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Cystic Fibrosis Related NTM Infections

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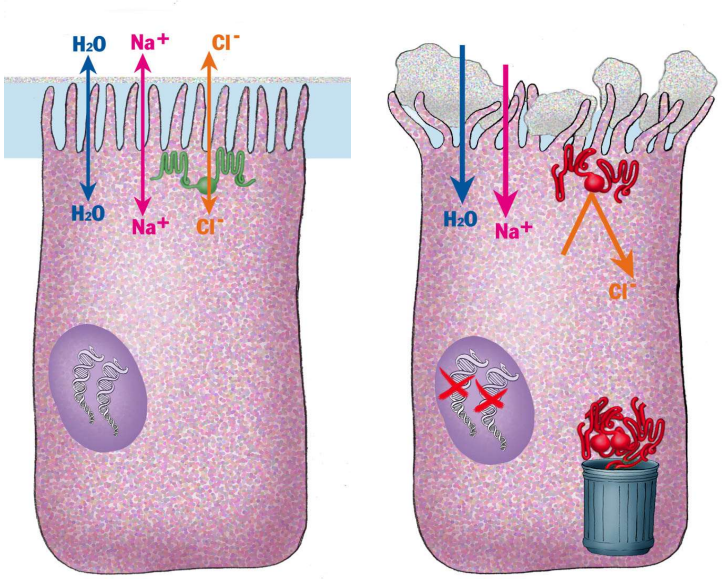
Disclosures

- Research funding from Cystic Fibrosis Foundation

Cystic Fibrosis

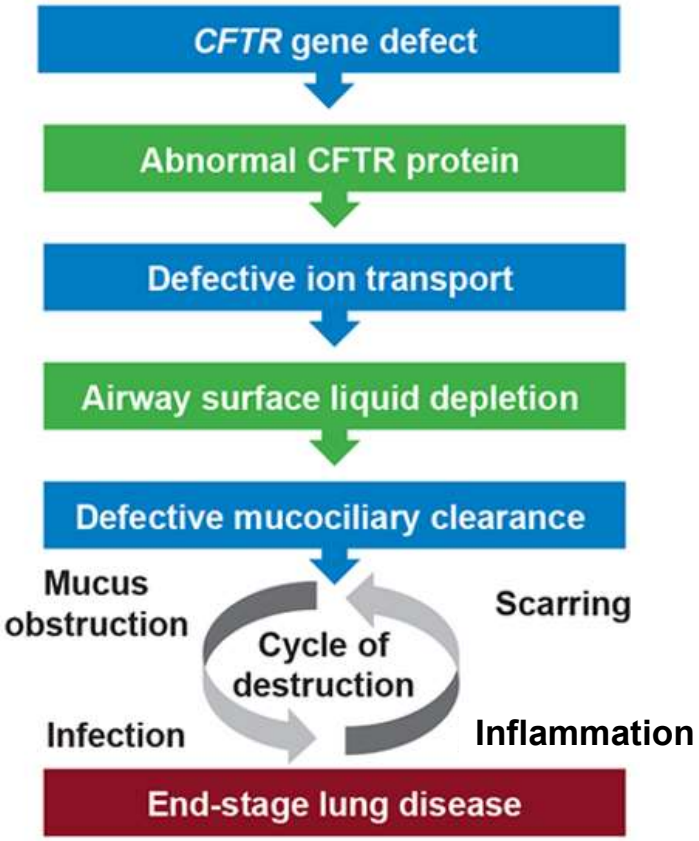
- Multisystem, progressive genetic disease
  - About 40,000 people in the US
- Characterized by **chronic sinopulmonary infections**, **malabsorption**, and **nutritional abnormalities**
  - Variants in the CF gene which encodes for the cystic fibrosis transmembrane conductance regulator (*CFTR*) protein

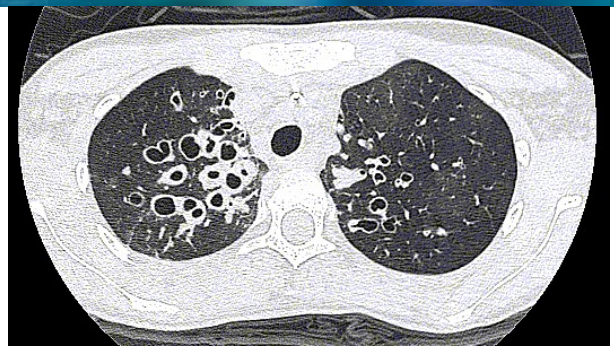


Normal Cell **CF Cell**

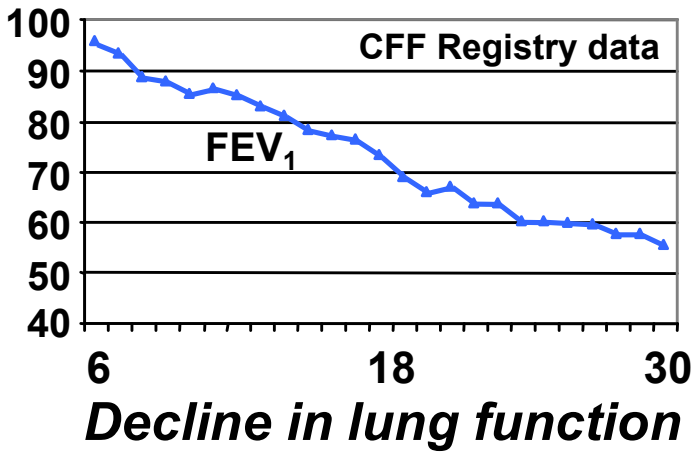
CFF.org; CFF Registry; Ashlock NACFC 2003

Pathogenesis of CF lung disease





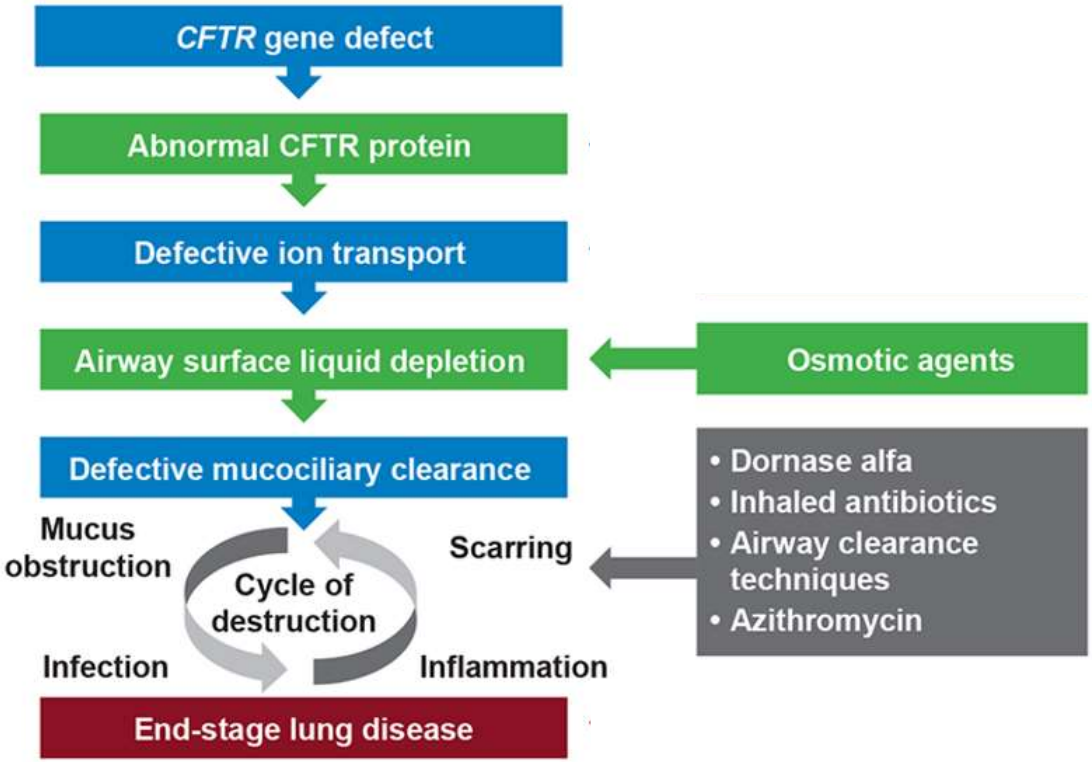
Bronchiectasis



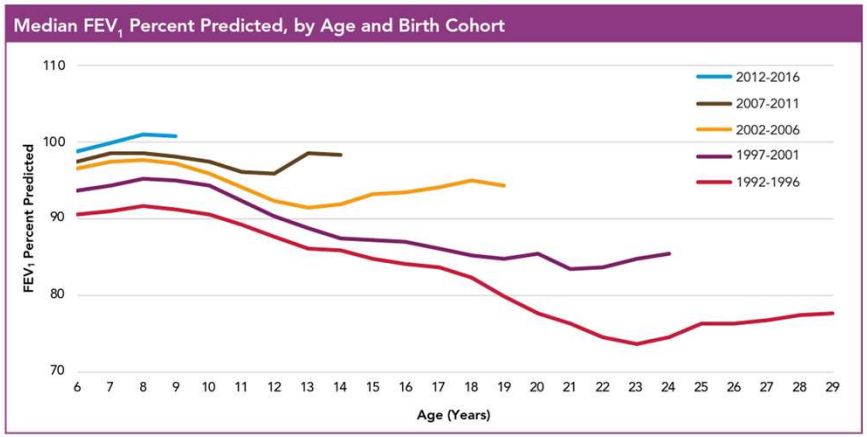
Decline in lung function

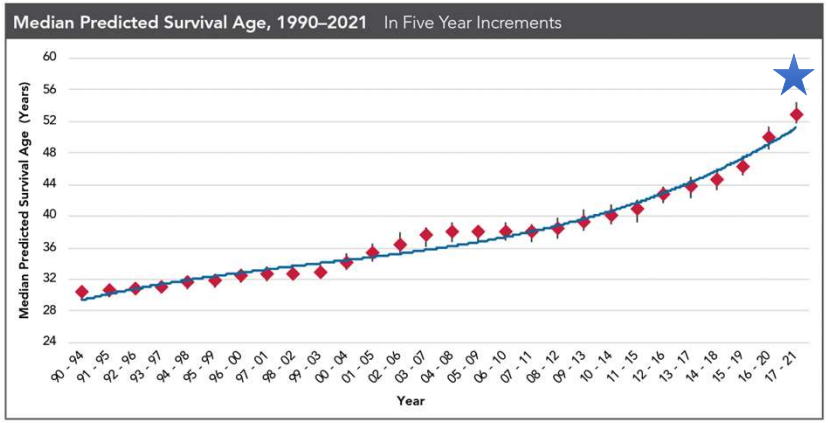
http://www.nhlbi.nih.gov/health/health-topics/topics/cf/signs.html

Therapeutic approaches to treat *CFTR* dysfunction in the lung



CFTR modulators (90%+ of the CF population) have significantly improved pulmonary function & survival

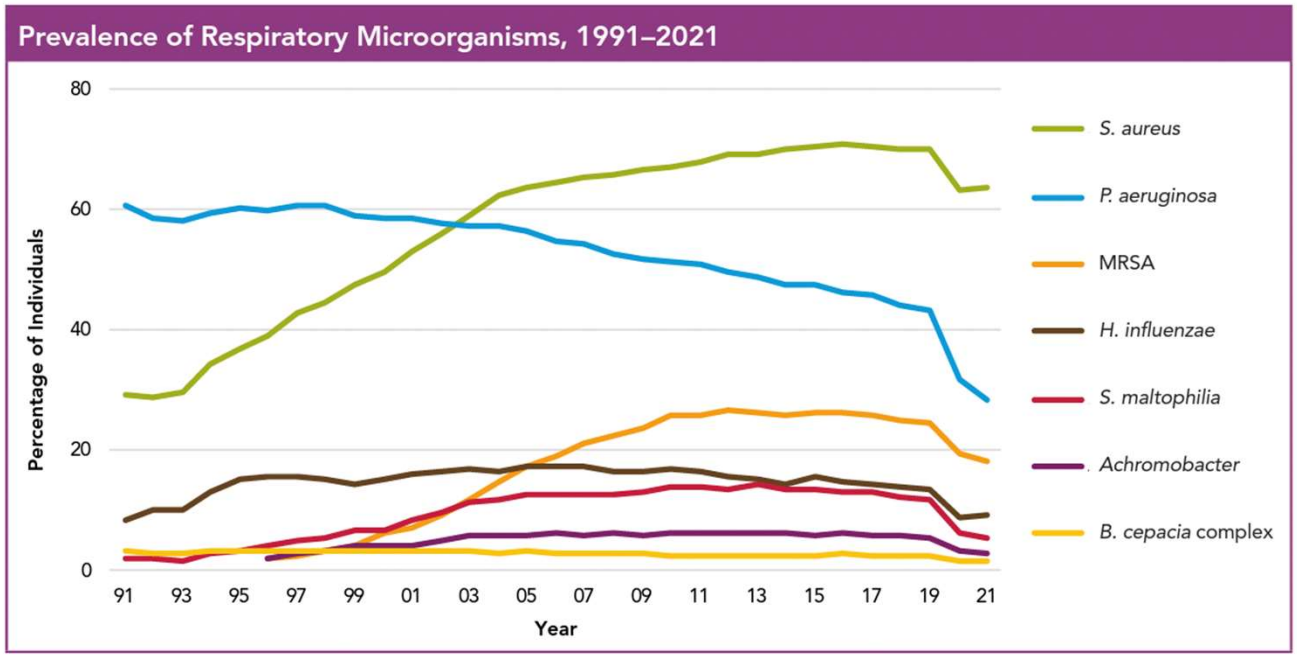




- Current median predicted age of survival is 56 years
- With recent advances in therapies, shift toward a lifelong chronic disease and phenotypic overlap with non-CF bronchiectasis population

2021 United States CFF Patient Registry

Prevalence of respiratory pathogens has improved, but chronic airway infections persist

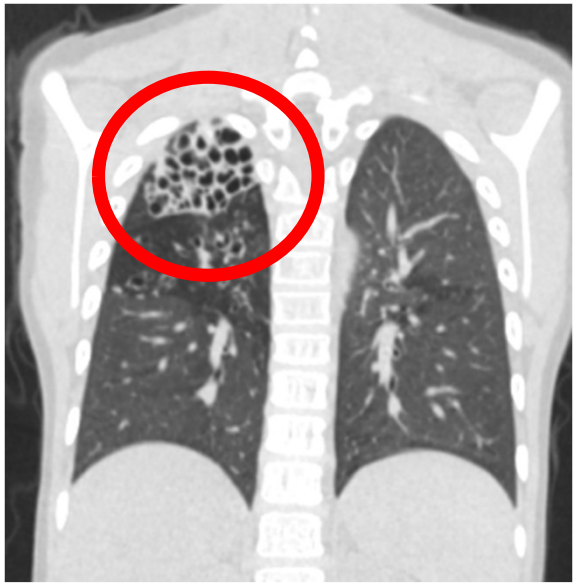


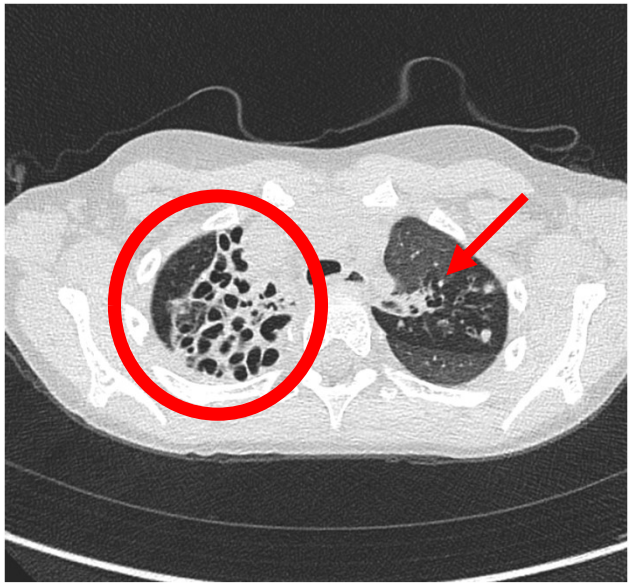
2021 United States CFF Patient Registry

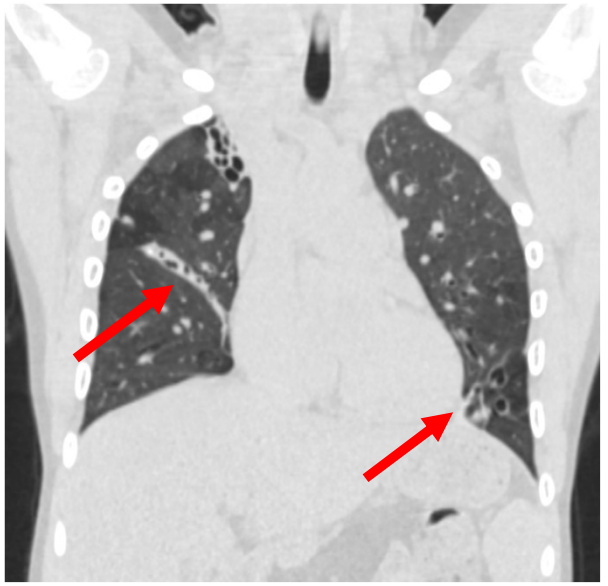
Patient Case

- 8 yo boy with CF (F508del/F508del)
- Diagnosed via newborn screen
- Historically healthy
- Healthy weight and BMI
- Chronic *S. aureus* infection with intermittent *P. aeruginosa* (last positive at 6 years old)
- No other CF co-morbidities
- Limited in-person evaluations in 2020 due to COVID
- Developed chronic cough, crackles and significant decline in FEV_1 from 90% to 40-50%
- Admitted and treated with IV antibiotics against *S. aureus* and *P. aeruginosa*, however symptoms persisted
  - Treated with 3 courses of IVs over 6 months
  - Started on CFTR modulator (ETI)
- New best FEV_1 71%, chronic cough

Patient Case







- BAL and sputum culture: + AFB smear & culture
- + *Mycobacterium avium* (R amikacin, S clarithromycin)

Patient Case

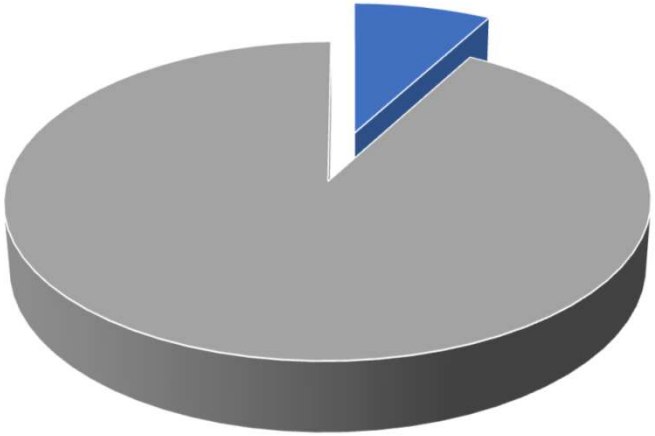
- Diagnosis of NTM pulmonary disease made
- Treatment initiated
  - Oral azithromycin, oral ethambutol, inhaled (IV) amikacin
  - On treatment, cough has improved and pulmonary function has stabilized with FEV_1 ~ 70% predicted
- Treatment > 1 year, still with persistent positive NTM cultures
  - Replaced inhaled (IV) amikacin with inhaled liposomal amikacin
  - Added oral clofazimine through and single patient IND
  - Subtherapeutic drug levels noted for 2 of 3 drugs; increased doses
  - Added new antimycobacterial treatment option (bedaquiline)
    - Culture conversion with negative cultures x 3 months on 5 drugs, recent positive again

What proportion of the CF population in the U.S. had a +NTM culture in 2022? (CFF Registry)

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

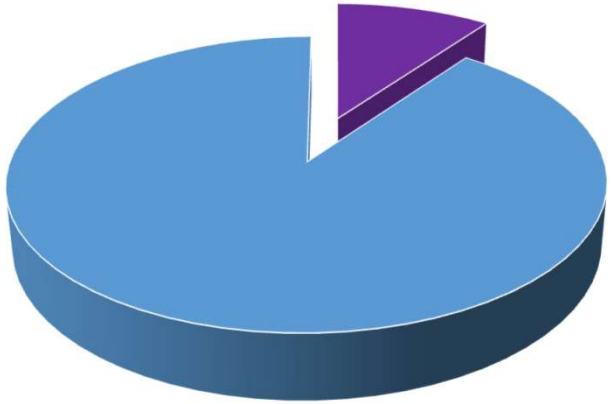
Estimated Prevalence of NTM in CF

Current Global Prevalence of NTM Infection **~8%**



52% MAB, 47% MAC

US Prevalence of NTM Infection in 2022
10%
Longitudinal US Prevalence (2010-2016)
20%

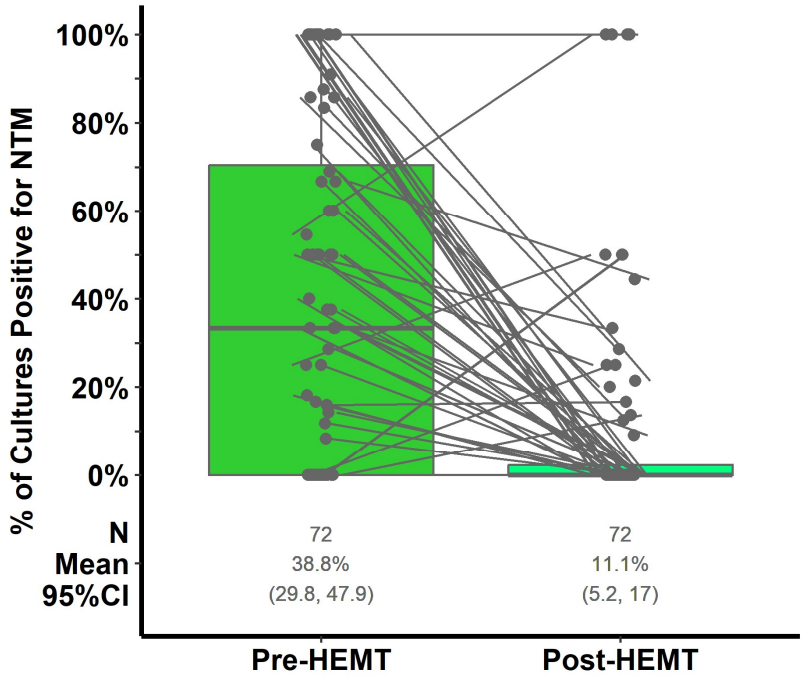


46% MAC, 35% MAB, 19% Unk.

Prieto MD, et al. ERJ Open Res. 2023.
CF Foundation Patient Registry 2022 Annual Data Report
Adjemian J, et al. Ann Am Thorac Soc. 2018.

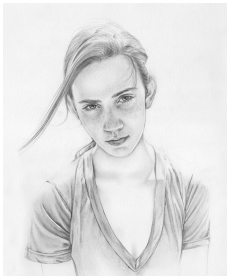
NTM culture positivity since CFTR modulators in PREDICT

- CF population with recent positive NTM culture
  - Prior to ETI availability, culture positivity rate was 37%
- 72 subjects with data pre- and post- starting ETI or Iva
  - Culture positivity rates decreased from 39% to 11%
    - Median difference -27% (p<0.001)



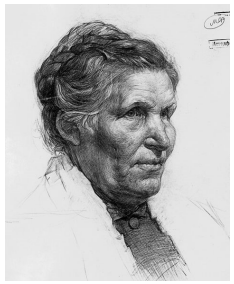
NTM in Cystic Fibrosis *vs.* Non-CF

Cystic Fibrosis



- CF Care Center
- Infrastructure for clinical trials
- Lifelong sputum culture surveillance
- Earlier detection without clinical features
- Mix of co-infections with other bacteria
- Greater variability in drug PK
- Evidence of diminished response to treatment
- Long-term impact of modulators unknown

Non-CF Bronchiectasis

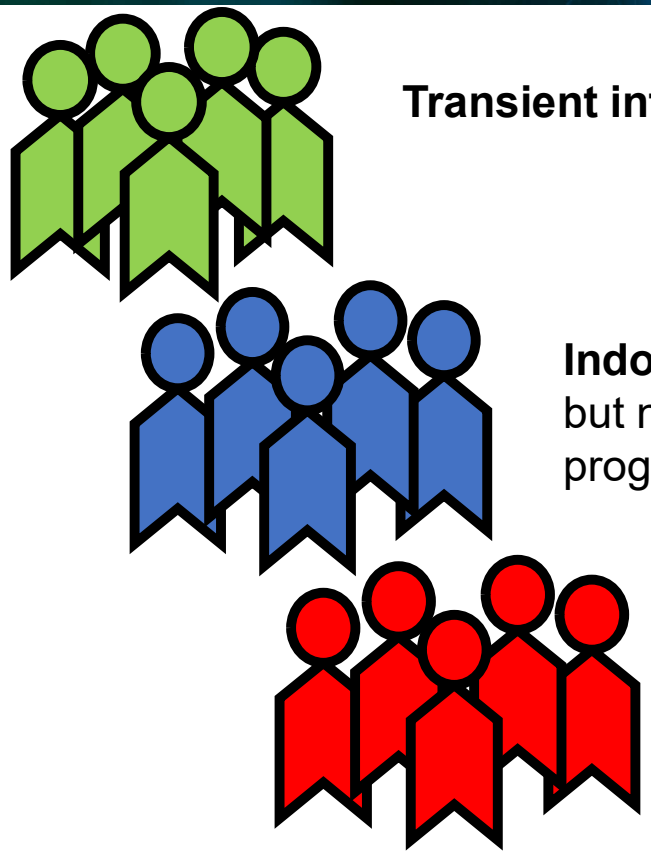


- Community-based care
- Overall greater population size
- Often infrequent airway cultures
- Clinical symptoms prompt cultures
- Mix of underlying diseases and co-morbidities

- **Trend towards studying CF and NCFB separately**
- **Opportunities to combine CF and non-CF populations for clinical trials, perhaps with focus on specific phenotype/endotypes within NCFB**

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

NTM patient cohorts in CF



Transient infection: Only one positive culture

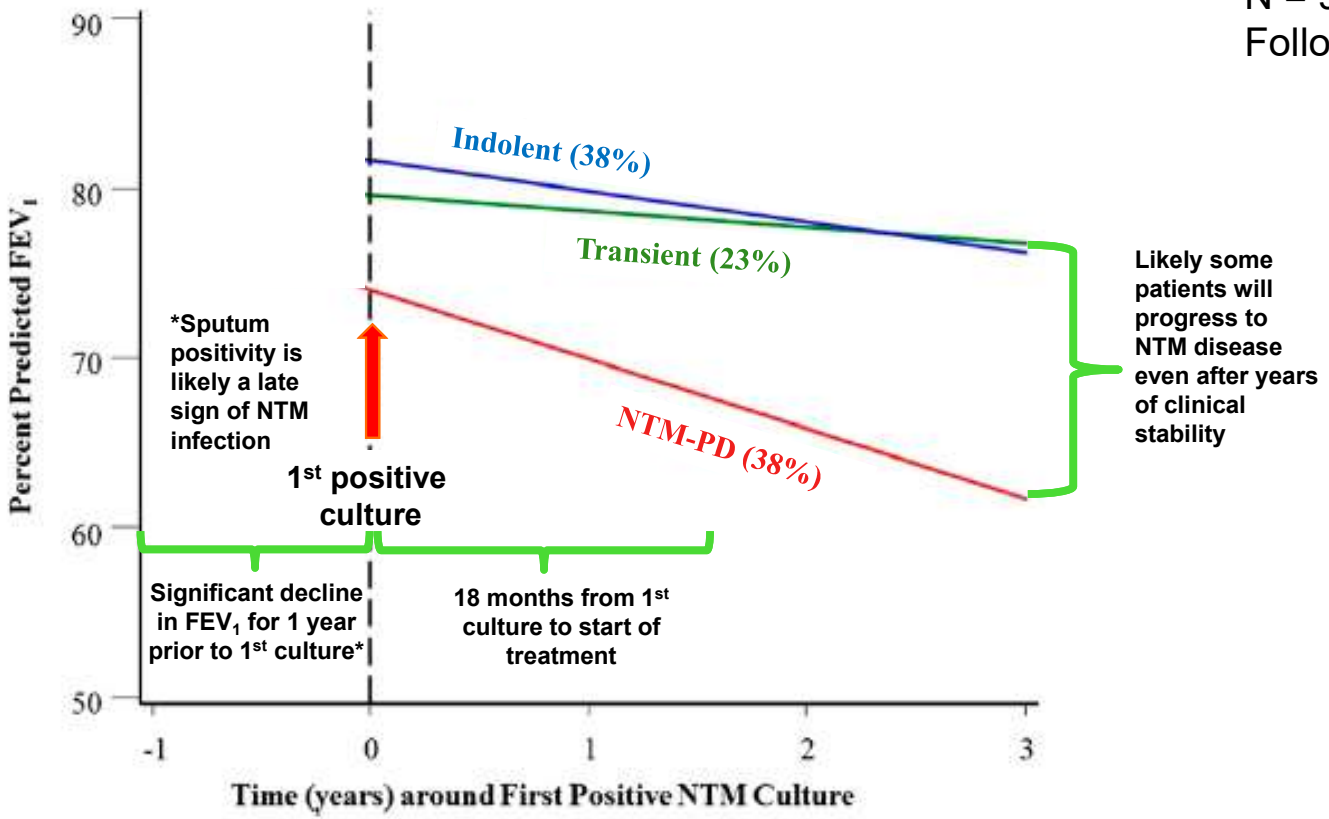
Indolent infection: > 1 positive cultures but no clinical evidence of accelerated progression of CF lung disease

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;

Clinical significance of NTM infection in CF

N = 96
Follow-up: 4.4 years



Martiniano AATS 2014

Must establish diagnosis of NTM-PD *prior* to starting treatment

- Microbiologic criteria
- Radiographic criteria
- Clinical criteria

- “Appropriate exclusion of other diagnoses”

- Prompt diagnosis for those with NTM-PD is critical

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

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

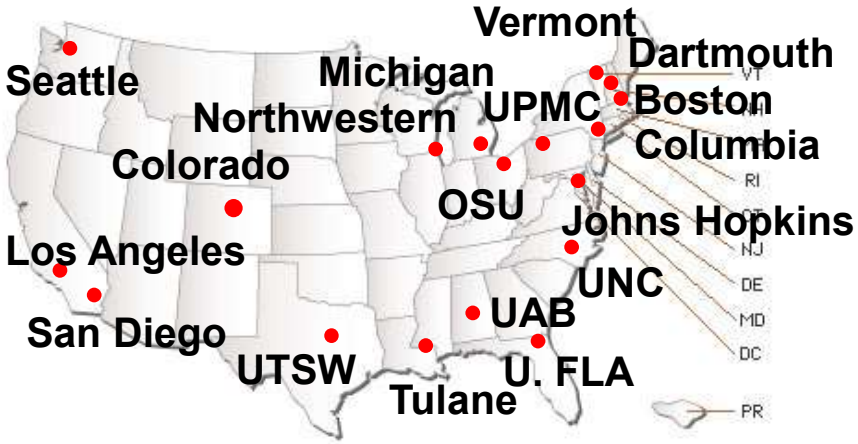
- Prospective, multicenter, observational study at pediatric and adult CF Care Centers in the US
  - Standardized approach to NTM-PD diagnosis, including optimization of CF cares and treatment of co-pathogens
  - Inclusion: People with CF, 6 years and older, with a recent positive NTM culture of a species that has never been treated

Martiniano, et al. J Cyst Fibros. 2023
NCT02073409

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

- 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.

CFF NTM Consortium



Martiniano, et al. J Cyst Fibros. 2023
NCT02073409

PREDICT Preliminary Results

- Total enrollment N = 274
  - NTM-PD Diagnosis ~25%

- Similar rates of MAC & MAB
- Similar sex, lung function, and CF genotype distribution
- Children showing higher rates of NTM-PD

36% children aged 6-18yr (N = 18/50) diagnosed with NTM-PD

VS.

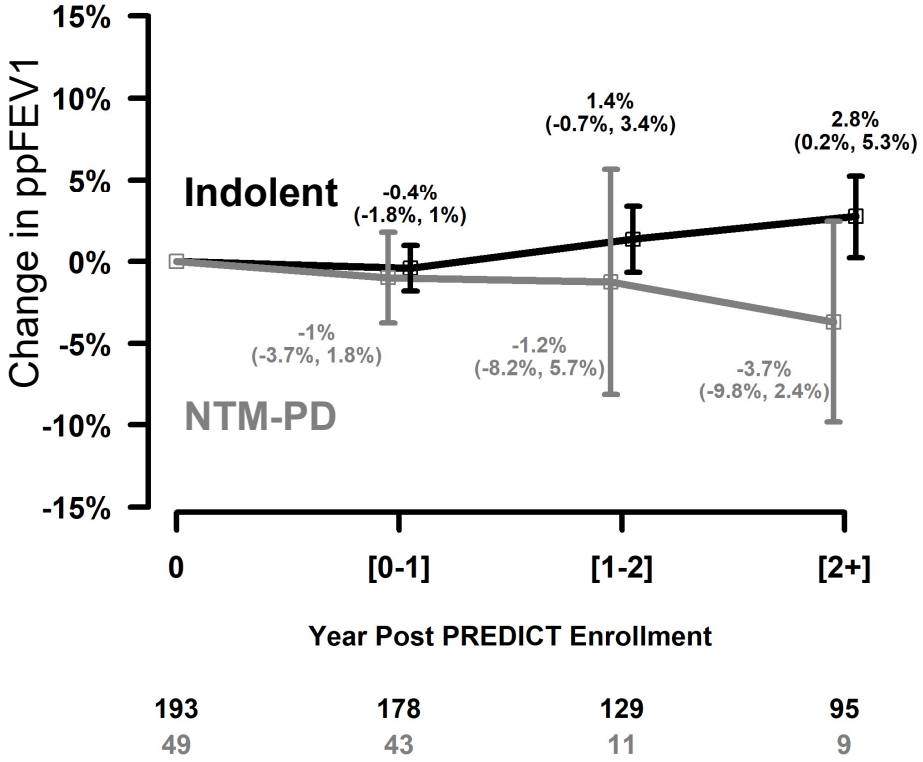
19% adults aged >18yr (43/224) diagnosed with NTM-PD

Chi-square 0.017

NTM PREDICT PATIENCE

NCT02073409

Prompt diagnosis of NTM-PD is important



- Pulmonary function improves for those with indolent infection
- Mean time to NTM-PD diagnosis is 12 months
  - Majority are diagnosed < 2 years
  - Lung function loss is minimized with efficient NTM-PD diagnosis

What is the recommended first-line treatment for macrolide-susceptible, non-cavitary MAC-PD 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

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 pathogens. What is the next recommended treatment regimen for this patient?

1. Oral azithromycin, ethambutol, and rifampin
2. Surgical resection of the cavity without antibiotics
3. Inhaled amikacin alone
4. IV amikacin, IV imipenem, and oral azithromycin

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1. Oral azithromycin, ethambutol, and rifampin
2. Surgical resection of the cavity without antibiotics
3. Inhaled amikacin alone
4. **IV amikacin, IV imipenem, and oral azithromycin**

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

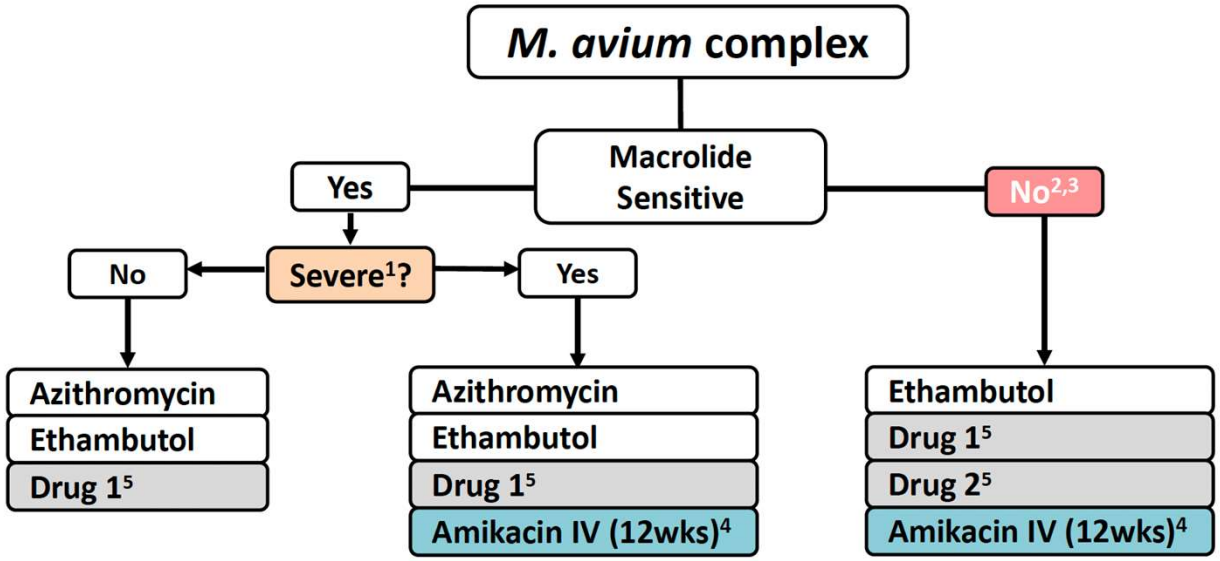
- Prospective, open label treatment trial of Guidelines-based therapy at CF Care Centers (PREDICT sites)
  - Inclusion: Diagnosis of NTM-PD through PREDICT and intent-to-treat
  - First-line and alternate drug regimens are recommended for MAC and MAB treatment
  - Specific guidelines for safety and toxicity monitoring

- 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

NTM PREDICT PATIENCE

NCT02419989

PATIENCE Algorithm



[2] Expert Consultation Recommended

[3] Azithromycin may be used independent of NTM treatment

[4] The use of 4 antibiotics may extend beyond 12 weeks based on clinical response and judgment of provider

[1] Severe Disease:

Smear positive +/or
Cavitary infection by CT +/or
Systemically ill

[5] MAC drug (order of preference):
Rifampin (if no Ivacaftor)
Clofazimine
ALIS > Amikacin (inh)*
*Skip past inhaled Amikacin if on Amikacin IV
Tedizolid > Linezolid
Bedaquiline

NTM PREDICT PATIENCE

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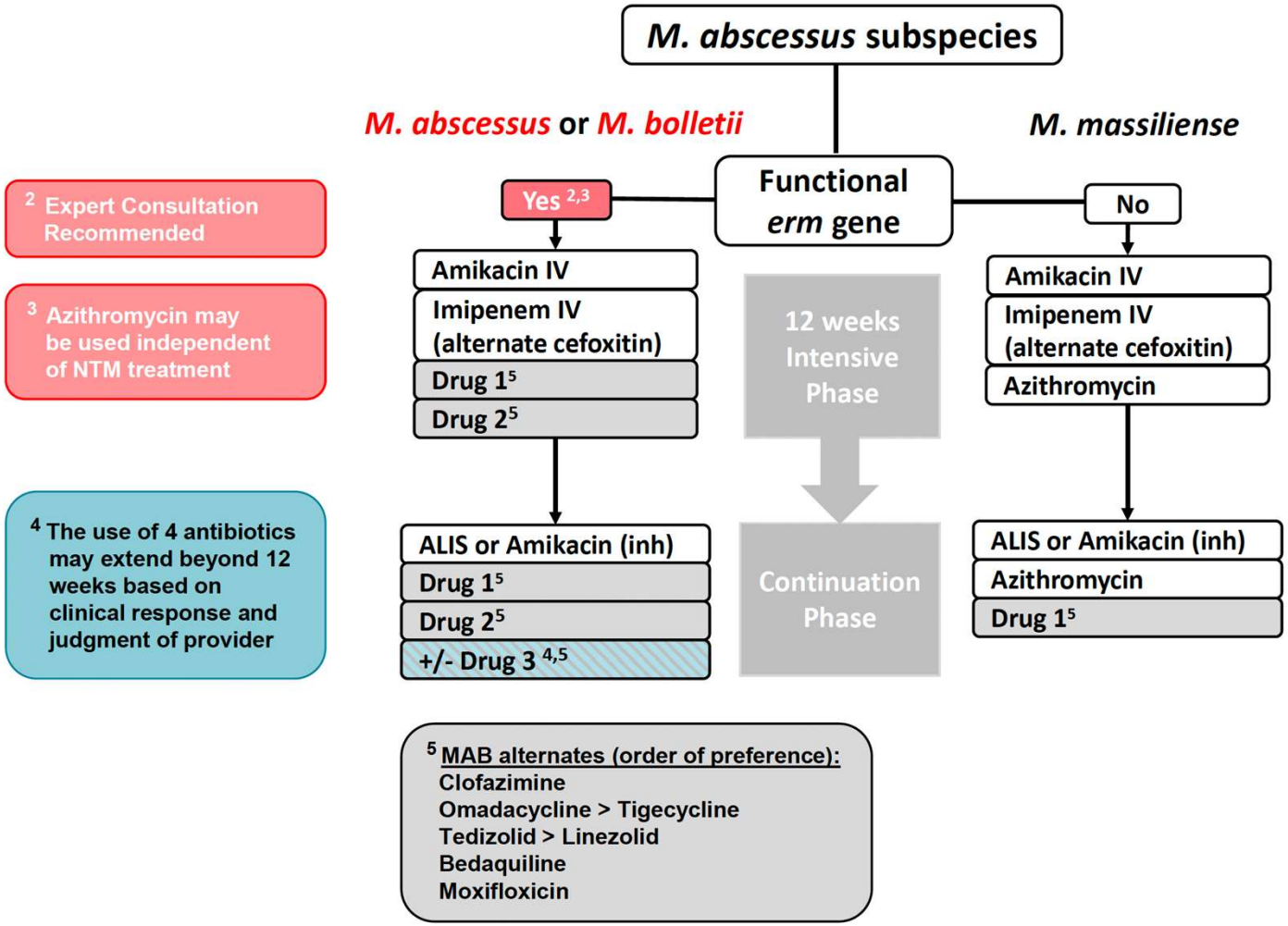
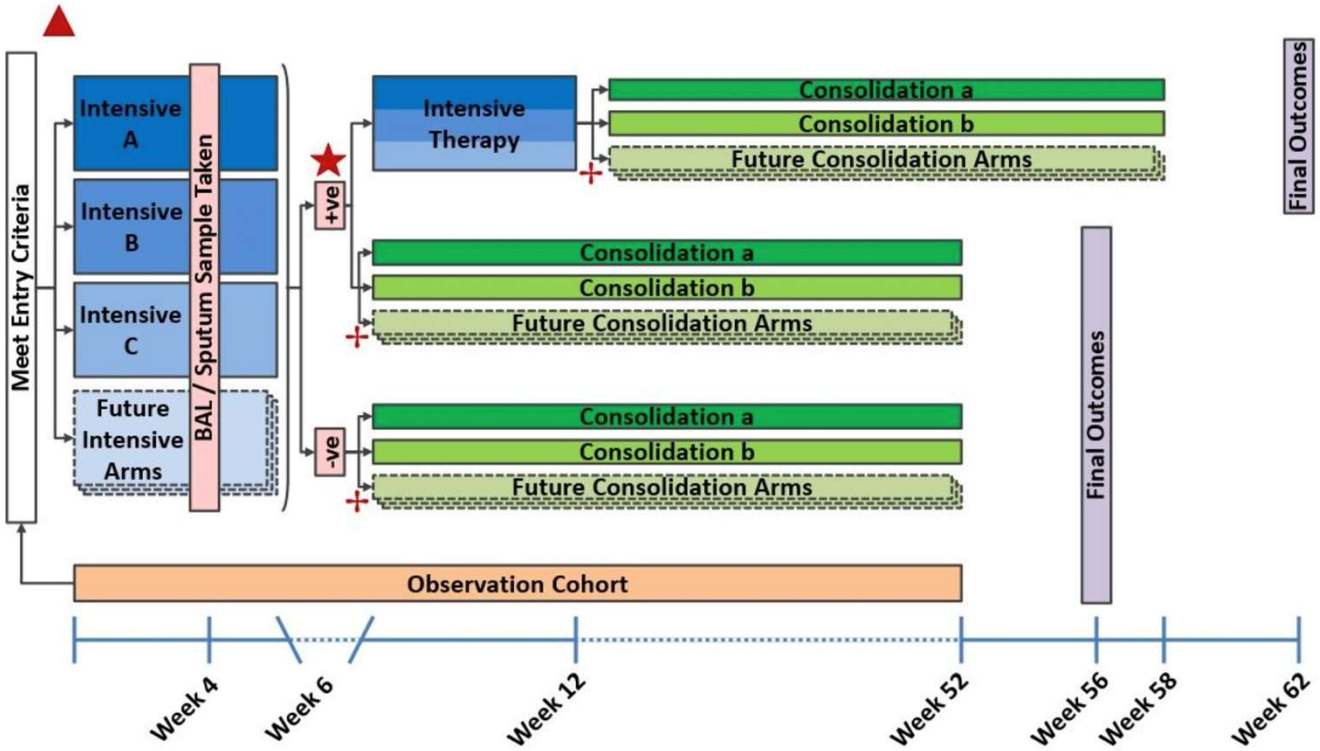
PATIENCE Algorithm



NTM PREDICT PATIENCE

NCT02419989

Finding the Optimal Treatment for MAB Trial (FOR*Ma*T)



FORMAT
Finding the Optimal Regimen for Mycobacterium Abscessus Treatment

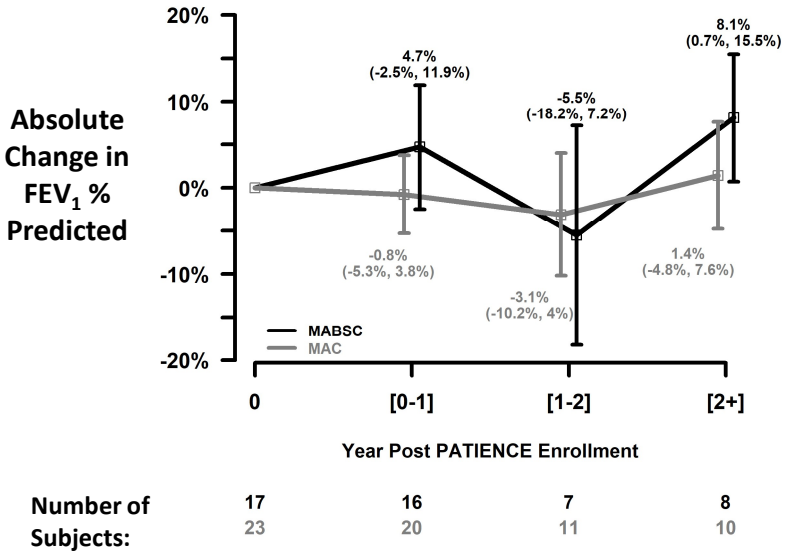
PI: Dr. Claire Wainwright, Brisbane, Australia
Trial ID: ACTRN12618001831279
https:formattrial.com

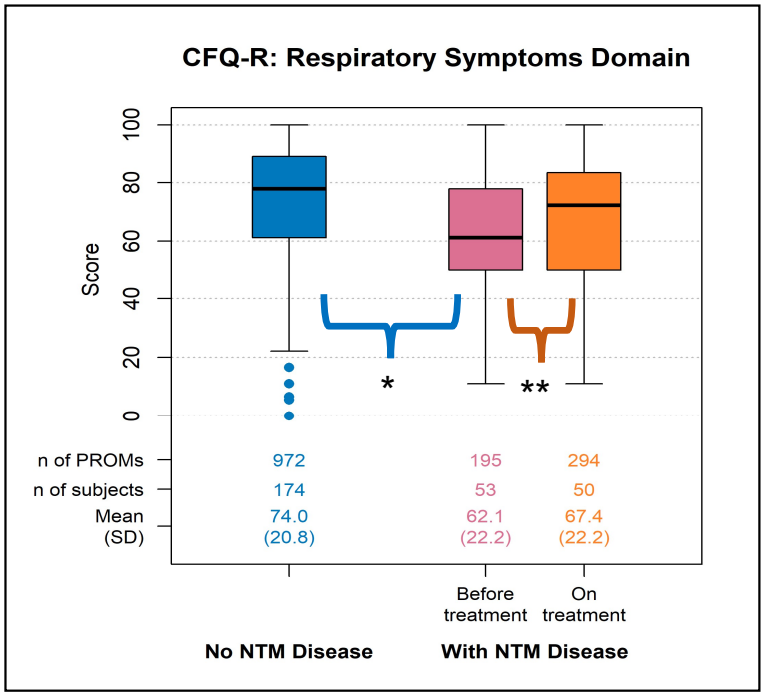
Treatment outcomes

- For initial treatment of NTM-PD, outcomes are improved with a guidelines-based, standardized treatment approach
- Historic treatment “success” rates:
  - MAC= 75%; MAB = 30-50%;
- Preliminary PATIENCE trial culture conversion rates
  - MAC = 70%; MAB = 70%
- 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
- Consider alternative treatments, include bacteriophage treatment (POSTSTAMP Trial)

Nick JA, et al. Cell. 2022
NCT06262282

Pulmonary function decline stabilizes and clinical symptoms improve on treatment





*Respiratory symptom domain is 14 points lower after NTM disease onset prior to treatment, 95% CI 8 to 20, p<0.001.

**Respiratory symptom domain 10 points higher post treatment in those with NTM disease, 95% CI 6 to 13, p<0.001.

NTM PREDICT PATIENCE

NCT02419989

Treatment considerations in CF

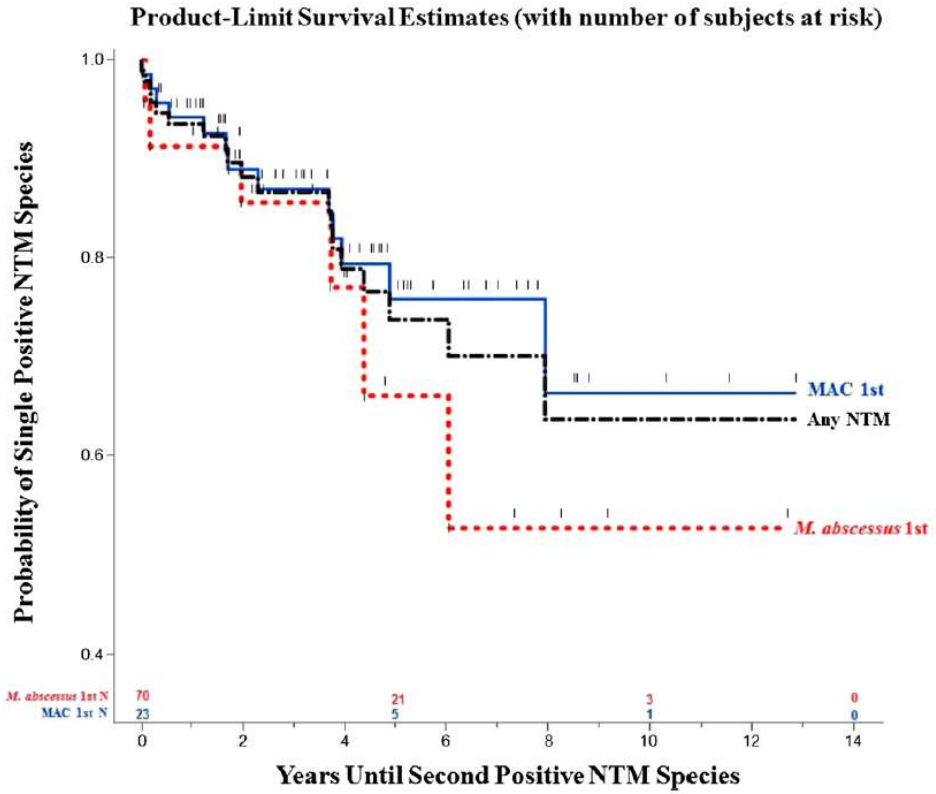
- Consider therapeutic drug monitoring for all people with CF
  - Abnormal intestinal absorption and altered pharmacokinetics in CF
  - Single-dose PK study of azithromycin, ethambutol and rifampin in CF
    - 19 of 20 CF subjects had >= 1 abnormal peak drug level when compared to healthy controls
    - Food & enzymes did not improve levels and lowered rifampin levels

Drug	Initial Oral Dose	Condition	Peak Drug Measurement
Azithromycin	10mg/kg (max 500mg) once daily	With or without food	2 hours post dose
Ethambutol	15mg/kg (max 2500mg) once daily	With or without food	2 hours post dose
Rifampin	10mg/kg (max 600mg) once daily	Empty stomach	2 hours post dose

- 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

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

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 by Collaborators

Breath: CFF Clinical Pilot Award

- ***Volatile breath metabolites*** (Jane Hill, PhD, University of British Columbia).

Whole Blood: CFF Clinical Pilot Award

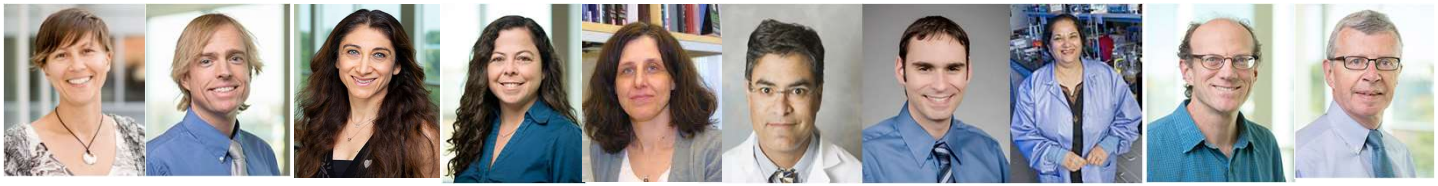
- ***Circulating leukocyte RNA signatures*** (Mimi Saavedra, MD, NJH).

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).



Jane Hill, PhD | M. Strong, PhD | M. Saavedra, MD | R. Davidson, PhD | J. Philips, MD, PhD | P. Singh, MD | S. Salipante, MD, PhD | D. Chatterjee, PhD | K. Malcolm, PhD | D. Lynch, MD

Slide courtesy of Jerry Nick, MD

Summary

- NTM is common in the sputum of children and adults with CF
- NTM pulmonary disease diagnosed in about 25% of infected patients
- In the era of CFTR modulator therapies, NTM continues to be a pathogen but is harder to detect in sputum and clinical syndrome may be more subtle
- 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 (and combined trials) will continue to guide treatment of NTM in persons with CF

Acknowledgements

PREDICT & PATIENCE Study Team

Colorado Study Team
co-PI: Jerry Nick, MD
Co-PI: Stacey Martiniano, MD
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Charlie Haworth, MD (Papworth, UK)
Ken Olivier, MD (NIH)
Mike Boyle, MD (CFF)
Bruce Marshall, MD (CFF)

CFF TDN National Resource Centers

https://www.cff.org/researchers/national-resource-centers

Colorado NTM Outcome Measure Advancement Core NRC
PI: Jerry Nick, MD

Colorado NTM Core Clinical Research Service NRC
PI: Jerry Nick, MD

Questions?

PATIENCE Treatment Dosing Table

Drug Name	Route	Typical Denver Pediatric Dose	Typical Denver Adult Dose	Max Total Daily Dose	Key Alternative Dose Ranges in CFF/ECFS Guidelines
AMIKACIN	IV	15mg/kg/dose once daily	15mg/kg/dose once daily 3X/week	1500mg	Peds: 15-30mg/kg/dose once daily Adolesc: 10-15mg/kg/dose once daily Adults: 10-30mg/kg/dose once daily
AMIKACIN	INH	500mg once daily	500mg once daily	500mg	Option: 250mg twice daily
AMIKACIN LIPOSOME INHALATION SUSPENSION (ALIS)	INH	590mg/8.4ml once daily	590mg/8.4ml once daily	590mg	
AZITHROMYCIN	Oral	10mg/kg/dose once daily	500mg once daily	500mg	Peds: 10-12mg/kg/dose once daily Adolesc/adult: 250-500mg once daily
BEDAQUILINE	Oral	≥12 years 400mg once daily for 2 weeks then 200mg 3 times a week	400mg once daily for 2 weeks then 200mg 3 times a week	400mg	
CEFOXITIN	IV	50mg/kg/dose 3X/day	2000mg 3X/day	6000mg	Adult: 200mg/kg/day divided q8 hr (max 12g/day)
CLOFAZIMINE	Oral	<40kg = 50mg once daily	100mg once daily	100mg	1-2 mg/kg/dose once daily (max 100mg) adult: 50-100mg once daily
ETHAMBUTOL	Oral	15mg/kg/dose once daily	1200mg once daily	1200mg	
IMIPENEM	IV	20mg/kg/dose twice daily	1000mg twice daily	2000mg	PEDS: 15-20 mg/kg/dose twice daily
LINEZOLID	Oral or IV	10mg/kg/dose twice daily	600mg once daily	600mg	<12y/o: 10mg/kg/dose 3X daily 12+ y/o: 10mg/kg/dose once or twice daily Adult: 600mg once or twice daily
MOXIFLOXACIN	Oral	10mg/kg/dose once daily	400mg once daily	400mg	Peds: 7.5-10 mg/kg/dose once daily

PATIENCE Treatment Dosing Table 2020_1203

OMADACYCLINE	Oral	>8 years old & >50 kg: 300mg once daily	300mg once daily	300mg	
OMADACYCLINE	IV	>8 years old & >50 kg: 300mg once daily	100mg once daily	100mg	
RIFAMPIN	Oral	10mg/kg/dose once daily	600mg once daily	600mg	10-20mg/kg/dose once daily <50kg: max dose 450mg
TEDIZOLID	Oral or IV	≥12 years 200 mg once daily	200mg once daily	200mg	
TIGECYCLINE	IV	1.2mg/kg/dose twice daily	25mg twice daily	50mg	>12y/o: 100mg loading dose, then 50mg/day once or twice daily *consider pre-dose with anti-emetics and gradual increase from 25mg daily to goal dose

PATIENCE Suggested Drug Toxicity Monitoring Schedule

	CBC[1]	LFTs[2]	Creatinine[3]	Audiograms[4]	Visual[5]	Serum Peak Levels[6]	Exam for peripheral neuropathy[7]	ECG for QTc [8]
Amikacin (IV)			Weekly	Monthly (peds) Q3 months (adults)		After 1 week and as needed		
Amikacin (inh)				every 3 months				
Amikacin Liposome Inhalation Suspension				every 3 months				
Azithromycin				every 6 months				Month 1 and 6
Bedaquiline		Monthly						At month 1 and 6
Cefoxitin	Monthly							
Clofazimine		Monthly						Month 1 and 6
Ethambutol		Monthly			Daily and/or formal every 3 months		every 3 months	
Imipenem	Monthly	Monthly						
Linezolid	Monthly				Daily and/or formal every 3 months		every 3 months	
Moxifloxicin								Month 1 and 6
Omadacycline		Monthly						
Rifampin	Monthly	Monthly	Monthly					

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PATIENCE Suggested Drug Toxicity Monitoring Schedule

Tedizolid	Monthly				Daily and/or formal every 3 months		every 3 months	
Tigecycline		Monthly (plus alb/bili)						

Consider drug discontinuation or dose modification at the following suggested thresholds:

[1]CBC parameters: ANC<500, plts<50K, Eosinophilia concerning for drug rxn, and/or anemia requiring transfusion.
[2]LFT parameters: ALT >5xULN or >3XULN if symptomatic, Bilirubin >3XULN, Albumin: a clinically significant decrease from baseline.
[3]Creatinine: Increased by 0.3-0.5 above baseline
[4]Audiogram: Assess if drop of 10+ decibels Standard Threshold Shift
[5]Visual changes: Discontinue for blurred vision, eye pain, red-green color blindness (Ishihara test: https://www.colour-blindness.com/colour-blindness-tests/ishihara-colour-test-plates/) or any loss of vision. Recommend daily self-assessment for adults and formal assessment with Ophthalmology every 3 months for pediatrics
[6]Peak level 30 minutes after end of infusion, goal peak level 30-60
[7]Neuropathy above ankle
[8]QTC >470 for woman or >480 for man (consider repeating on a different day and/or over-read by cardiologist before making a change)