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Disclosures

- Funding from the Cystic Fibrosis Foundation
- Paratek Pharmaceuticals Drug Safety Monitoring Board

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Learning Objectives

- Understand the pathophysiology of typical pulmonary disease in cystic fibrosis (CF)
- Learn how to diagnose NTM pulmonary disease in a CF patient and recognize differences from non-CF patients
- Discuss differences in NTM treatment strategies for the CF population
- Identify unmet needs in the study of NTM in the CF patient and opportunities for collaboration and research

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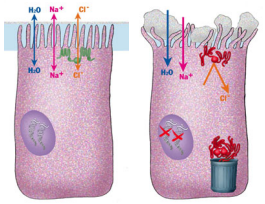
Cystic Fibrosis

- Syndrome of chronic sinopulmonary infections, malabsorption and nutritional abnormalities
- Most common lethal genetic disease in Caucasians
- CF gene encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein



From Ashlock NACFC 2003; CFF.org

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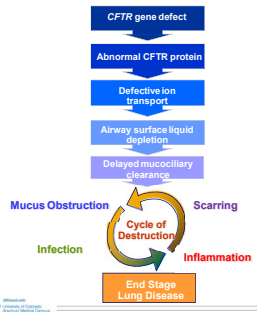
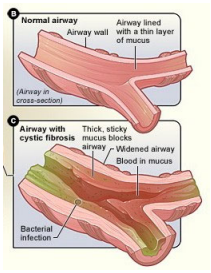
Pathogenesis of CF lung disease





http://www.nhlbi.nih.gov/health/health-topics/topics/cf/signs.html

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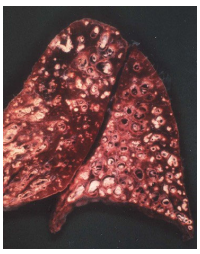
Lung disease in CF



- Bronchiectasis
- Infection
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*
- Inflammation
- Mucous Plugging

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NTM pulmonary disease: Cystic Fibrosis *vs.* Non-CF

Cystic Fibrosis

- CF Care Center
- Infrastructure for clinical trials
- Lifelong sputum culture surveillance
- Earlier detection without clinical features
- Co-infection with other bacteria
- Greater variability in drug PK
- Evidence of diminished response to treatment
- Uncertainty regarding the effect of elexacaftor/tezacaftor/ivacaftor

Non-CF Bronchiectasis

- Community-based care
- Overall greater population size
- Often infrequent airway cultures
- Clinical symptoms prompt cultures
- Mix of underlying diseases and co-morbidities

- **Trend towards excluding CF from NTM trials, or studying CF separately**
- **Mixed CF and non-CF populations no longer feasible in US**

Martiniano SL, JCF 2021; Olivier, KN, AJRCCM 2017
Slide courtesy of Jerry Nick, MD

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What is the current estimated NTM prevalence in CF patients in the U.S.? (CFF Registry 2010-2016)

1. 4%
2. 10%
3. 20%
4. 50%

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What is the current estimated NTM prevalence in CF patients in the U.S.? (CFF Registry 2010-2016)

1. 4%
2. 10%
3. **20%**
4. 50%

9

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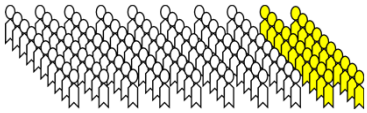
Epidemiology of NTM in CF

an orphan disease within an orphan disease



- **Longitudinal prevalence** (2010-2016) **20%**

2019 United States CFF Patient Registry

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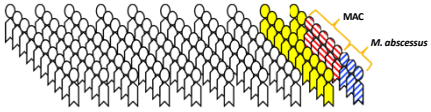
Epidemiology of NTM in CF

an orphan disease within an orphan disease



- **Longitudinal prevalence** (2010-2016) **20%**
- Based on preliminary data from the PREDICT trial, **40%** of patients with a positive NTM culture will meet ATS criteria for NTM-Pulmonary Disease, or **8%** of the total CF population.

Martiniano, SL, AATS, 2014

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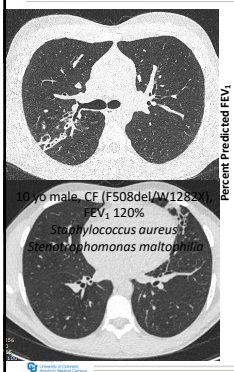

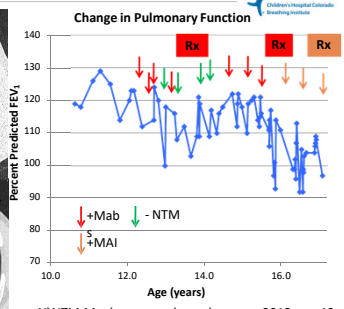

- 1st NTM *M. abscessus* subsp. *abscessus*, 2012, age 12
- 2nd NTM *M. intracellulare*, 2015, age 16
- Hearing loss and allergies to several meds

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NTM screening in CF

CFF/ECFS Recommendations:

- Annual NTM cultures in spontaneously expectorating individuals with a stable clinical course
  - Screen for NTM prior to starting chronic azithromycin therapy
- In the absence of clinical features suggestive of NTM pulmonary disease, individuals who are not capable of spontaneously producing sputum do not require screening cultures for NTM
- Culture and smears for acid fast bacilli from sputum should be used for NTM screening
  - Recommend against the use of oropharyngeal swabs for NTM screening.

US CFF/ECFS: "Consensus recommendations for the management of NTM in CF," Thorax, 2016

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Diagnostic criteria for NTM pulmonary disease

Clinical and Radiographic Criteria:

1. Pulmonary or systemic symptoms, **AND**
2. Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules

AND

Microbiological Criteria:

1. Positive culture results from at least 2 separate expectorated sputum samples, **OR**
2. Positive culture results from at least 1 bronchoalveolar lavage, **OR**
3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) plus biopsy or respiratory culture positive for NTM

ATS/IDSA Statement: "Diagnosis, Treatment, and Prevention of NTM Disease" AJRCCM 2007
US CFF/ECFS "Consensus Recommendations for the Management of NTM in CF" Thorax 2016
ATS/ERS/ESCMID/IDSA: "Treatment of NTM Pulmonary Disease" Eur Respir J. 2020

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CF-Specific considerations in NTM-PD diagnosis

"Appropriate exclusion of other diagnoses"

- CF Co-pathogens:
  - Usual CF pathogens
  - New bacterial infection
  - Pulmonary Exacerbations
- CF Co-morbidities:
  - Allergic bronchopulmonary aspergillosis (ABPA) or asthma
  - CF-related diabetes
  - Sinus disease
  - Gastroesophageal reflux
  - Chronic aspiration
  - Nutritional deficiencies

ATS/IDSA Statement: "Diagnosis, Treatment, and Prevention of NTM Disease" AJRCCM 2007
US CFF/ECFS "Consensus Recommendations for the Management of NTM in CF" Thorax 2016
ATS/ERS/ESCMID/IDSA: "Treatment of NTM Pulmonary Disease" Eur Respir J. 2020

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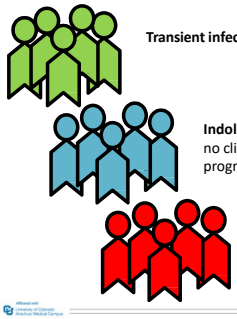
NTM patient cohorts



Transient infection: Only one positive culture

Indolent infection: > 1 positive cultures but no clinical evidence of accelerated progression of CF lung disease

NTM pulmonary disease: Multiple positive cultures and radiographic and clinical evidence of accelerated progression of CF lung disease

From Nick Symposium NACFC 2013; Olivier AJRCCM, 2003; Esther J Cys Fibr, 2010; Martiniano AATS 2014;

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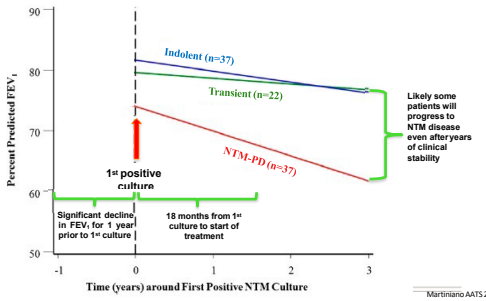
Clinical significance of a first positive NTM culture in CF



Martiniano AATS 2014

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Prospective evaluation of NTM disease in cystic fibrosis (PREDICT) Trial

- Prospective, observational study at CF Care Centers
- Primary Objective
  - Develop user-friendly, evidence-based protocol for NTM disease diagnosis to be used for all CF patients in the US.
- Secondary Objectives:
  - Define an expected rate of development of NTM pulmonary disease for patients with CF with positive NTM cultures.
  - Identify specific clinical features associated with the development of disease.
  - Facilitate research in CF host susceptibility, NTM virulence and biomarker discovery.

NCT02073409

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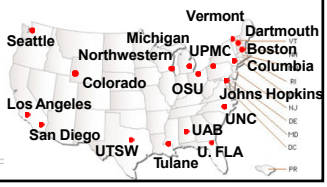
Prospective evaluation of NTM disease in cystic fibrosis (PREDICT) Trial

- Began in Colorado at Children's Hospital Colorado and National Jewish Health in 2013
  - Expanded to 33 programs across 18 sites
- Inclusion: CF patients, 6 years and older, with a recent positive NTM culture (last 2 years)
- Exclusion: Previous NTM treatment or history of lung transplant



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Diagnosis of NTM Disease in PREDICT

Positive NTM culture ← Enrollment here

1. Repeat NTM culture
2. Evaluate for NTM Clinical Syndrome (1 or more):
   - ↑ Respiratory symptoms (cough, sputum production, dyspnea, hemoptysis)
   - Constitutional symptoms (fever, night sweats, fatigue, weight loss)
   - ↓ FEV_1 and ↓ response to treatment
   - Radiographic changes consistent with NTM

Definitively treat other known co-pathogens and CF-related co-morbidities

NCT02073409

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Definitive treatment of other airway co-pathogens

Recommend a two week-course of IV antibiotics focused on known (non-NTM) co-pathogens in patients with a clinical syndrome, even in the absence of clear evidence of an acute pulmonary exacerbation

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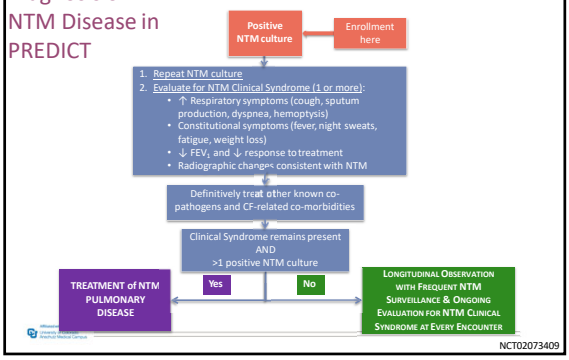
Diagnosis of NTM Disease in PREDICT



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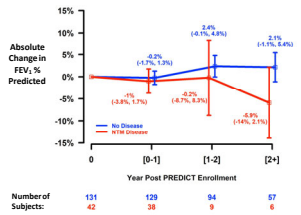
PREDICT: follow up & change in FEV_1 % predicted

No NTM Disease (75%):
27 (20) months
9 (6) clinic visits

NTM Disease Diagnosis (25%):
12 (15) months
6 (4) clinic visits



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What is the recommended first-line treatment for macrolide-susceptible, non-cavitary MAC pulmonary disease in a CF patient?

1. Thrice weekly oral azithromycin, ethambutol, rifampin
2. Daily oral clarithromycin, ethambutol, rifampin
3. Daily oral azithromycin, ethambutol, rifampin
4. Daily inhaled amikacin and oral azithromycin

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25

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A child with CF has 3 consecutive positive sputum cultures for *M. abscessus* subspecies *massiliense,* a chest CT scan with evidence of new cavity formation and diffuse tree-in-bud opacities, and decline in her pulmonary function despite treatment of her primary CF pathogen, Methicillin-susceptible *Staphylococcus aureus.* What is the next recommended treatment regimen for this patient?

A. Oral azithromycin, ethambutol, and rifampin three times weekly
B. Oral isoniazid, pyrazinamide, and rifampin once daily
C. Surgical resection of the cavity without antibiotics
D. Inhaled amikacin alone
E. IV amikacin, IV imipenem, and oral azithromycin

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Treatment considerations in CF

- MAC treatment should be daily
  - Abnormal intestinal absorption and altered pharmacokinetics in CF
    - Single-dose PK study of azithromycin, ethambutol and rifampin in CF
    - 19 of 20 CF subjects had one or more abnormal C_{max} z-scores (outside +/- 2SD) when compared to healthy controls
    - Recommend therapeutic drug monitoring for all CF patients
- Rifampin is not an option for most CF patients (~90% of the population) due to drug-drug interactions with modulator drugs containing ivacaftor

Martiniano SL, JCF 2021;
US CFF/ECFS "Consensus Recommendations for the Management of NTM in CF" Thorax 2016

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Treatment considerations in CF

- MABSC treatment should include an intensive phase followed by continuation phase
  - "Guidelines-based therapy"
- Macrolide-resistant MAC or *M. abscessus*, consider expert consultation

US CFF/ECFS "Consensus Recommendations for the Management of NTM in CF" Thorax 2016
ATS/ERS/ESCMID/IDSA: "Treatment of NTM Pulmonary Disease" Eur Respir J. 2020

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Prospective algorithm for treatment of NTM in cystic fibrosis (PATIENCE) Trial

- Prospective, open label treatment trial at CF Care Centers (PREDICT sites)
- Primary Objective:
  - To implement a standardized approach to the initial treatment of NTM pulmonary disease in CF patients
- Secondary Objective:
  - Define an expected rate of clinical response and tolerance of guideline-based treatment of NTM pulmonary disease

NCT02419989

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Prospective algorithm for treatment of NTM in cystic fibrosis (PATIENCE) Trial

- Inclusion: Diagnosis of NTM-PD through PREDICT and intent-to-treat
- First-line and alternate drug regimens are recommended for MAC and MAB treatment
- Specific guidelines for safety and toxicity monitoring
- Target 12 months of treatment following first negative NTM culture
- Primary endpoint: 12 months follow-up following completion of treatment
- Sample collection for studies of NTM virulence and biomarker discovery

NCT02419989

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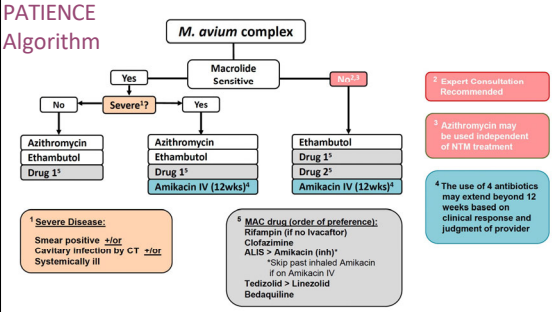
PATIENCE Algorithm



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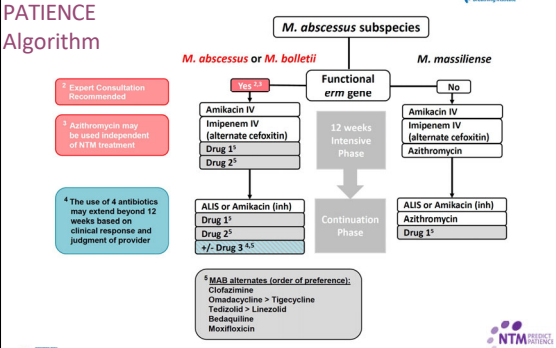

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Treatment goals in CF and non-CF are similar

- Microbiological improvement
  - Colorado CF Center historic treatment "success" rates:
    - *M. avium* complex = 71%; *M. abscessus* complex = 30%;
  - *Preliminary* PATIENCE trial culture conversion rates:
    - *M. avium* complex = 82%; *M. abscessus* complex = 74%
- Symptomatic improvement
- Radiographic improvement

- Chronic suppression
  - Clearing sputum of NTM not possible for many patients
  - Significant and sustained benefit can still be achieved with antibiotic therapy even with + cultures
  - Must balance patient quality of life and limit toxicities

Martiniano et al, AATS, 2014

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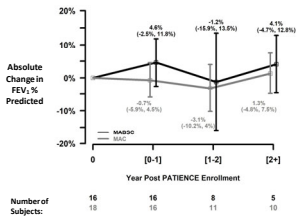
Pulmonary function decline stabilizes on treatment



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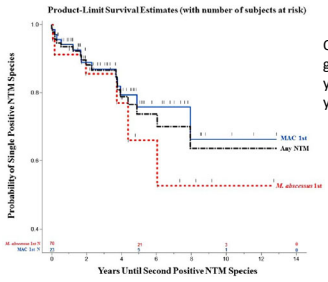
High risk for second NTM infection



Overall, 26% of subjects grew a second NTM at 5 years and 36% at 10 years of follow-up.

Martiniano et al, AATS, 2014

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Ancillary studies linked to PREDICT & PATIENCE

NTM Markers Currently Being Tested in Trials

NTM genome: Colorado Adult P&P Award
WGS (Michael Strong, PhD, NJH).
Radiographic predictors: CFF CRSP Award
HRCT (Stacey Martiniano, MD, CHCO, David Lynch, MD, NJH).
Sputum: NIH-funded ancillary study (R01 HL146228)
Microbiome (Rebecca Davidson, PhD, NJH).
Volatile sputum metabolites (Jane Hill, PhD, University of British Columbia).
Urine: CFF IRI Clinical Trial Award (PAINLESS Trial)
Urine lipoarabinomannan (Delphi Chatterjee, PhD, CSU).
Metabolic biosignature (John T. Belisle, PhD, CSU).
Saliva: CFF Clinical Trial Award (pending)(PIVOT Trial)
Targeted amplicon (Rebecca Davidson, PhD, NJH).
Antibodies (Ken Malcolm, PhD, NJH).

NTM Markers Under Evaluation to be Added to P&P

Breath: CFF Clinical Pilot Award
- ***Volatile breath metabolites*** (Jane Hill, PhD, University of British Columbia).

Whole Blood: CFF Clinical Pilot Award
- ***Circulating leukocyte RNA signatures*** (Mimi Saavedra, MD, NJH).

Plasma: CFF Clinical Pilot Award
- ***Circulating DNA signatures*** (Pradeep Singh, MD, Steve Salipante, MD, PhD, University of Washington).

Serum: CFF Clinical Pilot Award
- ***Antibodies and inflammatory markers*** (Ken Malcolm, PhD, NJH).
- ***Mycolic Acid Antibodies*** (Diagnostig, UK).
- ***Cholesterol metabolites*** (Jen Philips, MD, PhD, Washington Univ).

Slide courtesy of Jerry Nick, MD

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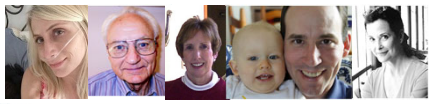
Summary

- NTM is common in the sputum of children and adults with CF
- NTM pulmonary disease diagnosed in about 40% of infected patients
- The role of NTM in lung disease can only be assessed following aggressive care of all other aspects of CF
- Guidelines-based therapy is recommended for patients with CF with a few caveats
- Results from trials in non-CF bronchiectasis will continue to guide treatment of NTM in persons with CF



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