
- M. szulgai
- M. terrae Complex
- M. chelonae
- M. fortuitum
- M. genavense
- M. gordonae
- M. marinum
- M. mucogenicum
- M. scrofulaceum
- M. simiae
- M. ulcerans
- M. xenopi
- Other NTM*

* Complete list can be found at http://www.bacterio.cict.fr/m/mycobacterium.html

Common NTM species

- Slow growers
  - *M. avium* complex (MAC)
  - *M. kansasii*

- Rapid growers (RGM)
  - *M. abscessus* complex
  - *M. chelonae*
  - *M. fortuitum*

Common NTM species

- M. avium complex (MAC)
  - *M. avium*
  - *M. intracellulare*
  - *M. chimaera*
- M. abscessus complex
  - *M. abscessus*
  - *M. massiliense*
  - *M. bolletii*

Prevalence in Cystic Fibrosis

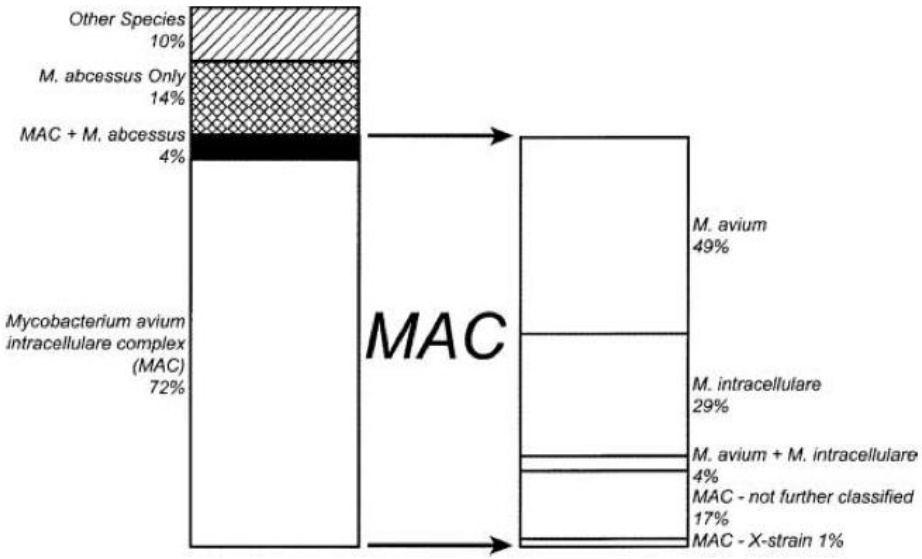
- Before 1990 rarely reported
  - No routine AFB testing
  - Poor culture technique
  - Younger CF population

- 1990s-2000: 2-28% N. America/Europe
  - based on single sputum sample
  - Poor culture techniques
  - Only screened patients when ill
  - No adult data

Olivier, et al. AJRCCM. 2003

Prevalence in Cystic Fibrosis

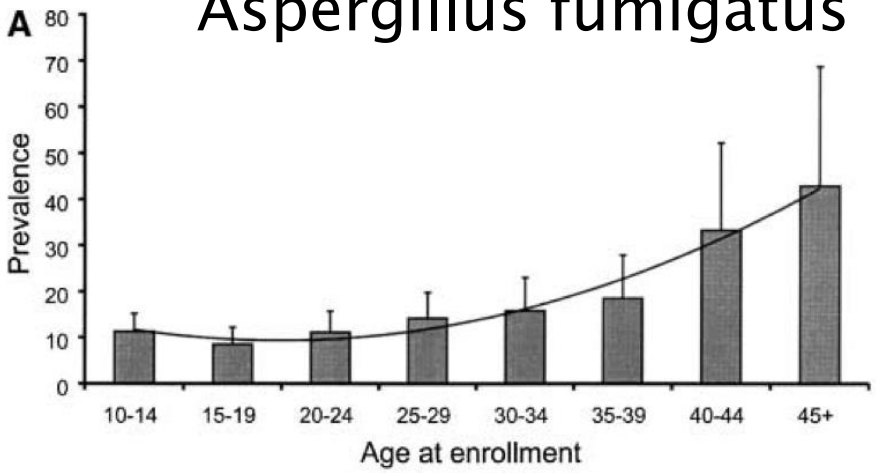
- United States overall prevalence ~13%
  - MAC (75%)
  - *M. abscessus* (21%)
  - Mac *and M. abscessus* (2%)
  - Other species (2%)

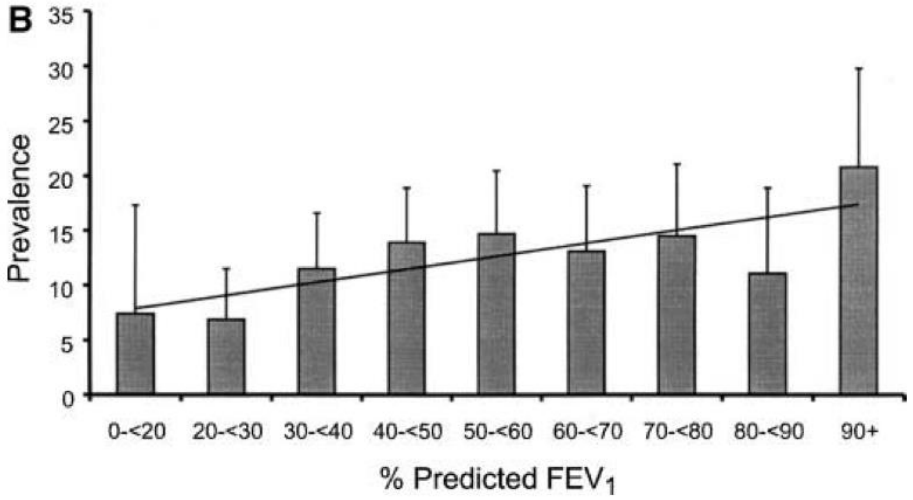


Olivier, et al. AJRCCM. 2003
Martiniano et al., AATS. 2014

Associated Risk Factors

- NTM Associated with
  - More frequent in adults; lower age (median 32 yrs)
  - Higher baseline FEV-1
  - Lower frequency of *P. aeruginosa*
  - higher frequency of *S. aureus*
  - coinfection with Stenotrophomonas maltophilia and Aspergillus fumigatus





Olivier, et al. AJRCCM. 2003
Martiniano et al., AATS. 2014

NTM Transmission

- No Person-to-person transmission
- No nosocomial acquisition

  - Most patients had unique bacterial strains
  - Only cases of same strain laboratory cross-contamination
  - No correlation between NTM culture status and
    - Number of hospitalizations
    - Days in the hospital
    - Outpatient visits

Olivier, et al. AJRCCM. 2003

Relevance of Positive Culture

- Single positive culture
  - Clears spontaneously
- Recurrent, no disease
  - $\geq$ 2+ cultures
  - No symptomatic progression
  - No radiographic progression
- NTM disease
  - $\geq$ 2+ cultures and
  - Symptomatic progression and
  - Radiographic progression

Martiniano et al., AATS. 2014

Diagnosing NTM Disease

- Symptoms — Overlapping
- Radiology — Overlapping; Difficult to interpret in CF; Cannot account for all NTM species
- Microbiology — Bacterial overgrowth; Distinguishing treatment failure/reinfection
- Appropriate exclusion of other diagnoses

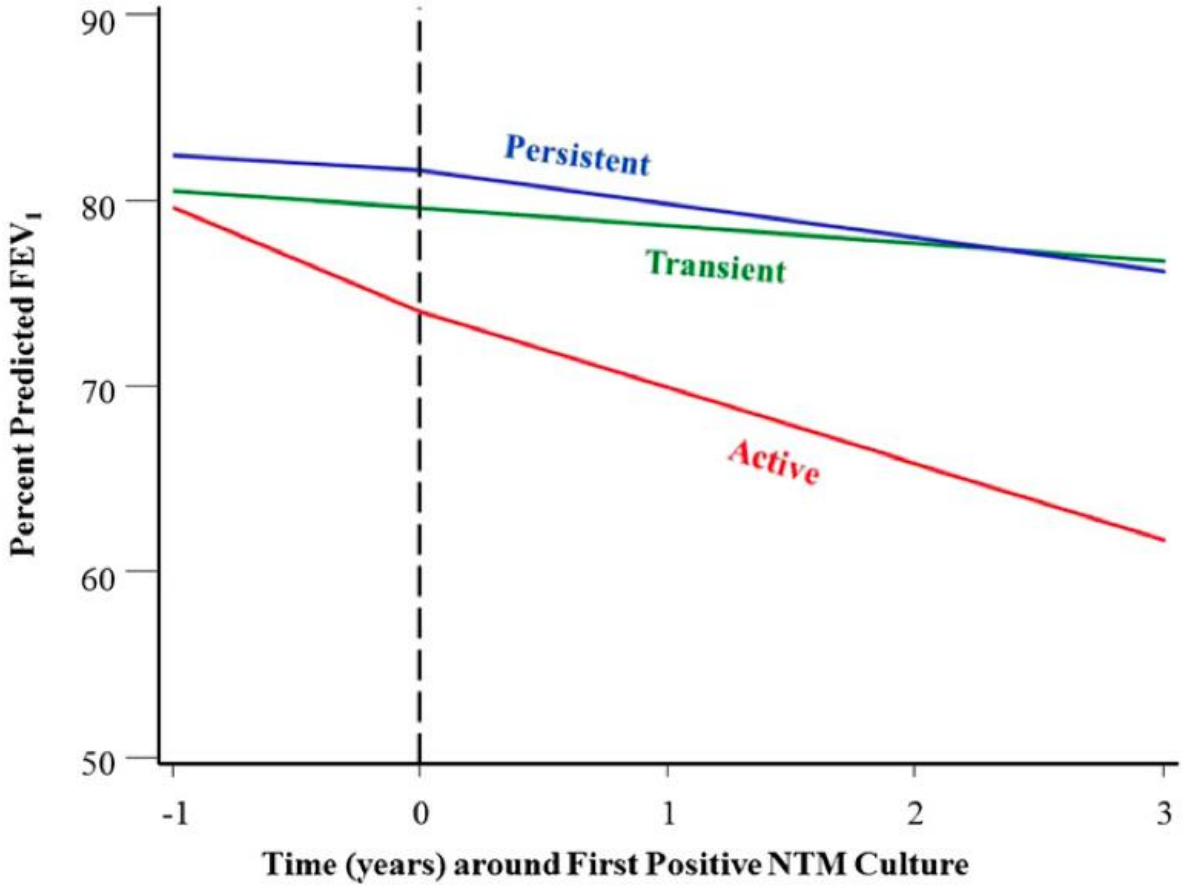
ATS Statement AJRCCM 2007

Diagnosis: Symptoms

- Single or recurrent infections (61.5%)
  - no significant difference in decline in FEV1 before or after 1st +NTM culture.
- Active NTM disease (38.5%)
  - lower baseline FEV1 at first positive culture
  - FEV_1 decline in year before 1st +culture -5.8% predicted/yr
  - FEV_1 decline 3 years after 1st + culture -4.1% predicted/yr
- Not linked to other clinical characteristics
  - Gender/age
  - Azithromycin use/resistance
  - CF genotype
  - Co-infection with other CF pathogens

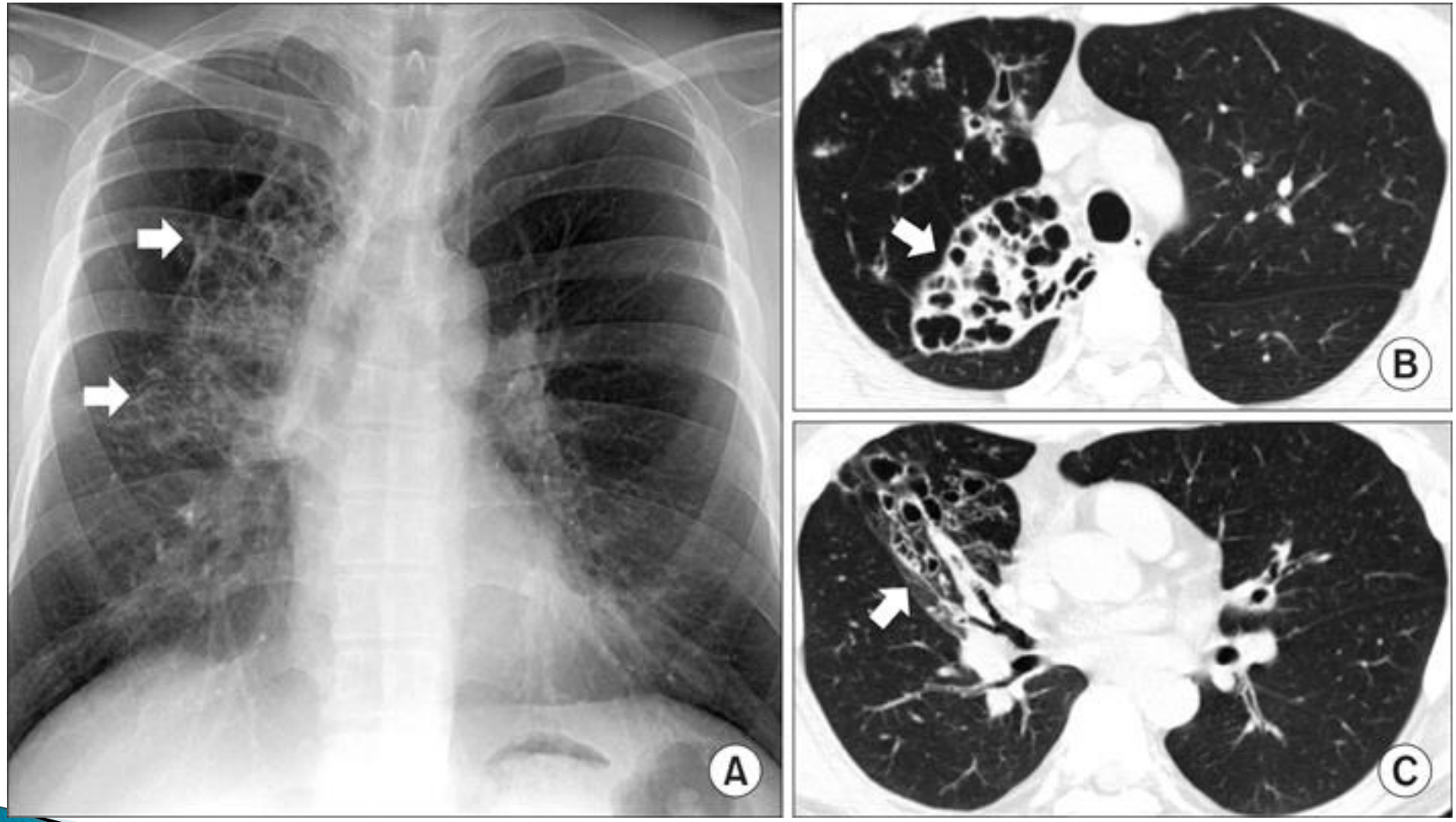
Martiniano et al., AATS. 2014

Diagnosis: Symptoms



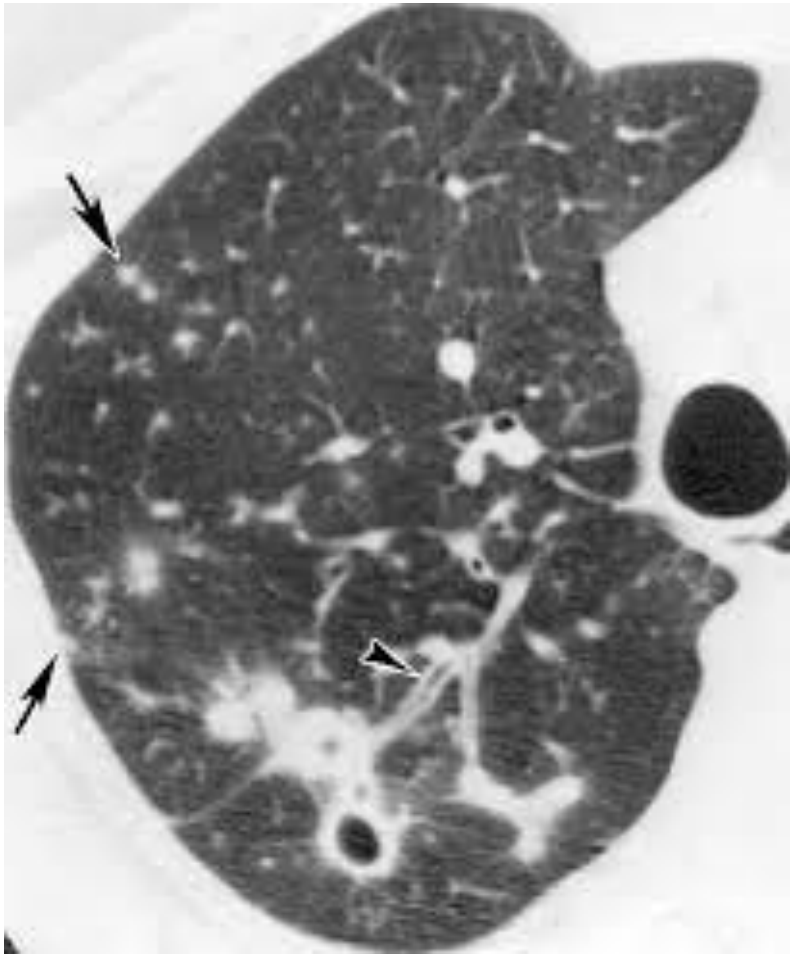
Martiniano et al., AATS. 2014

Diagnosis: Radiology



http://synapse.koreamed.org

Diagnosis: Radiology



radiographics.highwire.org

Diagnosis: Radiology

- MAC recovered from 299 non-CF patients

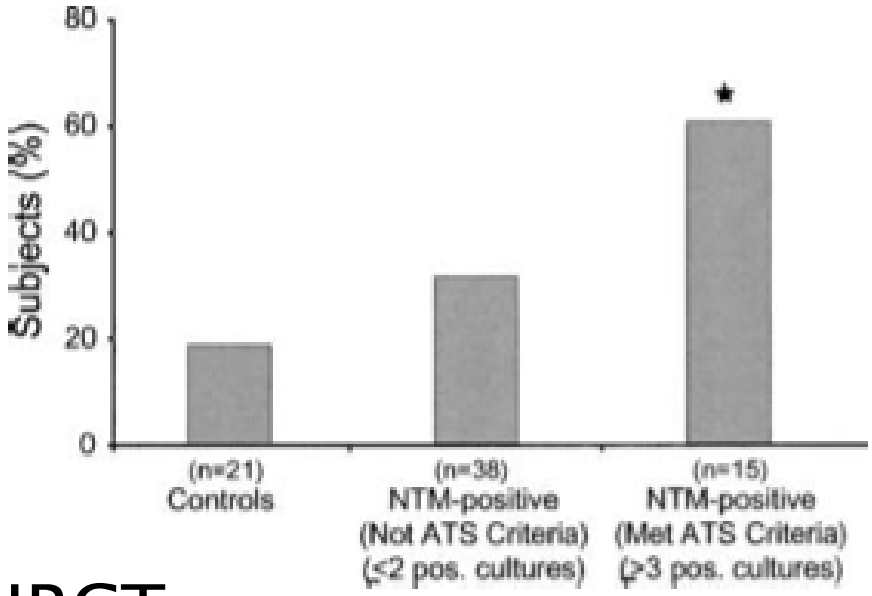
Patients	MAC Isolates	New cavitation or infiltrate
114	1	2%
29	2	90%
40	3	98%
116	$\geq$ 4	100%

- 98% of patient with $\geq$ 2 isolates showed radiographic progression.

M Tsukamura. Chest. 1991

Diagnosis: Radiology

- NTM in CF patients
- Entry HRCT:



- Progression on exit HRCT:
  - 38% control subjects
  - 22% $\leq$2 NTM+ culture
  - 100% $\geq$3 NTM+ cultures

Olivier, et al. AJRCCM. 2003

Diagnosis: Microbiology

- Initial MAC isolate
  - 24% grew 2nd NTM (primarily *M. abscessus)*
- Initial *M. abscessus*
  - 34% grew 2nd NTM (primarily MAC)
- Overall
  - 5 years: 26% with second NTM species
  - 10 years: 36% with second NTM species

Martiniano et al., AATS. 2014

Diagnosis: Other Diseases

- In the setting of CF, documented deterioration from baseline and "reasonable exclusion of other disease to explain (the patient's) condition" is an essential component.
  - Suboptimal CF care
  - Pulmonary exacerbation (usual pathogens)
  - New bacterial infection (*B. cepacia,* etc)
  - Poorly controlled sinus disease
  - ABPA
  - CFRD
  - Poorly controlled sinusitis
  - Chronic aspiration

ATS Statement AJRCCM 2007

Clinical Criteria for diagnosis

- Symptoms – Overlapping
- Radiology – non specific
- Microbiology – difficult
- Appropriate exclusion of other diagnoses

Despite these limitations, and given the most recent data, the ATS definition appears most appropriate for CF

ATS/IDSA 2007 Definition of NTM Pulmonary Disease

- Pulmonary Symptoms
  - Increased Cough/SOB
  - Massive hemoptysis
- Radiology
  - CXR with nodular or cavitary opacities
  - In absence of cavitation, HRCT with multifocal bronchiectasis*** with **multiple small nodules.**
- Microbiology
  - + AFB > 2 separated sputum samples, or
  - + AFB from ≥ BAL, or
  - TBBx with mycobacterial histopathologic feature +
  - One or more sputum or BAL +ve for NTM
- Appropriate exclusion of other diagnoses
  - Underlying CF lung disease ***
  - Tuberculosis (TB)

ATS Statement AJRCCM 2007

ATS/IDSA 2007 Definition of NTM Pulmonary Disease

- Expert consultation once NTM recovered
- Close follow up of patients with suspected NTM lung disease who don't meet ATS criteria
- NTM lung disease ≠ initiation of therapy
  - Risk vs benefit

ATS Statement AJRCCM 2007

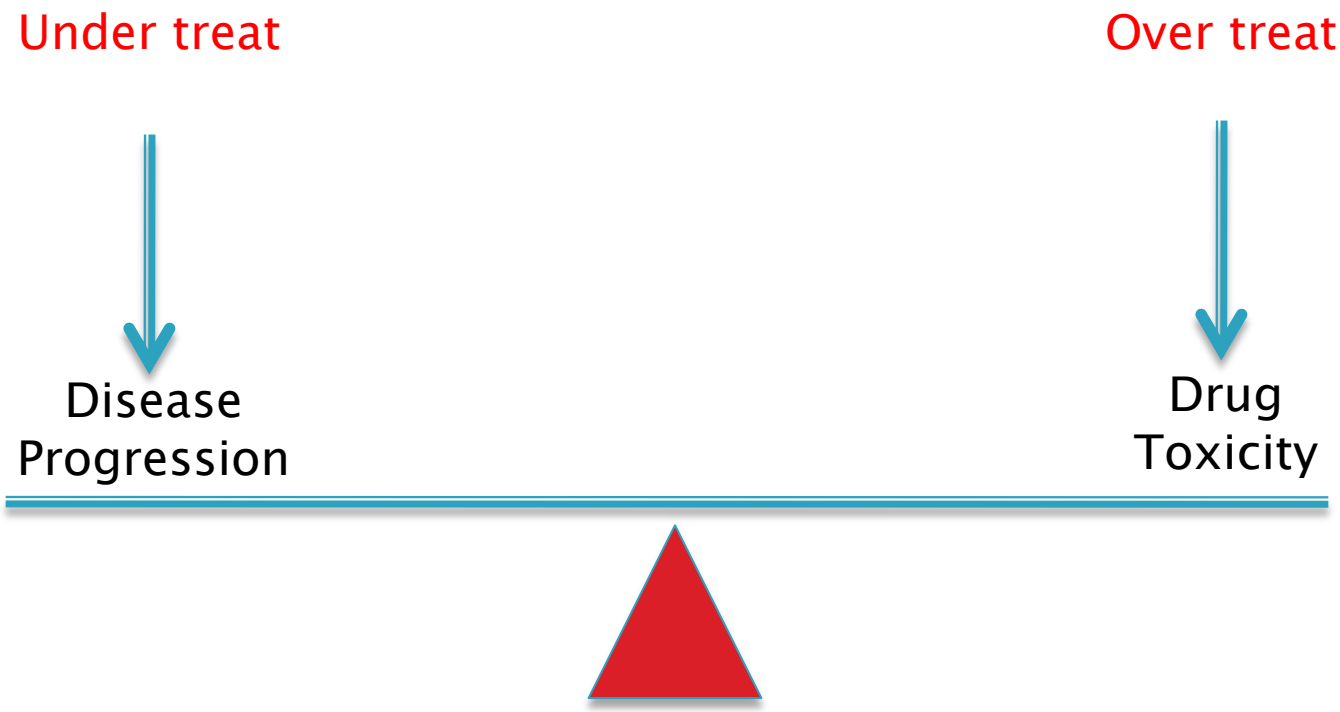
Diagnosis of NTM in CF: CFF and ECFS Recommendations

- ATS/IDSA criteria should be used in individuals with CF
- Rule out other CF pathogens and co-morbidities with decline in symptoms and radiological changes with 1st + NTM cultures.
- Discontinue azithromycin treatment while evaluation for NTM disease is underway.
- Minimum annual sputum AFB cultures in Non-sputum producers: if no clinical/radiologic features resembling NTM pulmonary disease, do not require screening cultures for NTM.

Stanford NTM Surveillance Protocol

- Follow CFF guidelines: biannual AFB cultures
- If positive, monthly AFB
- If 2-3 persistent positive, CT of chest
- If FEV-1 stable and no disease on CT
  - Cont monitoring AFB
  - Annual chest CT or sooner if increase in symptoms or decline in FEV-1

When Should NTM Therapy Start?



When Should NTM Therapy Start?

- The patient
  - Symptoms, overall condition of patient
  - Imaging progression
  - Transplant listed or post transplant
- The organism
  - Species
  - Bacterial load
- Treatment goals?
  - Eradication
  - Prevent progression
  - Symptoms relief

Time to Treat

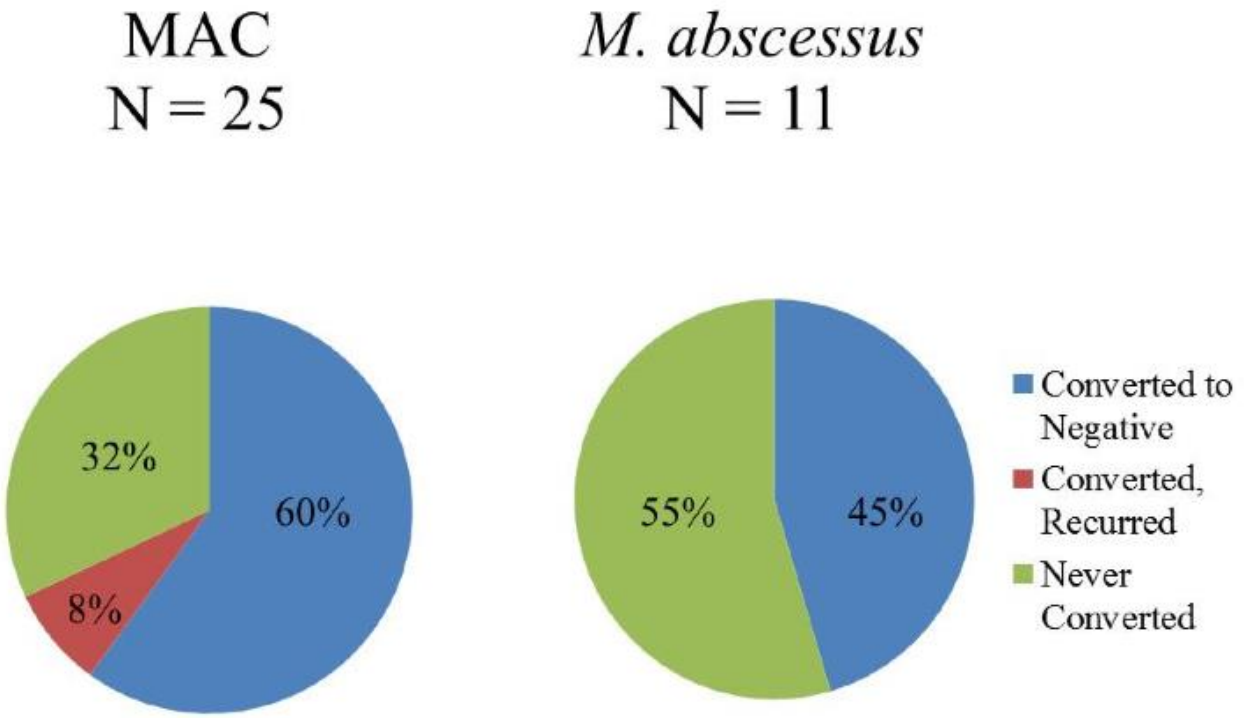
- The CFF and the ECFS recommend that NTM treatment should be considered for individuals with CF who have ATS/IDSA defined NTM pulmonary disease.

Treatment Goals:

- Symptomatic improvement
- Radiographic improvement
- Microbiological improvement:
  - Conversion to negative cultures
  - 12 months negative cultures **ON** Rx

Treatment Success

- 43% DID NOT clear NTM after 1st +culture



Martiniano et al., AATS. 2014

Common MAC Treatment

- Azithromycin
  - HIGH DAILY DOSING ONLY.
  - NEVER USE AS MONOTHERAPY
- IV/IH Amikacin
- Other agents
  - in collaboration with experts in CF/NTM

ATS Statement AJRCCM 2007

Common M. Abscessus Therapy

- Intensive phase:
  - Daily oral macrolide + IV amikacin
  - And one or more of:
    - Tigecycline
    - Imipenem
    - Cefoxitin (?)

3-12 weeks

- Continuation phase:
  - Daily oral macrolide + IH amikacin
  - And 2-3 of the following:
    - Moxifloxacin
    - Linezolid
    - Minocycline (?)
    - Clofazimine (?)

- *Guided but not dictated by susceptibility results*

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Drug Toxicities

Drug	Toxicities
Clarithromycin	-GI (metallic taste, nausea, diarrhea -Rare: REVERSIBLE vestibular and hearing impairment
Azithromycin	-GI (diarrhea, nausea) -Rare: REVERSIBLE vestibular and hearing impairment
Rifampin	-Orange discoloration of secretions and urine -GI (Nausea, vomiting) -Hypersensitivity reactions (fever/rash)
Rifabutin	-GI (Nausea, vomiting) -Neutropenia -Myalgia and arthralgia
Ethambutol	-Ocular toxicity/optic neuritis (loss of acuity, red-green discrimination) -Peripheral neuropathy, headache, disorientation
Amikacin	-Hearing impairment -Renal impairment -Vestibular impairment
Tigecycline	-GI (nausea, vomiting, diarrhea) -Renal impairment
Linezolid	-Bone marrow suppression -Peripheral neuropathy

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Management of NTM in CF patients is complex/difficult

- Validated CF-specific diagnostic criteria
- Standardize treatment protocols
- Understanding NTM species/behavior
- Analysis of standard antimicrobial agents
- NTM-specific antibiotics for prolonged treatment
- Defined rates of treatment response
- Markers of response and treatment endpoints specific to CF
- MORE DATA, MORE RESEARCH!!!

References

- American Thoracic Society. An Official ATS/IDSA Statement: Diagnosis,Treatment, and Prevention of Nontuberculous Mycobacterial Diseases. Am J Respir Crit Care Med 2007; 175: 368–406.
- Binder AM, Adjemian J, Olivier KN, Prevots DR. Epidemiology of Nontuberculous Mycobacterial Infections and Associated Chronic Macrolide Use among Persons with Cystic Fibrosis. Am J Respir Crit Care Med Vol 188, Iss. 7, pp 807–812, Oct 1, 2013
- Cystic Fibrosis Foundation. About Cystic Fibrosis: What y ou Need to Know. Available at http://www . cff . org/ AboutCF/. Accessed February 20, 2014
- Griffith, et al. An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases. Am J Respir Crit Care Med Vol 175. pp 367–416, 2007
- Olivier KN, Weber DJ, Wallace RJ et al. Nontuberculous Mycobacteria I: Multicenter Prevalence Study in Cystic Fibrosis. Am J Respir Crit Care Med. 2003;167: 828–834.
- Olivier KN, Weber DJ, Wallace RJ et al. Nontuberculous Mycobacteria
- II: Nested-Cohort Study of Impact on Cystic Fibrosis Lung Disease. Am J Respir Crit Care Med. 2003;167:
- M Tsukamura. Diagnosis of disease caused by Mycobacterium avium complex.Chest. 1991;99(3):667–669
- Martiniano SL, Sontag MK, Daley CL, et al. Clinical Significance of a First Positive Nontuberculous Mycobacteria Culture in Cystic Fibrosis. Ann Am Thorac Soc Vol 11, No 1, pp 36–44, Jan 2014
- *Wikipedia. en.wikipedia.org/wiki/Nontuberculous_mycobacteria/. Accessed February 24, 2014*