Cystic Fibrosis Related NTM Infections

Jerry A. Nick, MD
Professor of Medicine
National Jewish Health
University of Colorado
Disclosures

Support for this work
CF Foundation

Other research support (past 5 years)
NIH
Gates Foundation
Department of Defense
State of Colorado
Genentech
Vertex
Gilead

Committees, Advisory Boards and/or Consulting (past 5 years)
CFF Center Committee, TDN Protocol Review Committee, TDN Steering Committee, NTM Guidelines Committee, Gilead, Novartis, Vertex, Pharmaxis, Genentech
Classic CF
(Childhood Diagnosis)

- Chronic sinusitis
- Severe chronic bacterial infection of airways
- Severe hepatobiliary disease (5–10% of cases)
- Pancreatic exocrine insufficiency
- Meconium ileus at birth (15–20% of cases)
- Sweat chloride value usually 90–110 mmol/liter; sometimes 60–90 mmol/liter
- Obstructive azoospermia

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Nonclassic CF (Adult Diagnosis)  
- Chronic sinusitis
- Chronic bacterial infection of airways (later onset, but variable)
- Adequate pancreatic exocrine function (usually); pancreatitis (5–20% of cases)
- Sweat chloride value usually 60–90 mmol/liter; sometimes normal (<40 mmol/liter)
- Obstructive azoospermia

Evolving understanding of the CF Phenotype

- CNS
- Short stature (IGF-1)
- Psychosocial and behavioral
- Tooth enamel
- Reactive airways disease
- Diabetes
- Granulocyte dysfunction
- Risk for malignancy
- Risk for IBD
- Gallstones
- Kidney stones
- Bone disease

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Unique Aspects of NTM infection in the CF airway

- Disease with the highest prevalence of pulmonary NTM
- Universal occurrence in the setting of other bacterial co-infections
- Susceptible to both slow and rapid-growing NTM
- Appears that only a subpopulation of CF patients are vulnerable
- Early detection in asymptomatic patients through the Care Center model contributes to a high rate of transient and indolent infection
- Reduced and/or highly variable antibiotic absorption, distribution and elimination
- Reduced treatment response when co-enrolled with non-CF patients in the liposomal amikacin for inhalation (Insmed 112).
Genus *Mycobacterium* and the “NTM”

- Rapid-growing mycobacteria (RBM)
- Slow-growing mycobacteria (SBM)

- **M. abscessus complex**
- **M. tuberculosus complex**
- **M. leprae**
- **M. avium complex**

Epidemiology - very generally speaking....

**M. abscessus complex**
- Associated with more advanced disease or patients with more rapid pulmonary decline
- Often in the presence of *P. aeruginosa*
- Associated with more aggressive treatment
- High prevalence in Europe

**M. avium complex**
- Strong age association, often in milder, adult-diagnosed patients
- Not associated with *P. aeruginosa*
- Often with *S. aureus* and *Stenotrophomonas*
- High prevalence in N. America
- Also, CF patients who spend a lot of time in the dirt!
Geographic Risks of Pulmonary NTM Disease in the United States

Water + Heat = Evaporation
Soil conditions

High-Risk County
Low-Risk County

Urban
Higher income
Higher education

AJRCCM (2012) 186:553-58
Environmental Differences in NTM prevalence in CF Patients Worldwide

- **CFF Registry (2010)**: 62 MAC, 18 Other, 6 other
- **U.S. Multicenter (2003)**: 72 MAC, 18 Other, 10 other
- **Colorado (2010)**: 72 MAC, 27 Other
- **UK (2009)**: 68 MAC, 27 Other, 5 other
- **France Multicenter (2009)**: 32 MAC, 27 Other, 21 Other
- **Scandinavia (2015)**: 56 MAC, 32 Other, 23 Other

*Co-infection classified as *Mycobacterium abscessus*
Is MAC even a CF pathogen?

...or is it as virulent as *M. abscessus*?
Clinical Significance of a First Positive NTM Culture in CF

Change in FEV₁ pre- and post first positive NTM culture
Average time of follow-up 4.4 yrs. (n=96)

- Significant decline in FEV₁ for 1 year prior to 1st culture
- 18 months from 1st culture to start of treatment

Likely some patients will progress to NTM disease even after years of clinical stability
Whole-genome sequencing can identify similarity between isolates

M. abscessus subsp. massiliense

M. abscessus subsp. abscessus

M. abscessus subsp. bolletii

Phylogenetic tree built through the number and locations of SNPs

<20 SNP difference

Fig. 1 Global phylogeny of clinical isolates of *M. abscessus*.

“Emergence and spread of a human transmissible multidrug-resistant nontuberculous mycobacterium”
Colorado CF Research & Development Program

Advancing our understanding of NTM in the CF airway

Molecular Core
Director Michael Strong, PhD
- whole genome sequencing (WGS)

548 WGS

NTM Culture, Biorepository, and Coordinating Core
Director: Charles Daley, MD
Co-Director Max Salfinger, MD
- culture
- basic molecular identification
- antimicrobial susceptibility
- isolate banking
- data coordination

>1000 isolates
>60 CF Centers

Clinical Research Core
Director, Stacey Martiniano, MD
Co-Director Jerry Nick, MD
- clinical data
- supports trials PREDICT PATIENCE PK/PD trials Biomarkers

https://www.nationaljewish.org/Colorado-CF-Research-and-Development-Program/Home
Phylogenetic analysis for surveillance of *M. abscessus* transmission or shared environmental exposure in U.S. Cystic Fibrosis patients

21% of patient from from 19 facilities are within 8 clusters

79% of patient from from 39 facilities are unclustered
Phylogenetic analysis for surveillance of MAC not c/w transmission or shared environmental exposure in U.S. Cystic Fibrosis patients
Acquisition and Host response

Case: 39y/o female, F508del/F508del.
CFRD (poorly controlled)
P. aeruginosa and Staph aureus
M. intracellulare

2 isolates (1 lineage)

3072 SNPs
M. avium

8 isolates (5 lineage)

221SNPs
Acquisition and Host response

FEV₁ (% predicted)

M. abscessus
MAC
MAI
MAC
PREDICT Trial
Rx

1/1/08 1/1/09 1/1/10 1/1/11 1/1/12 1/1/13 1/1/14 1/1/15 1/1/16


N=5
N=3

1 1 1 1
Repeated exposure to different strains of MAC
Cleared *M. abscessus* and some MAC without treatment
Now with pulmonary disease from one or more MAC strains, implying differences in virulence between various stains of MAC
May be able to identify virulence genes based on which strain(s) persist
Similar multiple lineage infections with MAC seen in other patients, not with *M. abscessus* complex
Clinical Trials (at last!)
Colorado PREDICT and PATIENCE Trials

**Primary Objective:**
- Develop user-friendly, evidence-based protocols for NTM disease diagnosis and treatment to be used for all CF patients in the US.

**Secondary Objectives:**
- Define an expected rate of development of NTM disease for patients with positive cultures.
- Identify clinical features associated with the development of disease.
- Define the expected rate of response to treatment using the current CFF/ECFS NTM guidelines, independent of expert consultation or specialized facilities.
- Define the rate of side effects or toxicities requiring alternate drug combinations.
- Establish the feasibility of future multi-center clinical trials at the site of care.
- Facilitate molecular analysis of NTM isolates from CF patients.
- Facilitate research in CF host susceptibility, NTM virulence and biomarker discovery.
PREDICT and PATIENCE Study Milestones

August 2012  
Initial PREDICT and PATIENCE Proposal

April 2013  
External Advisory Committee Meeting (Denver)

Dec 2013
Jan 2014  
First patient enrolled in PREDICT  
First patient enrolled in PATIENCE

  
  55 subjects in PREDICT  
  24 subjects in PATIENCE  
  4 protocol revisions

April 2016  
Proposal to expand PREDICT and PATIENCE

Oct 2016
Nov 2016  
External Advisory Committee Meeting (Orlando)  
External Advisory Committee Meeting (Denver)

Feb 2017  
TDN Meeting (Seattle)

Jul 2017  
Investigators Meeting (Denver)

April 2018  
Multi-center enrollment (Denver) PREDICT and PATIENCE

AUG 2018  
First enrollment (outside Denver) PREDICT and PATIENCE
Prospective Evaluation of NTM Disease in Cystic Fibrosis (PREDICT Study)

- Prospective, single-center, observational trial at the Pediatric and Adult Colorado CF Care Center
  - Single diagnostic algorithm based on CF Foundation and European CF Society Guidelines (*Thorax*, 2016)

- **Inclusion:**
  - Diagnosis of CF
  - Positive NTM culture (last 2 years) with *M. avium* complex (MAC) or *M. abscessus* complex (MABSC)

- **Exclusion:**
  - Recent or current treatment of NTM
Diagnosis of NTM by the PREDICT Protocol

High Frequency NTM Screening:
Consider at every clinical encounter

Positive Culture

Previous positive cultures?
No

2-8 wks
Notify and schedule visit
Discontinue azithromycin

Yes
Repeat NTM culture
Consent and enroll in protocol
Blood/sputum samples
CFQ-R

Visits 1-2
3-12 wks
Clinical syndrome?
No clinical syndrome present

Adequate airway clearance
Address potential comorbidities
2 wk course of IVs for CF pathogens
Repeat NTM culture every clinical encounter
HRCT (if > 6 mo. since last)

Clinical syndrome present?
No clinical syndrome present

Yes

>1 Positive culture in past 2 years?
(a single BAL positive culture not sufficient)

Yes
NTM Disease

No
Blood/sputum samples
CFQ-R
Baseline comparison of subjects with NTM disease diagnosed compared to those without disease

<table>
<thead>
<tr>
<th></th>
<th><strong>NTM Disease</strong></th>
<th><strong>No NTM Disease</strong></th>
<th><strong>P-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range)</strong></td>
<td>25 (8 – 55)</td>
<td>26 (9 – 67)</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>16F, 7M</td>
<td>17F, 15M</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>NTM Species</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MAC (N = 36)</td>
<td>15 (65%)</td>
<td>21 (66%)</td>
<td>0.7</td>
</tr>
<tr>
<td>MABSC (N = 18)</td>
<td>8 (35%)</td>
<td>10 (31%)</td>
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</tr>
<tr>
<td>Other (N = 1)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Recent Best FEV₁ (within last 2 years), mean (SD)</strong></td>
<td>84 (25)</td>
<td>94 (24)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Recent Best BMI (within last 2 years), mean (SD)</strong></td>
<td>21.7 (3.4)</td>
<td>21.6 (3.0)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Known history of CF-related Diabetes (%)</strong></td>
<td>48%</td>
<td>30%</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Know history of ABPA (%)</strong></td>
<td>39%</td>
<td>29%</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Subjects diagnosed with NTM disease had significantly lower enrollment FEV$_1$ compared to those without disease.
Subjects with NTM disease had a more significant decline in %FEV$_1$ compared to those without disease.
Similar improvements in BMI in subjects with and without NTM disease while enrolled in PREDICT
Comparison of clinical syndrome assessments between subjects with and without NTM disease

<table>
<thead>
<tr>
<th>Assessments</th>
<th>NTM Disease N = 23 97 visits</th>
<th>No NTM Disease N = 32 246 visits</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional symptoms (any)</td>
<td>33 (34%)</td>
<td>36 (15%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Night Sweats*</td>
<td>15 (15%)</td>
<td>6 (2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Increased respiratory symptoms**</td>
<td>56 (58%)</td>
<td>97 (39%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Pulmonary exacerbation hospitalization/IVs in past year***</td>
<td>67 (72%)</td>
<td>79 (35%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Oral antibiotics started at the visit</td>
<td>28 (55%)</td>
<td>57 (71%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Significant FEV1 decline: &lt; 90% of best baseline</td>
<td>69 (70%)</td>
<td>96 (40%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight loss: &gt; 10% drop in BMI</td>
<td>31 (31%)</td>
<td>26 (11%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Radiographic findings suggestive of NTM$</td>
<td>36 (47%)</td>
<td>104 (57%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Radiographic findings have worsened</td>
<td>14 (18%)</td>
<td>44 (23%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*No difference in fever, decreased appetite, or fatigue  
**No difference in increased cough, sputum, hemoptysis, new/increased O2, or exercise intolerance  
***Likely influenced by our standard approach of treatment with IVs prior to NTM treatment  
$More middle lobe collapse in disease (8% vs. 1%, p=0.004, no difference in cavity, tree-in-bud, nodules
Preliminary Conclusions

- Use of a standardized NTM Diagnostic Protocol and data collection method in the CF care center setting is feasible and improves care
- 42% of PREDICT subjects met CFF/ECFS criteria for NTM disease after a median of 5 months
- Subjects in PREDICT without NTM disease showed stabilization of BMI and FEV₁ through optimization of CF cares
- Compared to the group without NTM disease, the subjects diagnosed with NTM disease had:
  - Significantly lower FEV₁ at enrollment and a more significant and rapid decline in FEV₁
  - Similar comorbidities and BMI trends
  - More frequent report of constitutional symptoms, severe exacerbations, and acute decline in BMI
Prospective Algorithm for Treatment of NTM in Cystic Fibrosis (PATIENCE)

Prospective, open-label, treatment trial at the Colorado CF Care Center
- Single treatment algorithm based on CF Foundation and European CF Society Guidelines (Thorax, 2016)

**Inclusion:** confirmed diagnosis of CF
- Age 7 years or greater
- Diagnosis of NTM disease (via PREDICT or Provider)
- Intention to treat the NTM disease, based on the judgment of the CF clinic physician that the patient may benefit from treatment

**Exclusion:**
- Pregnant
- History of transplantation
- Currently undergoing treatment for NTM infection
- Prior treatment failure for current NTM species, as defined by positive sputum cultures within 12 months of discontinuation of antibiotic treatment

NCT02419989

I. Stenzel
Photo by Derek Powazek
http://www.thebreathingroom.org/
**PATIENCE Treatment Protocols**

1. **Severe Disease:**
   - Smear positive +/or
   - Cavitary infection radiographically +/or
   - Systemically ill

2. **M. avium complex**
   - Yes
     - Macrolide sensitive
       - Yes
         - Azithromycin
         - Rifampin
         - Ethambutol
         - Amikacin IV (12 wks)
       - No
         - Azithromycin
         - Rifampin
         - Ethambutol

3. **M. abscessus or M. bolletii**
   - Yes
     - Functional erm gene
       - Intensive Phase
         - Amikacin
         - Imipenem
         - Linezolid
         - Azithromycin
       - No
         - Amikacin (neb)
         - Moxifloxacin
         - Linezolid
         - Azithromycin
     - No
       - Amikacin (neb)
       - Moxifloxacin
       - Linezolid
       - Azithromycin

4. **M. abscessus complex**
   - Yes
     - Functional erm gene
   - No
     - Amikacin (neb)
     - Moxifloxacin
     - Linezolid
     - Azithromycin

5. **M. massiliense**
   - 12 wks
     - Amikacin
     - Imipenem
     - Azithromycin
     - Functional erm gene

6. **Continuation Phase**
   - Amikacin (neb)
   - Moxifloxacin
   - Linezolid
   - Azithromycin

7. **Additional alternates**
   - Amikacin (neb)
   - Clofazimine

8. **1st alternate**
   - Moxifloxacin

9. **2nd alternate**
   - Amikacin (neb)
   - Clofazimine

All NTM isolates are evaluated by WGS by the Colorado RDP Molecular Core
# PATIENCE Drug Dosing Guidelines

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Route</th>
<th>Typical Denver Pediatric Dose</th>
<th>Typical Denver Adult Dose</th>
<th>Max Total Daily Dose</th>
<th>Key Alternative Dose Ranges in CFF/ECFS Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIKACIN</td>
<td>IV</td>
<td>15mg/kg/dose once daily</td>
<td>15mg/kg/dose once daily 3X/week</td>
<td>1500mg</td>
<td>Peds: 15-30mg/kg/dose once daily</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adolesc: 10-15mg/kg/dose once daily</td>
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<td></td>
<td>Adults: 10-30mg/kg/dose once daily</td>
</tr>
<tr>
<td>AMIKACIN</td>
<td>NEB</td>
<td>500mg once daily</td>
<td>500mg once daily</td>
<td>500mg</td>
<td>Option: 250mg twice daily</td>
</tr>
<tr>
<td>AZITHROMYCIN</td>
<td>Oral</td>
<td>10mg/kg/dose once daily</td>
<td>500mg once daily</td>
<td>500mg</td>
<td>Peds: 10-12mg/kg/dose once daily</td>
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<tr>
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<td>Adolesc/adult: 250-500mg once daily</td>
</tr>
<tr>
<td>CEFOTAXIME</td>
<td>IV</td>
<td>50mg/kg/dose 3X/day</td>
<td>2000mg</td>
<td>12g</td>
<td>Adult: 200mg/day divided q8 hr (max 12g/day)</td>
</tr>
<tr>
<td>CLOFAZIMINE</td>
<td>Oral</td>
<td>&lt;40kg = 50mg once daily</td>
<td>100mg</td>
<td>100mg</td>
<td>1-2 mg/kg/dose once daily (max 100mg) adult: 50-100mg once daily</td>
</tr>
<tr>
<td>ETHAMBUTOL</td>
<td>Oral</td>
<td>15mg/kg/dose once daily</td>
<td>1200mg</td>
<td>1200mg</td>
<td></td>
</tr>
<tr>
<td>IMIPENEM</td>
<td>IV</td>
<td>20mg/kg/dose twice daily</td>
<td>1000mg</td>
<td>2000mg</td>
<td>PEDS: 15-20 mg/kg/dose twice daily</td>
</tr>
<tr>
<td>LINEZOLID</td>
<td>Oral or IV</td>
<td>10mg/kg/dose twice daily</td>
<td>600mg</td>
<td>600mg</td>
<td>&lt;12y/o: 10mg/kg/dose 3X daily 12+ y/o: 10mg/kg/dose once or twice daily</td>
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<tr>
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<td></td>
<td>Adult: 600mg once or twice daily</td>
</tr>
<tr>
<td>MINOCYCLINE</td>
<td>Oral</td>
<td>&lt;50kg = 2mg/kg/dose once daily &gt;50kg = 1mg/kg/dose twice daily</td>
<td>100mg twice daily</td>
<td>200mg</td>
<td>Peds: 2mg/kg once daily, max 200mg</td>
</tr>
<tr>
<td>MOXIFLOXACIN</td>
<td>Oral</td>
<td>10mg/kg/dose once daily</td>
<td>400mg</td>
<td>400mg</td>
<td>Peds: 7.5-10 mg/kg/dose once daily</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>Oral</td>
<td>10mg/kg/dose once daily</td>
<td>600mg</td>
<td>600mg</td>
<td>10-20mg/kg/dose once daily &lt;50kg: max dose 450mg</td>
</tr>
<tr>
<td>TIGECYCLINE</td>
<td>IV</td>
<td>1.2mg/kg/dose twice daily</td>
<td>50mg</td>
<td>50mg</td>
<td>&gt;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</td>
</tr>
</tbody>
</table>

*Property of Presenter*  
*Not for Reproduction*
<table>
<thead>
<tr>
<th>Drug</th>
<th>CBC Parameters</th>
<th>LFT Parameters</th>
<th>Creatinine</th>
<th>Audiograms</th>
<th>Visual</th>
<th>Serum Peak Levels</th>
<th>Exam for Peripheral Neuropathy</th>
<th>ECG for QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (IV)</td>
<td>CBC parameters: ANC&lt;500, plts&lt;50K, Eosinophilia concerning for drug reaction, and/or anemia requiring transfusion.</td>
<td>LFT parameters: ALT &gt;5xULN or &gt;3xULN if symptomatic, Bilirubin &gt;3XULN.</td>
<td>Creatinine: Increased from baseline.</td>
<td>Visual changes: Discontinue for blurred vision, eye pain, red-green color blindness (Ishihara’s test: Ishihara.com).</td>
<td>Serum: Peak level 30 minutes after end of infusion, goal peak level 30-60.</td>
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<td>Amikacin (inh)</td>
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<td>Azithromycin</td>
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<tr>
<td>Cefoxitin</td>
<td>Monthly</td>
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<tr>
<td>Clofazimine</td>
<td>Monthly</td>
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<tr>
<td>Ethambutol</td>
<td>Monthly</td>
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<tr>
<td>Imipenem</td>
<td>Monthly</td>
<td>Monthly</td>
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<tr>
<td>Linezolid</td>
<td>Monthly</td>
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<tr>
<td>Minocycline*</td>
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<tr>
<td>Moxifloxacin</td>
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<tr>
<td>Rifampin</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
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<tr>
<td>Tigecycline (plus alb/bili)</td>
<td>Monthly</td>
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</tbody>
</table>

*Minocycline has no required laboratory toxicity monitoring

ECG: QTC >470 for woman or >480 for man (consider repeating on a different day and/or over-read by cardiologist before making a change)

Neuropathy above ankle
PATIENCE NTM Culture Data
Subjects n=24, Strains n=29

>1 species, subspecies or isolate is common (7/24) and appears harder to treat
No reoccurrence after initial eradication detected to date after 12 month follow-up (7/24)
Stabilization of FEV₁ % predicted in PATIENCE

PREDICT = - 4.8 % (2.0)
Preliminary Conclusions

• Use of an NTM Treatment Protocol within a single CF care center setting is feasible
• Initiating a standardized, first-line treatment for MAC and MABSC pulmonary disease may result in:
  – Good culture conversion rates to negative
    • Only 6/29 (~21%) strains have not converted with treatment (to date)
    – Stabilization of FEV₁ percent predicted decline
• Improved culture conversion rates (compared to historic rates) may in part be due to optimizing CF care first (PREDICT)
• Emergence of dual infection is common on treatment (29%), and to date 52% of PREDICT patients have a history of >1 strains
  – Delayed response or failure to clear NTM after >6 months of treatment is often associated with dual infections
Multicenter expansion within the TDN

Rationale:
- Increased enrollment, with better “power” to support findings
- Test and refine protocols in a multicenter setting
- Represent greater geographic diversity and distribution
- Extend benefits to greater numbers of patients and providers
- Test feasibility and build “infrastructure” for future therapeutic trials
Unmet Needs For the CF Patient Population

- Definition of environmental niches for various NTM
- Population analysis of risk for acquisition
- Screening strategies for patient at low and higher risk of NTM infection
- Understanding of the potential for patient-to-patient spread of NTM
- Better appreciation of the relative significance of various species within the *M. abscessus* complex and the *M. avium* complex (MAC)
- Identification of specific bacterial virulence factors
- Identification of mechanisms of host susceptibility
- Validated CF-specific diagnostic criteria
- Standardized treatment protocols for initial infections with *M. abscessus* and MAC
- Pharmacokinetic analysis of standard antimicrobial agents
- New NTM-specific antibiotics for prolonged treatment courses
- Defined rates of treatment response for *M. abscessus* and MAC
- Markers of response and treatment endpoints specific to CF
- Lifelong treatment strategies for CF patients with persistent or recurrent NTM infections