Also in the NTM Family of Co-Morbidities: Cystic Fibrosis

Douglas Conrad

NTM Bronchiectasis Conference

May 17th, 2018

Disclosures

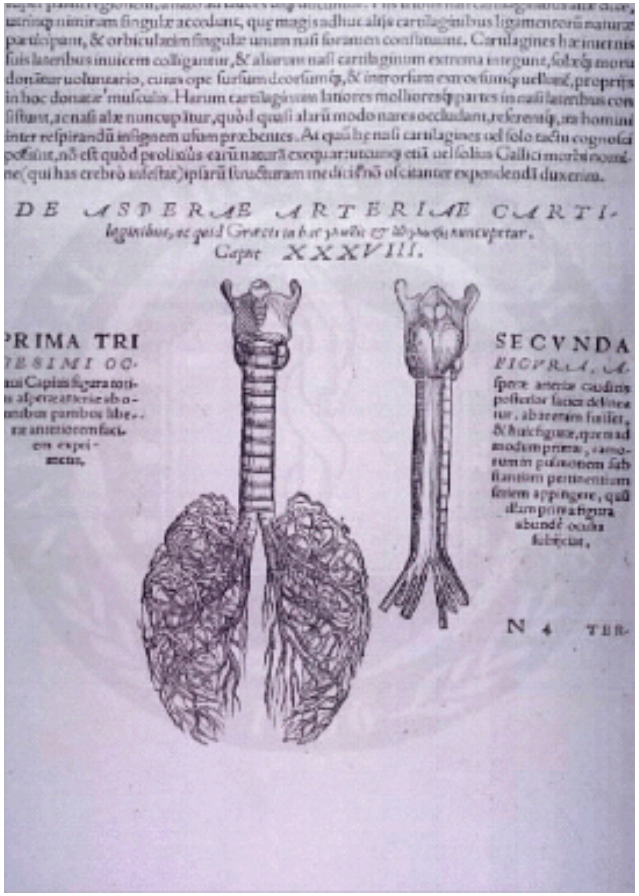
Disclosures

- **Local investigator for Vertex Pharmaceuticals clinical trials**
- **Research Funding from Gilead Sciences**

Conflict of Interests

- **No personal/family financial COI**
- **Funding comes from**
  - **NIH**
  - **CFF**
  - **Gilead Sciences**

Any FDA off label use of therapies will be indicated in the talk.



Outline

CF and Cystic Fibrosis Transmembrane Regulator (CFTR)

CF Diagnosis

CF Pathophysiology/Microbiology

Therapy

- **General concepts**
- **Modulator therapy**

Mycobacteria in CF

- **Why are NTM important in CF**
- **Why do CF patients get NTM**
- **Challenges of NTM pose in CF**

Bronchiectasis Case Presentation

- **72 year old white female presents in September, 2017 with progressive dyspnea on exertion**

  Currently walks 2 blocks. Could walk 1 mile a year earlier

- **Cough, chronic sputum production, fatigue.**

- **PMH:GERD, Hiatal hernia, Gastroparesis, LV diastolic dysfunction**

- **Clinically Pancreatic Insufficient. Failure to thrive as an infant.**

- **Chronic Sinusitis. Recurrent nasal polypectomy**

- **PMH:MAC Rx**

  a) 1996 x18 months

  b) 2002 x 13 weeks

  c) 2004 x 6 months

  d) 2015 x 8 months

  e) 2017 x10 months to current (fevers, weight loss, cough and dyspnea)

  Inhaled liposomal amikacin, clofazimine, bedaquiline, azithromycin

Bronchiectasis Case Presentation

- **Physical Exam**
  - **-BMI =18.5**
  - **-Mild maxillary Tenderness**
  - **-Chest: Decreased breath sounds with scattered rhonchi. Rare exp wheezing**

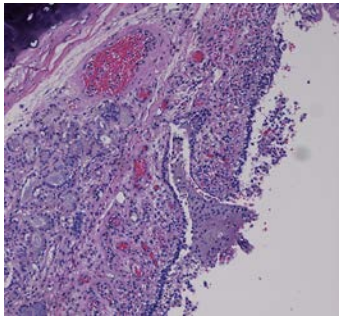
- **Laboratory Data**
  - **- CBC: Normal**
  - **-ESR : 110**
  - **-CRP: 5.2**
  - **-Chem20: Normal**
  - **-Ig and IgG subclasses: Normal**
  - **-IgE: 4**
  - **- ppFEV1= 45-55%**

- **Microbiology Data**
  - **AFB: AFB smear +; MAC/MAI**
  - **Fungal: Aspergillus intermittently**
  - **Routine: *Pseudomonas aeruginosa***
  - ***Stenotrophomonas maltophilia***

Cystic Fibrosis is a Rare, Life-Shortening, Genetic Disease

- **Approximately 30,000 patients in the United States (~70,000 worldwide)[1]**
- **Median predicted survival of 47 years, but with a median age of death of 30.1 years[1]**
- **Manifests clinically throughout the body[2] .**

-It is all about mucus function!!



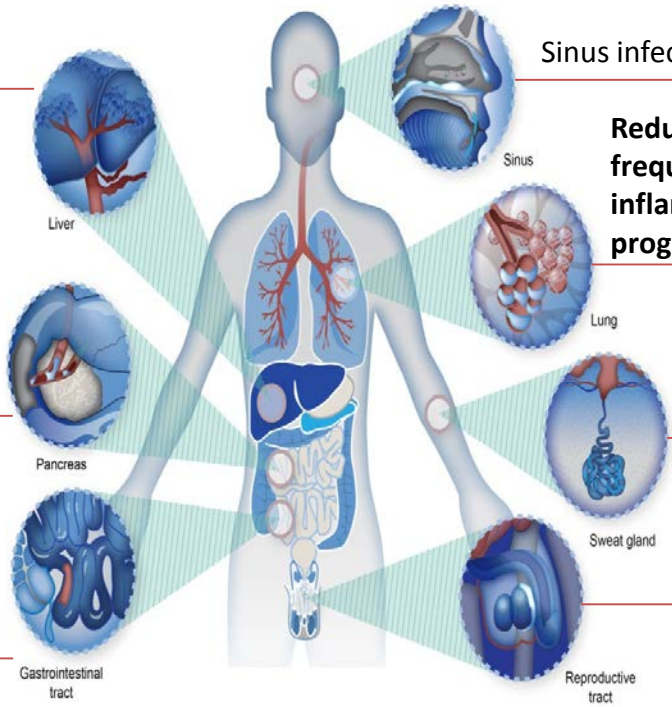
Bile duct obstruction, focal biliary cirrhosis

Exocrine pancreatic insufficiency and resulting malnutrition

Endocrine pancreatic insufficiency and resulting CFRD

Acute/Chronic Pancreatitis

Failure to thrive/gain weight due to pancreatic insufficiency, digestive problems, and intestinal blockages



Sinus infection, nasal polyps

Reduced lung function, frequent lung infections, inflammation, and progressive lung disease

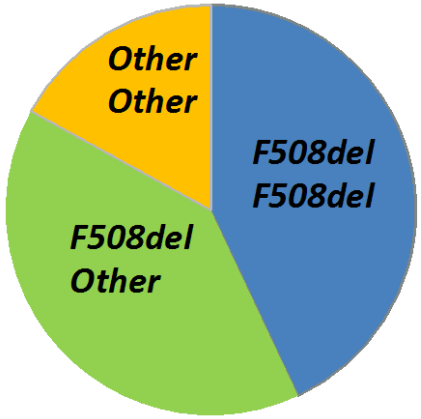
Abnormally high excretion of sodium and chloride (salt) in the sweat

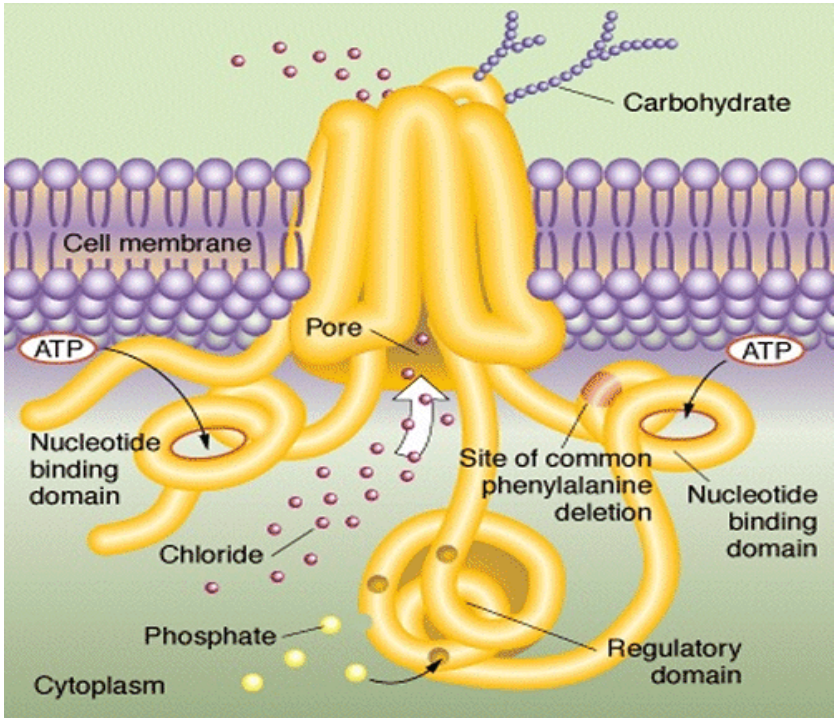
Infertility, congenital bilateral absence of the vas deferens in men

1. Cystic Fibrosis Foundation (CFF) Patient Registry. 2015 Annual Data Report. Bethesda, MD CFF, 2016 2. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904.

Cystic Fibrosis Transmembrane Regulator (CFTR)

- **CFTR protein is a transmembrane protein that functions as an *anion channel* (i.e. chloride and bicarbonate)**
- **There are over 2000 known CFTR genetic variations. Over 270 of these are known to cause CF disease**





Cystic Fibrosis-Laboratory Confirmation

CF is a clinical diagnosis facilitated by laboratory confirmation

- **Sweat chloride concentration-Pilocarpine iontopheresis**

  - Operator dependent. Experience and quality control are important

  - Requires 100mg sweat sample.

  - Values: < 30meq/l normal
    30-60meq/l borderline
    >60meq/l positive

  - Repeat all positive and borderline test and those with a classical clinical presentation

- **Nasal potential difference**

  -Alternative measure of chloride ion transport across nasal epithelium

- **Beta-adrenergic sweat production/Evaporimeter Assay**

Cystic Fibrosis-Laboratory Confirmation

- **CFTR Genetic mutation screening**

  - **F508del. If homozygous then stop.**

  - **Next step: 30-90 most frequent mutations in North America which account for 90% of the mutated alleles**

  - **CFTR gene sequencing : Consider in atypical CF cases. This usually is exome sequencing (with some well characterized intron variation)**

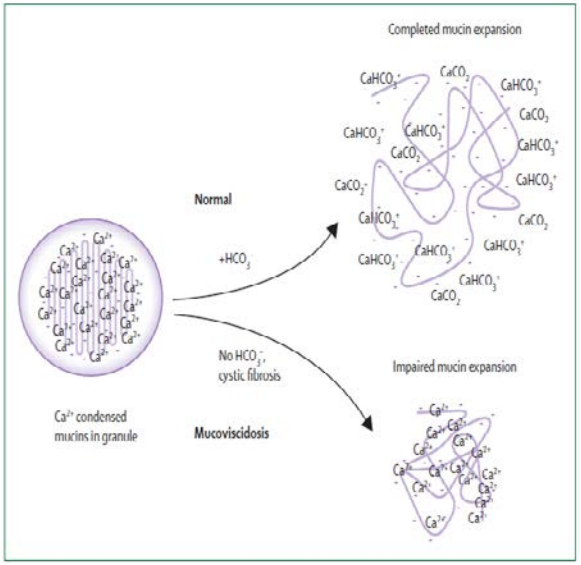
  - **Duplications and Deletions ~1% of general population**
    - **Not necessarily identified by sequencing**
    - **Require specialized techniques to identify.**

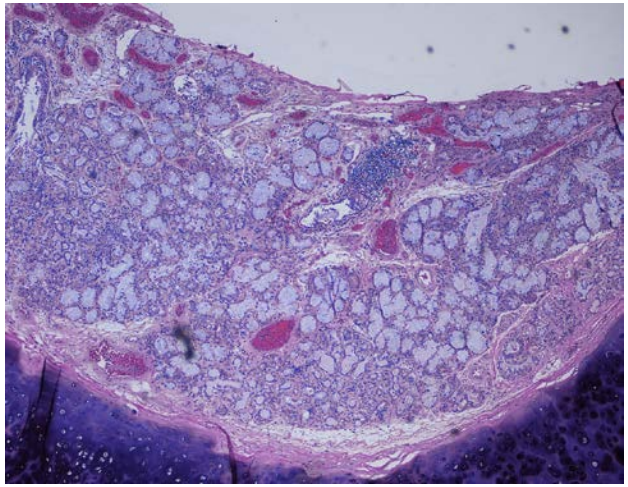
  - **Whole Genome Sequencing (intronic and modifier gene assessment). Research applications**

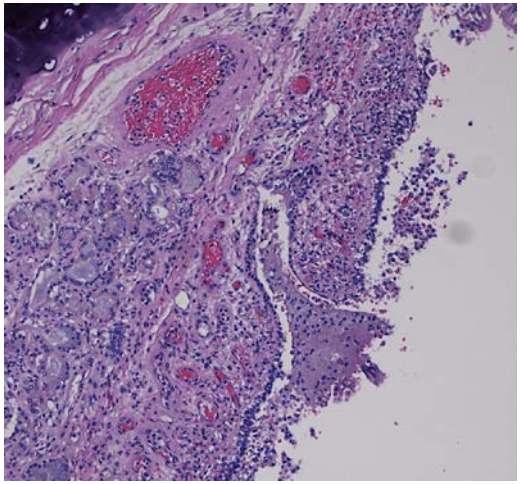
Not all clinical cases of CF have positive sweat chloride or CFTR genetic studies

CF Pathophysiology: Bicarbonate

- Ca^{2+} and H^{+} cations prevent the proper deployment of “mucus shield”
- Without HCO_3^-, mucins remain aggregated, poorly solubilized, and less transportable (mucus remains highly viscous = “mucovisidosis”)







Quinton: Am J Physiol Cell Physiol 299:C1222-C1233, 2010

In addition to facilitating mucus shield deployment….

- *pH sensitive mucus rheology and function of the mucociliary clearance mechanism*

NaHCO3- inhalation
5ml of 8%

And…

***raising the pH activates pH sensitive anti-bacterial peptides such as the defensins*.**

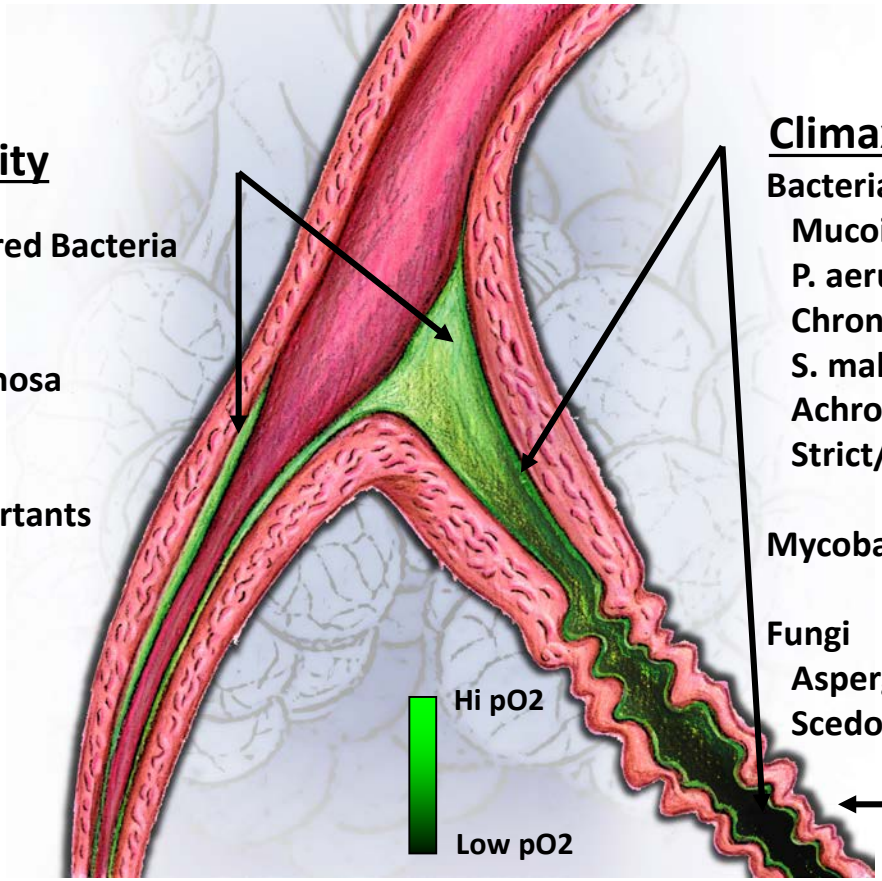
Climax-Attack Model

Attack Community

Environmentally acquired Bacteria
- S. aureus
- S. pneumonia
- non-mucoid P. aeruginosa
- H. influenza

Endogeneous Bacteria
- P. aeruginosa scv revertants

Eukaryotic viruses
- Rhinovirus
- Adenovirus
- Influenza A/B



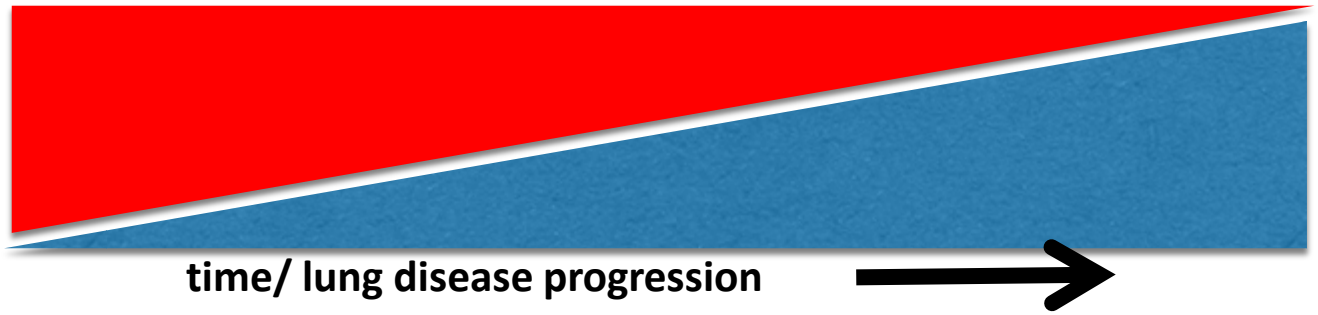
Climax Community

Bacteria
- Mucoid P. aeruginosa
- P. aeruginosa scv
- Chronic S. aureus
- S. maltophilia
- Achromobacter spp.
- Strict/Facultative anerobes

Mycobacteria

Fungi
- Aspergillus spp.
- Scedosporium spp.

Bronchiectasis



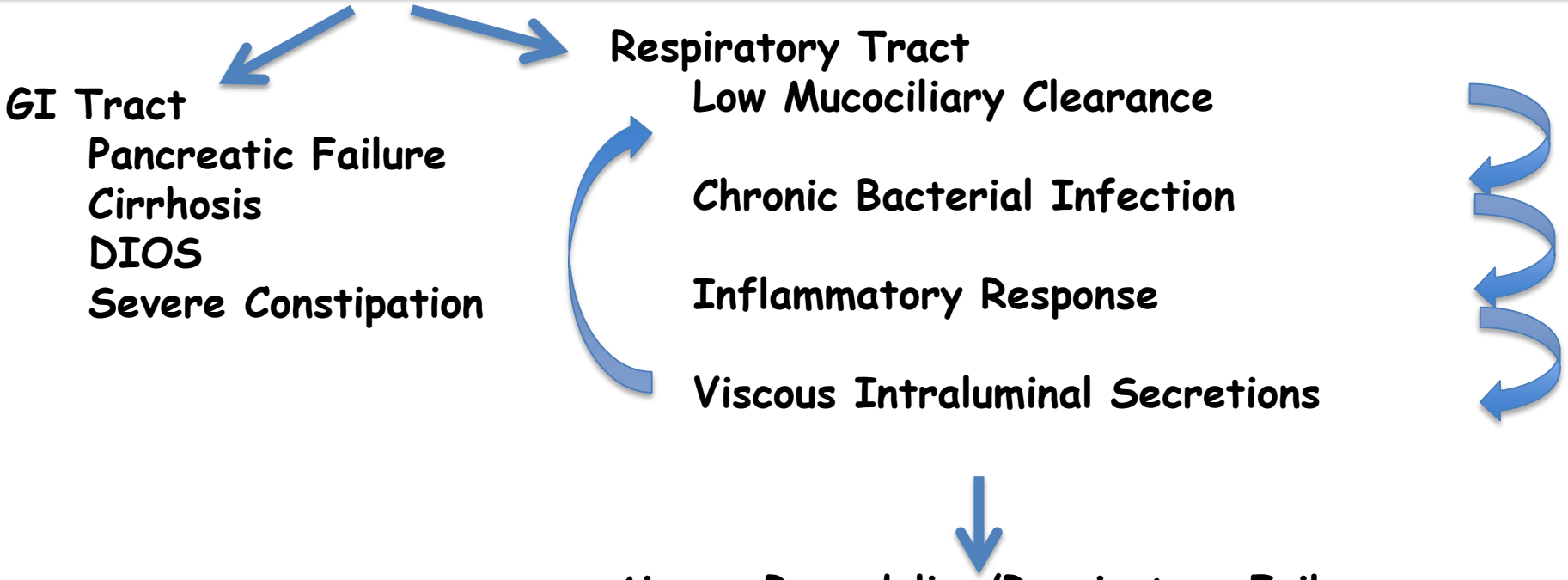
Pathophysiology and Treatment Options

Defective CFTR Gene

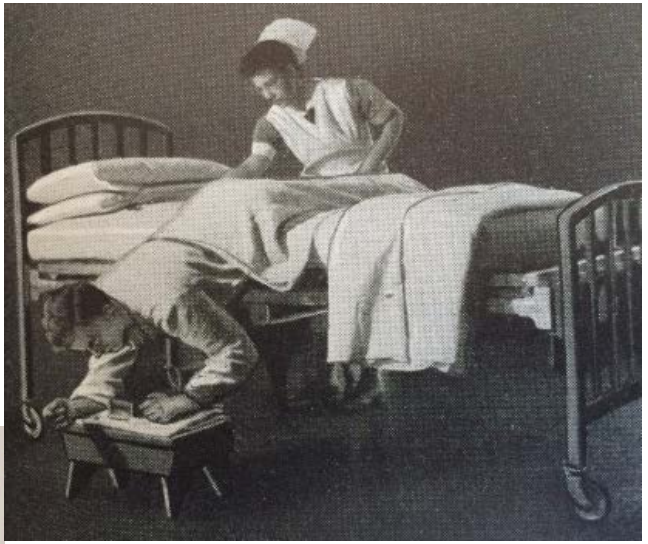
Low CFTR Activity

Abnormal Epithelial Anion Transport

Epithelial Mucus Dysfunction



Therapy: Airway Clearance!!



Essentials
of
Medicine

FOURTEENTH EDITION
THOROUGHLY REVISED AND RE-EDITED

BY

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194 ILLUSTRATIONS
and one colored plate

Pathophysiology and Treatment Options

Defective CFTR Gene

Gene Therapy/DNA or RNA editing

Low CFTR Activity

"Modulator" Therapy
ENAC inhibitors, CaCC activators

Abnormal Epithelial Ion Transport

Epithelial Mucus Dysfunction

GI Tract
- Pancreatic Failure
- Cirrhosis
- DIOS
- Severe Constipation

Respiratory Tract

Low Mucociliary Clearance
- Hypertonic saline, Inhaled Mannitol

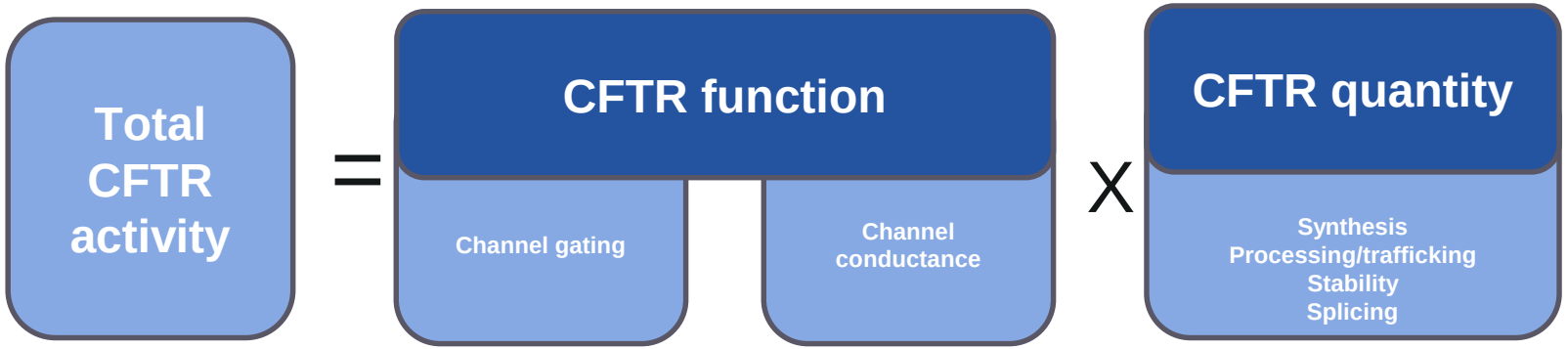
Chronic Bacterial Infection
- Oral, IV and Inhaled Antibiotics

Inflammatory Response
- Azithromycin, Ibuprofen, Steroids

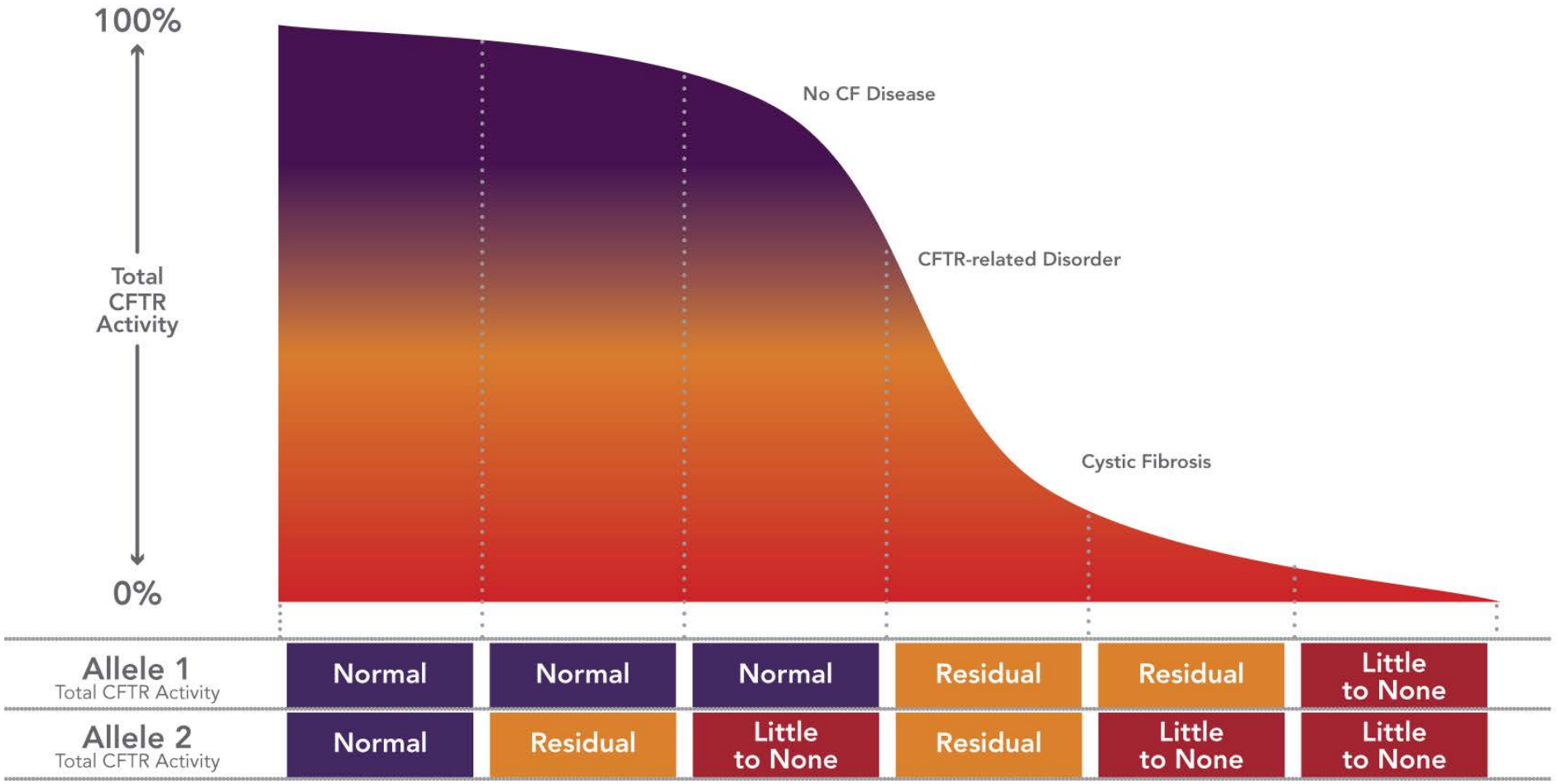
Viscous Intraluminal Secretions
- Chest Physiotherapy

Airway Remodeling/Respiratory Failure
- Lung Transplantation

Modulator Therapy

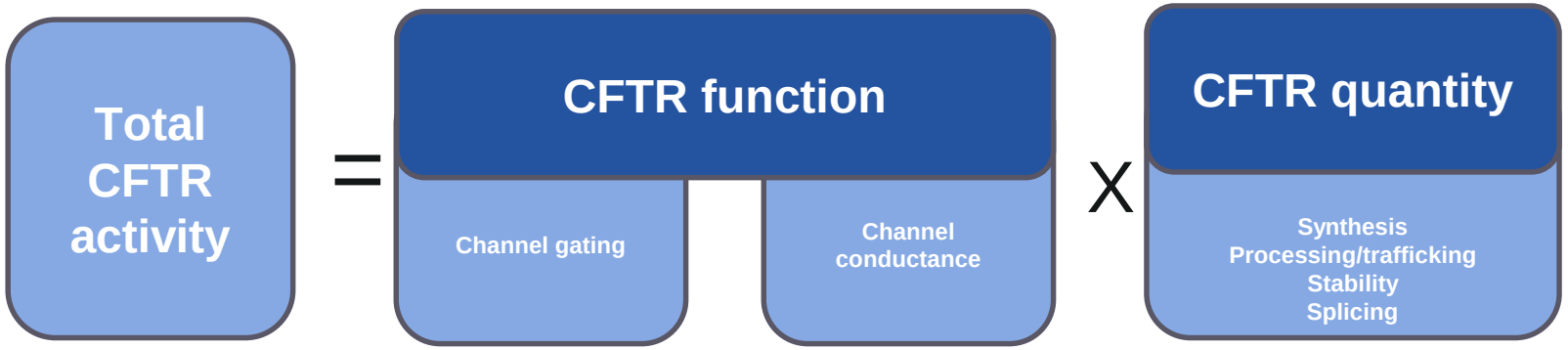


CFTR Genotype of Both Alleles is a Determinant of Total CFTR Activity and CF Phenotype



Adapted from Zielenski J. Respiration 2000;67:117–33

Modulator Therapy



Potentiator Therapy

-ivacaftor

- **Increases open probability of wild type as well as gating mutations.**
- **Works on wild-type (non mutated CFTR)**

Corrector Therapy

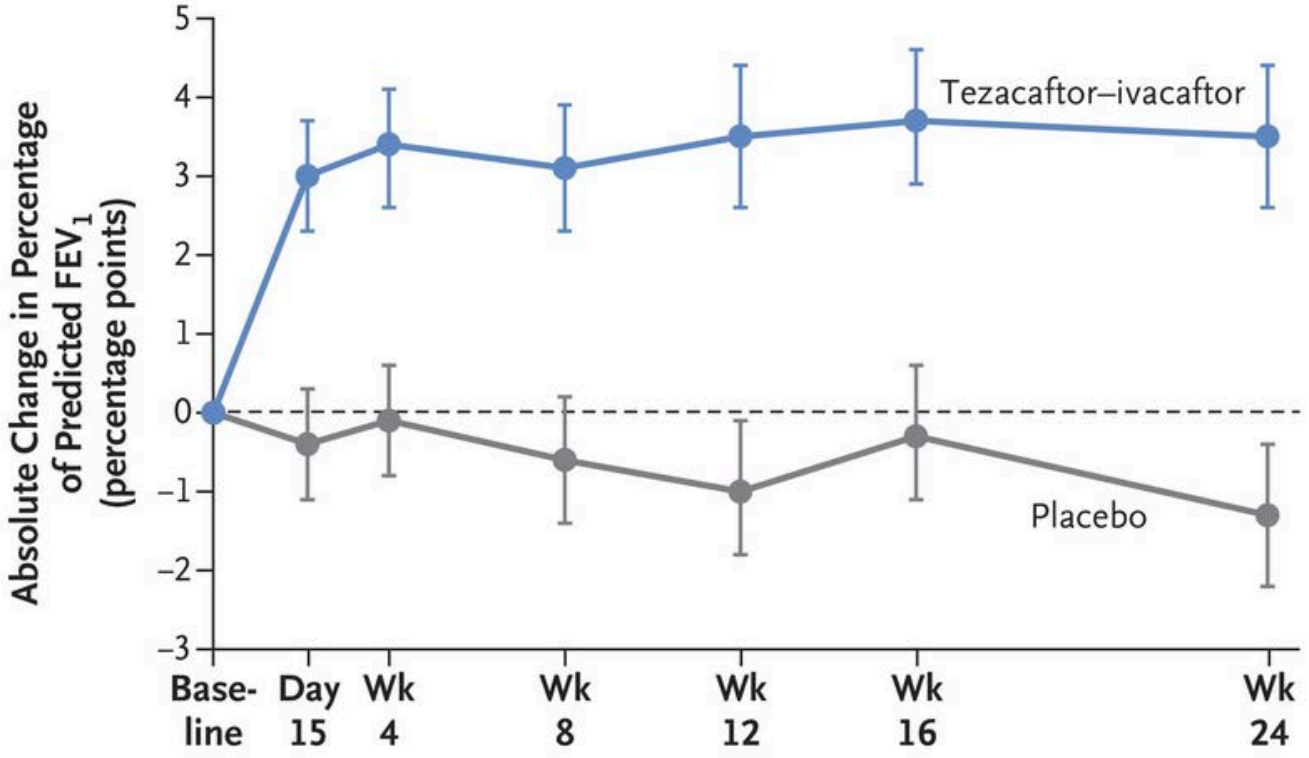
-lumacaftor
-tezacaftor

- **dF508**

FDA approved therapies:

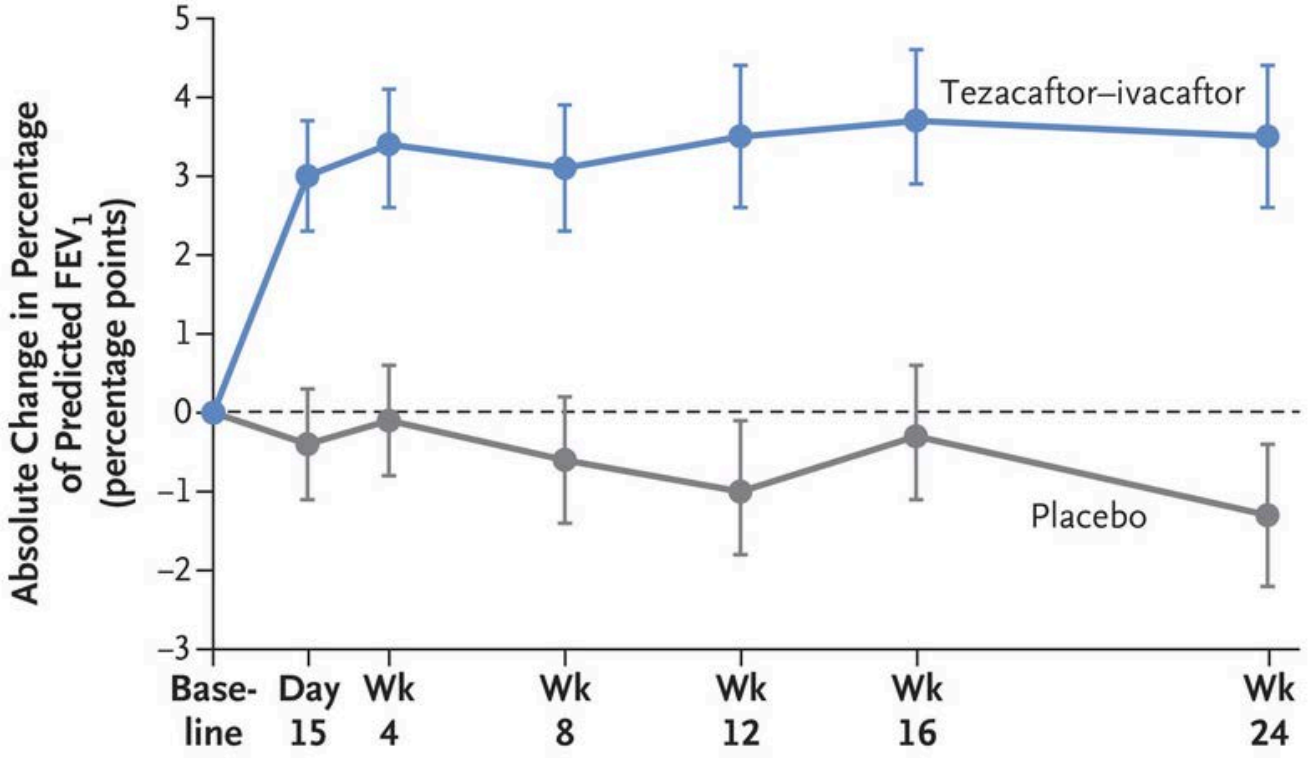
1) **Ivacaftor monotherapy for specific CFTR gating and residual function mutations**
2) **Lumacaftor/ivacaftor for dF508/dF508, dF508/residual function genotypes**
3) **Tezacaftor/ivacaftor for dF508/dF508, dF508/residual function genotypes**

Tezacaftor-Ivacaftor in dF508/dF508 CF Patients



N Engl J Med. 2017 Nov 23;377(21):2013-2023.

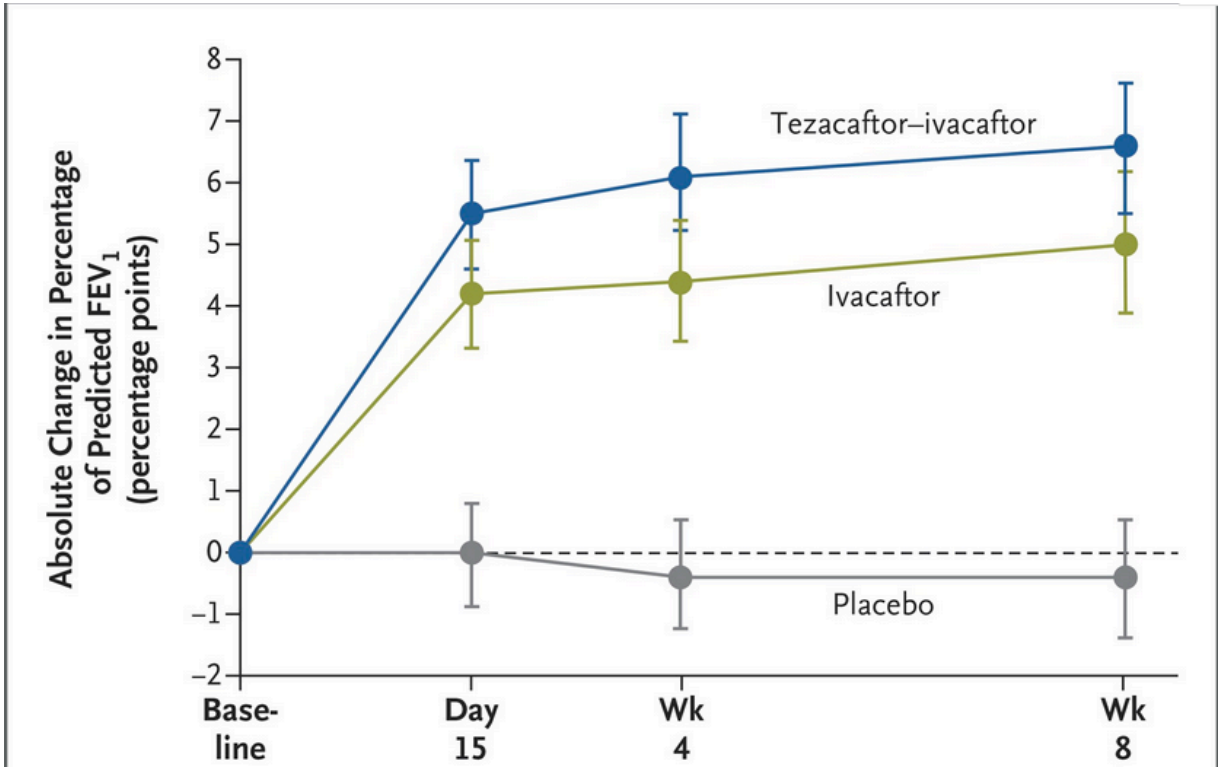
Tezacaftor/Ivacaftor in dF508/dF508 CF Patients



- **Safe**
- **Significant decrease in the the frequency of pulmonary exacerbations**
- **No change in BMI**
- **Improved respiratory PRO and decrease in Sweat Chloride by 10meq/L**

N Engl J Med. 2017 Nov 23;377(21):2013-2023.

Tezacaftor-Ivacaftor in dF508/Residual Function CF Patients



- **Safe**
- **Improved respiratory PRO: CFQ-R**
- **Decrease in Sweat Chloride**

N Engl J Med. 2017 Nov 23;377(21):2024-2035.

Bronchiectasis Case Presentation

- **Relevant PCD data**

  -EM cilia showed normal outer and inner dynein arms and questionable central apparatus.

  -Single DNAH5 variation

  p.F4392C: uncertain pathogenicity

  -Single DNAH11 variation

  p.D892V: uncertain pathogenicity

- **Relevant CF data**

  -Sweat Chloride: 25meq/ml

  -Borderline nasal potential difference

  -CFTR genetics

  a) M470V/M470V

  b) IVS 8 5T allele

  -Fecal pancreatic elastase was 52 ug/g (nl > 200ug/g)

  -Vitamins E and A were normal

  -Vitamin D was low

Bronchiectasis Case Presentation

Leading considerations for etiology of bronchiectasis

- **Cystic Fibrosis (?Atypical)**

  Strong clinical phenotype but lacks convincing laboratory confirmation

- **Chronic NTM (MAC/MAI) airway infection**
- **Chronic aspiration**
- **Atypical PCD**

  PCD is recessive.

  Unclear if the carrier state is clearly normal

- **“Multiple hit” concept**

Bronchiectasis Case Presentation

Leading considerations for etiology of bronchiectasis

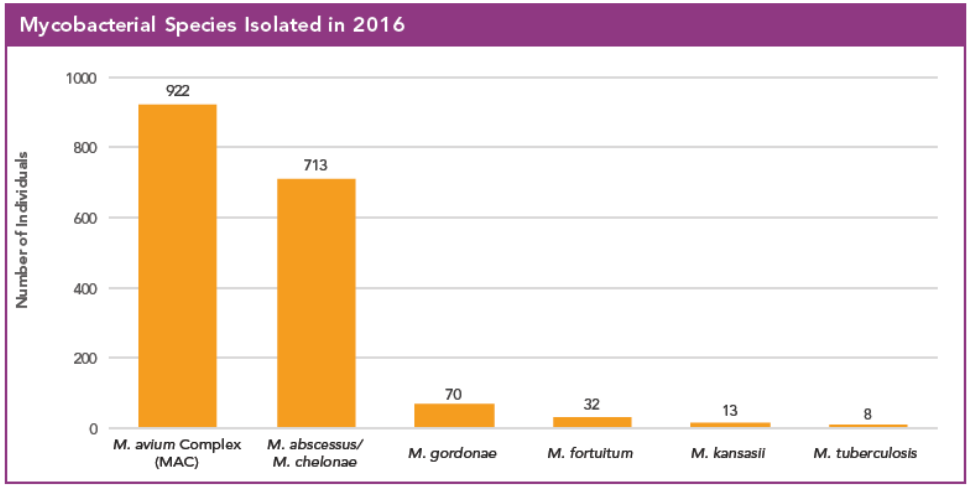
- Cystic Fibrosis (?Atypical)
  Strong clinical phenotype but lacks convincing laboratory confirmation
- Chronic NTM (MAC/MAI) airway infection
- Chronic aspiration
- Atypical PCD
  PCD is recessive.
  Unclear if the carrier state is clearly normal

- "Multiple hit" concept

Plan: 1) Maintain optimal airway clearance regimen and nutritional status
2) Continue current MAC/MAI therapy
3) Add ivacaftor through individual IND
- **The patient has a clinical syndrome CF**
- **M470V has decreased CFTR activity and is ivacaftor responsive**
- **Rationale: increased CFTR activity will a) stabilize or improve lung function, symptoms and facilitate mucociliary clearance (and hopefully eradicate MAC/MAI biofilm)**

Non Tuberculous Mycobacteria in CF

- **6-13% of CF patients have NTM**
- **Incidence is increasing**
- **MAC/MAI and M abs are most common**
- **Tendency of MAC/MAI seen in older, CF patients with milder or atypical disease**
- **Tendency to see M abs seen younger, CF patients with more severe or typical disease**
- **Associated with accelerated lung function decline**



Data are not mutually exclusive. Some individuals had more than one species isolated in 2016.

1846/14501=12.7% had one ore more positive studies: CFFPR 2016

Geographic Variation of NTM in CF (1)

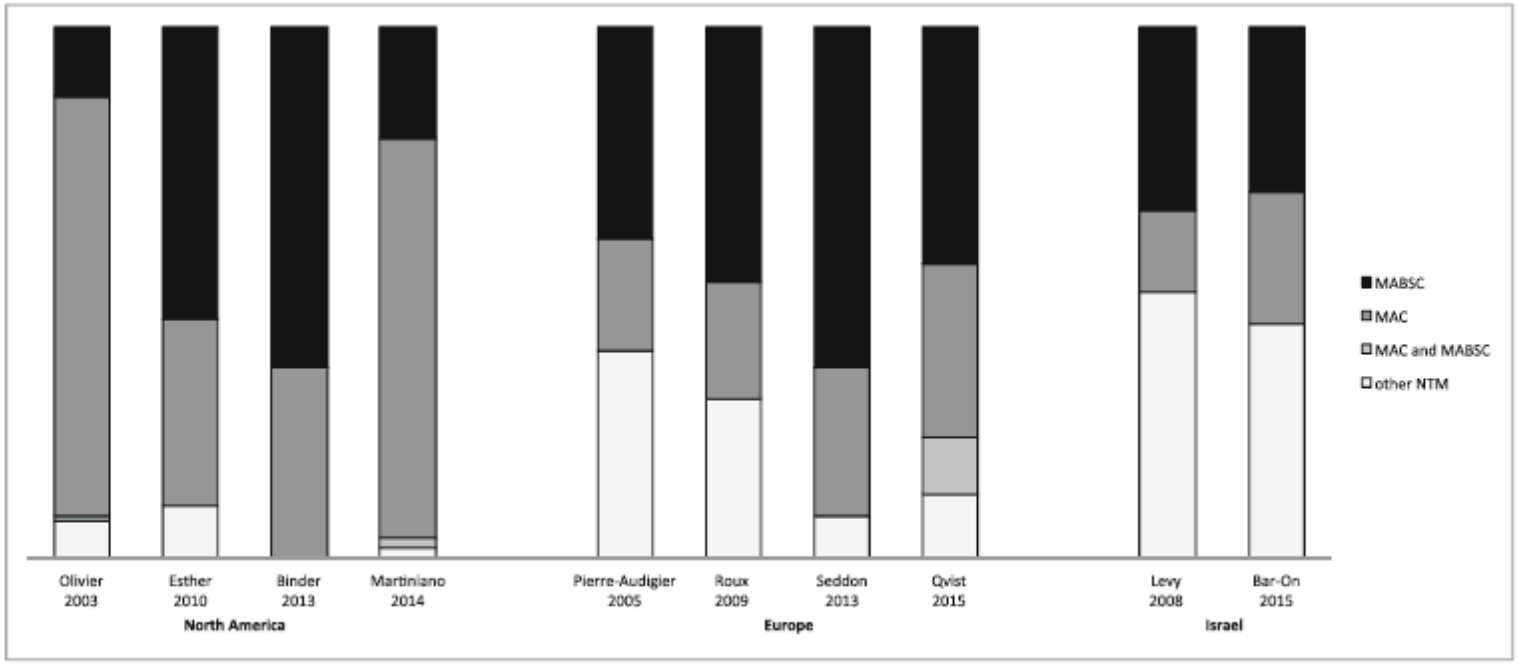


Fig. 1. Prevalence of NTM subtypes in CF from different regions of the world.

- **Relative of abundance of MAC/MAI, M abscessus and other NTM varies**
  - **-North America appears to have more MAC/MAI**
  - **-Europe has relatively more M abscessus**

CurrTreatOptions InfectDis (2016) 8:259–274

Geographic Variation of NTM in CF (2)

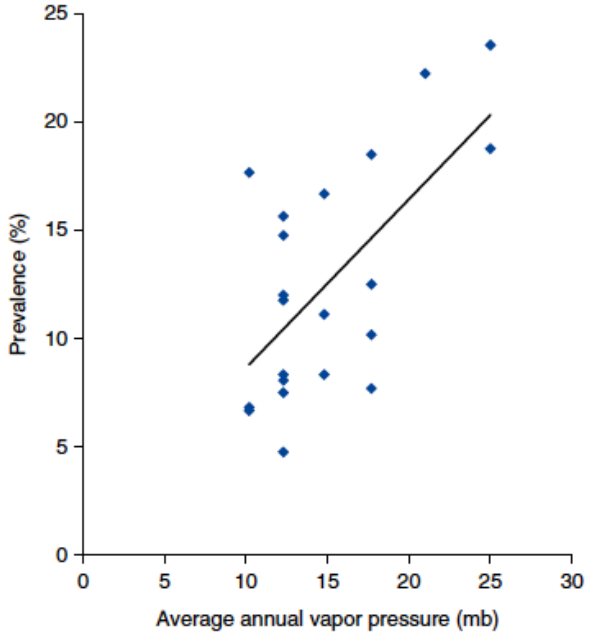
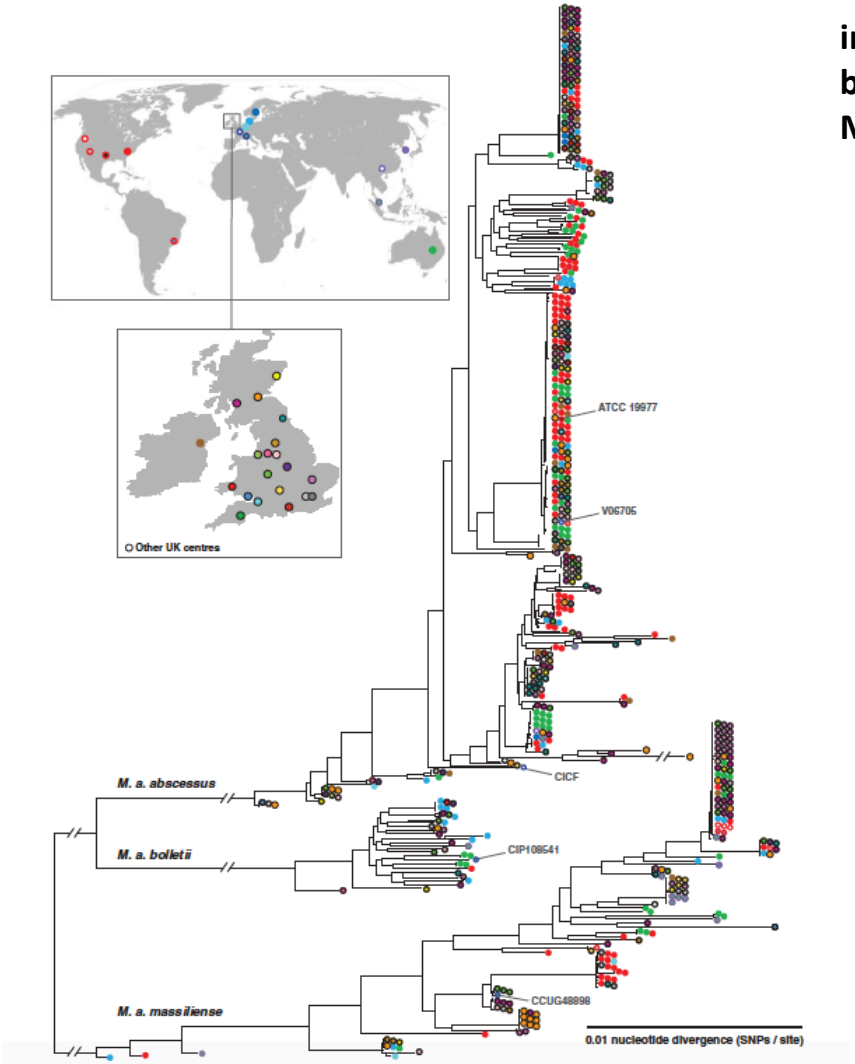


Figure 1. The correlation of CF center prevalence with average annual atmospheric water vapor content (R^2 = 0.4).

"Atmospheric conditions explain more of the variation in disease prevalence than individual behaviors."

Ann Am Thorac Soc Vol 11, No 7, pp 1032–1038, Sep 2014

Geographic Variation of NTM in CF (3)



- Using WGS of NTM from an international CF cohort, the investigators found that the majority of the isolates belonged to 3 genetic clusters (two M abscessus and one M. massiliense)

Science. 2016 Nov 11;354(6313):751-757.

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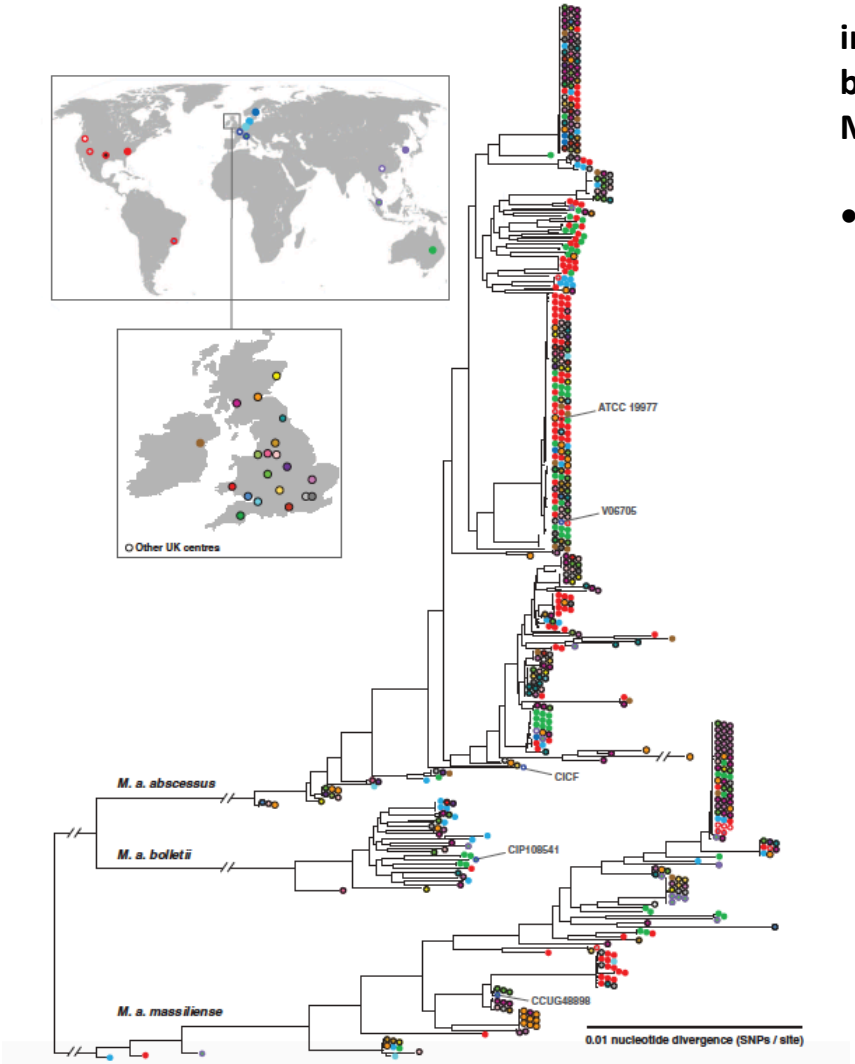

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- The clusters were associated with:
  - -chronic infection
  - -antibiotic resistance
  - -survived in macrophages
  - -worse clinical outcomes.

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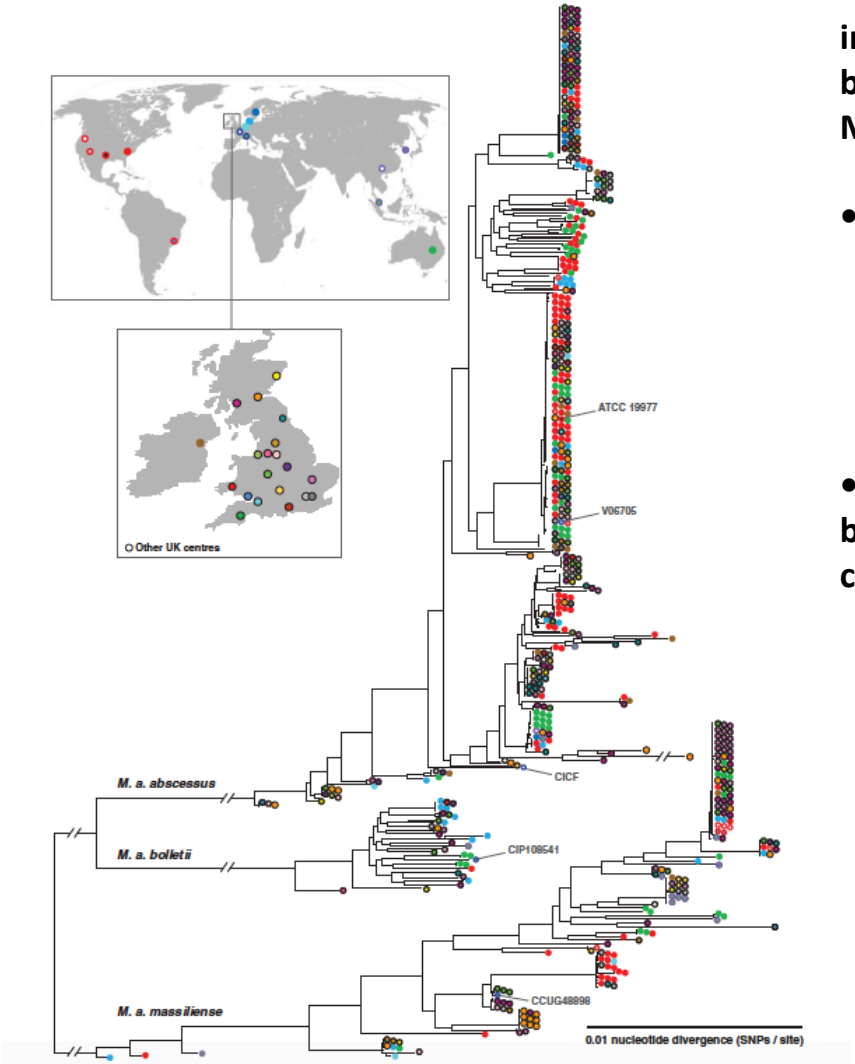

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- Provided strong genetic evidence for transmission between individuals that at one point shared common care settings suggesting:
  - -fomite driven transmission
  - -long-lived infectious aerosols

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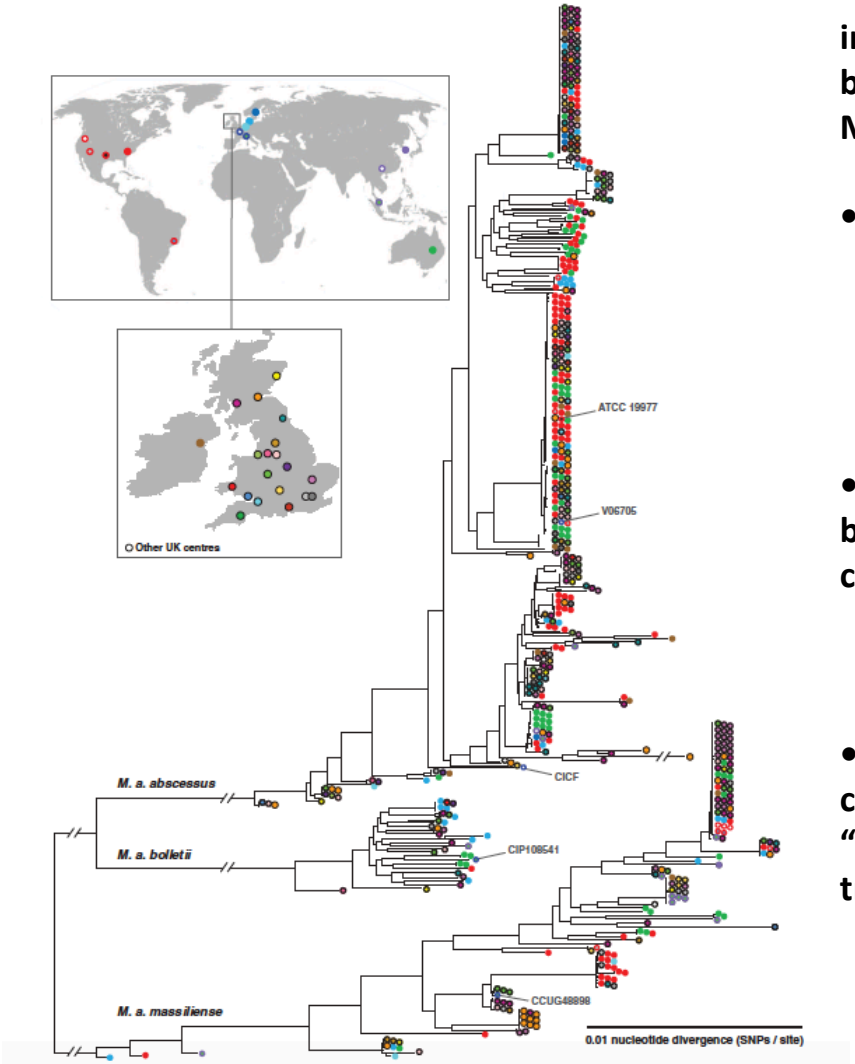

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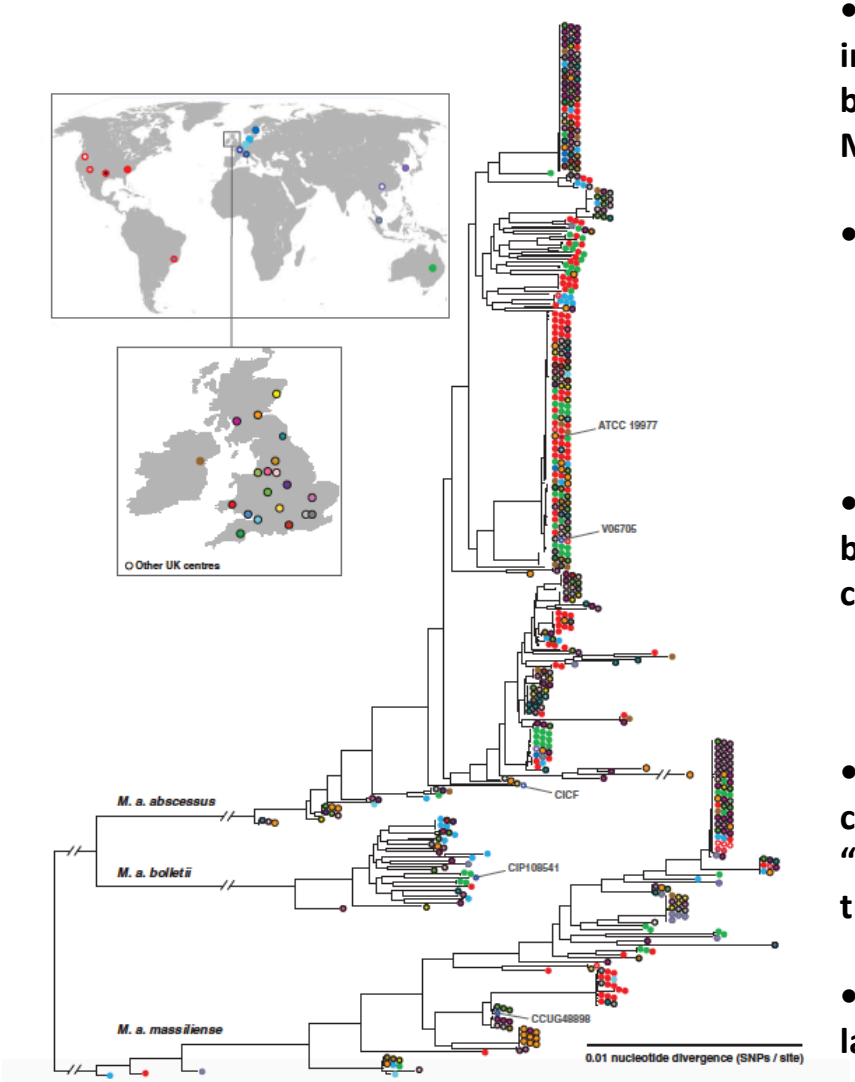

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- No plausible explanation for world-wide prevalence of closely related isolates other than the presence of “alternative human, zoonotic or environmental vectors of transmission

- Lacked non-CF disease isolates from the same regions or labs

Science. 2016 Nov 11;354(6313):751-757.

NTM Pathogenesis and CFTR Dysfunction

Non-CF NTM pulmonary disease is associated with a 30-50% CF carrier status

- **Mycobacterial characteristics:**

  -bacterial envelope

  -Mycobacterial metabolism supports slow growth and survival in environments that are hypoxic with a wide variety of carbon sources.

- **CFTR Dysfunction: Low of bicarbonate conductance contributes to acidic peri-cellular mucus layer.**

  -This environment is compatible with NTM slow growth metabolism

  -Innate response: pH sensitive antibacterial peptides

- **Ecology**

  -Co-occurrence of growth in subjects with Aspergillus spp and ABPA suggesting a metabolic symbiosis

  -Evidence of horizontal gene transfer of virulence and persistence factors from other CF pathogens

NTM Therapy in CF

- **References**

  -CFF/ECF:. Floto RA,et al.Thorax 2016;7 1 :88–90
  -ATS/IDS: Griffith D. et al. Am J Respir Crit Care Med. 2007;175:367-416
  -Denver: Pediatric Pulmonology. 2017;52:S29–S36.
  Curr Opin Pulm Med 2016, 22:629–636

- **When to Treat**

-Challenges when applying ATS/IDS guideline due to overlap of clinical and radiographic features of CF and NTM-PD

-Consider treating AFB culture positive patients with uncontrolled symptoms, swiftly progressing radiographic changes, rapidly declining lung function or frequent exacerbations

-Treat co-morbidities first including

a) standard CF pathogens
b) ABPA/Fungal pathogens
c) CFRD
d) Sinus Disease
e) Nutrition/GERD/GI disease

Drug-Drug Interactions

CFTR Modulators and antibiotics* used to treat NTM

	Adjustments of CFTR Modulator		
	Ivacaftor (Kalydeco®)	**Lumacaftor/ivacaftor (Orkambi®)**	**Tezacaftor/ivacaftor (Symdeko®)**
Strong CYP3A4 Inducers Ex: Rifampin, rifabutin	Contraindicated	Contraindicated	Contraindicated
Strong CYP3A4 Inhibitors Ex: Clarithromycin	Dose Adjustment**	Dose Adjustment**	Dose Adjustment**
CYP3A4 Substrate Ex: Bedaquiline	Monitor	Monitor	Monitor
CYP2C9 Substrates Ex: Bactrim	Monitor	Monitor	Monitor
Other Ex: Clofazimine	Monitor***	Monitor***	Monitor***

***Medications included in the analysis: amikacin, azithromycin, cefoxitin, clarithromycin, clofazimine, co-trimoxazole, ethambutol, imipenem, linezolid, moxifloxacin, minocycline, rifampin, rifabutin, streptomycin, tigecycline, bedaquiline

****For dose adjustments, refer to package insert or consult clinical pharmacist.

***** Clofazimine is metabolized by liver. Unclear which liver enzymes responsible for the metabolism of clofazimine. Consider monitoring clofazimine levels.

Ivacaftor – substrate of CYP3A4, potential inhibitor of CYP3A4 and P-gp. I*n vitro* studies suggest that ivacaftor may inhibit CYP2C9.

Lumacaftor – strong inducer of CYP3A. *In vitro* studies suggest it has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibit CYP2C8 and CYP2C9.

Tezacaftor – substrate of CYP3A4. *In vitro* studies suggest, it has a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. It has a low potential to induce CYP3A. It has a low potential to inhibit transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.

NTM Therapy in CF

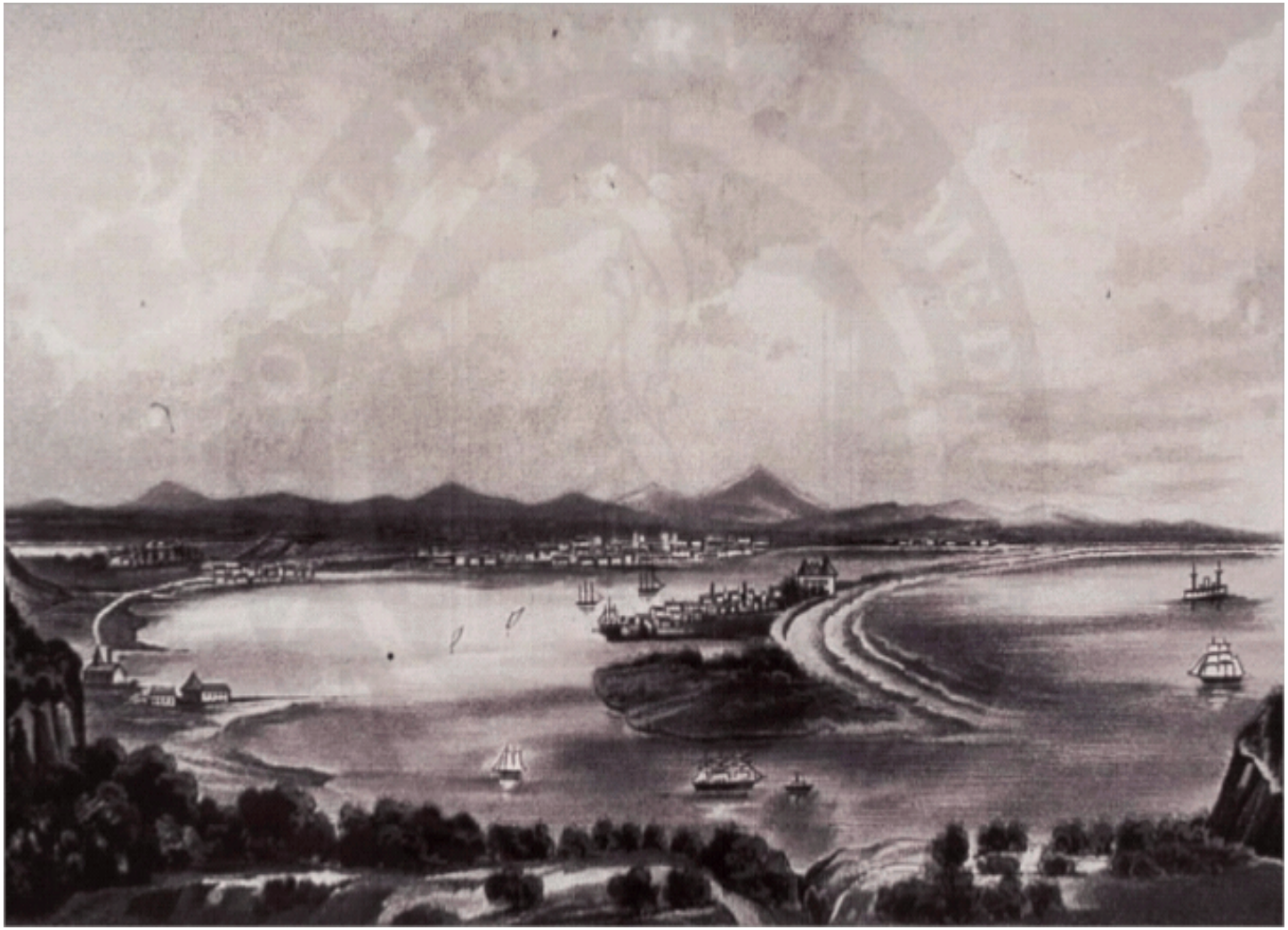
- **CF and NTM patient and physician communities recognize the importance of NTM in CF and related bronchiectatic disease**
  - **Generation of a disease registry is critical!**

- **Clinical trials focused on when and how to treat CF and CF-related NTM are currently underway.**

- **There are some new antibiotics under development that offer some hope of new therapeutic options.**

- **Highly speculative:**
  - **Potential role of CFTR modulator therapy in facilitating antibiotic Rx for patients with CFTR variations.**
  - **Bacteriophage therapy as an adjunct to antibiotic therapy**

Questions?



P.C. Remondino 1893. "The modern climatic treatment of invalids with pulmonary consumption in Southern California"