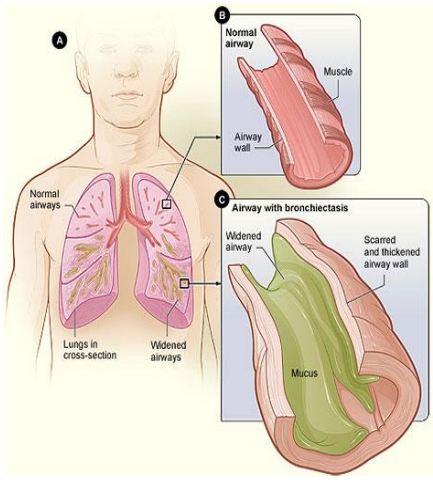
# Bronchiectasis and Cystic Fibrosis

**Veronica Indihar, MD**
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of Virginia

University of Virginia
School of Medicine

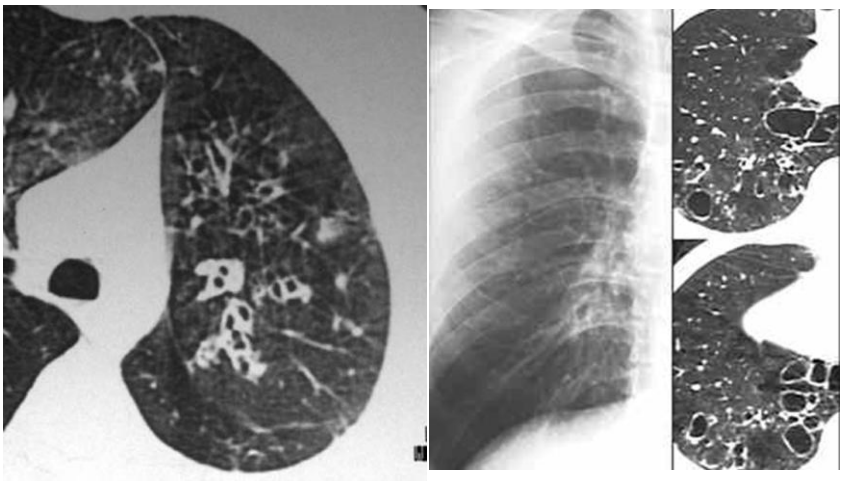
## Bronchiectasis-Epidemiology

- **Abnormal and permanent dilatation of the cartilage-containing airways**
- Estimated prevalence →increased **8.7%** per year between 2000-2007
- Increase in hospital admission rate **2-3%** since 1993-2006
- Exacerbation **1.5-6.7** per patient/year



# Different types

**Cylindrical** **Saccular/Cystic**

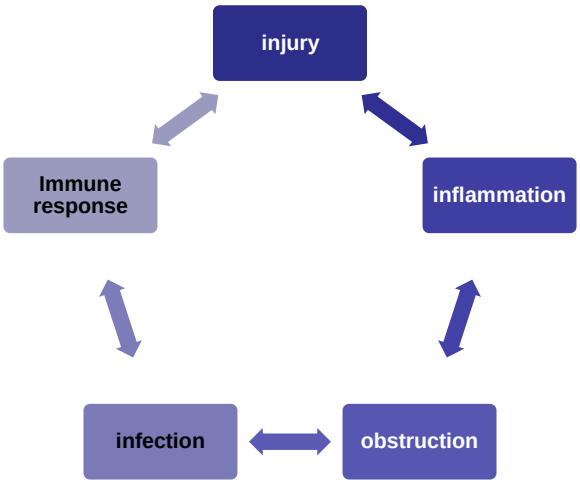


# Clinical presentation

- Chronic cough (“wet” vs “dry”)+ purulent secretions
- Recurrent infection
- Hemoptysis
- Chronic airflow obstruction
- Dyspnea
- Constitutional symptoms

# Pathogenesis

- Bronchial wall injury
- Bronchial lumen obstruction
- Traction from adjacent fibrosis




# Etiology (post infectious)

❖ Lower respiratory tract infection (Measles, Pertussis)

❖ Granulomatous ( TB)

❖ Severe pneumonias, necrotizing

# Etiology

**Impaired mucociliary clearance**

- Cystic Fibrosis
- Primary Ciliary dyskinesia
- Young's syndrome (obstructive azoospermia)

**Immunodeficiency**

- Common variable immunodeficiency (humoral)
- HIV (cellular)
- Secondary –CLL, leukemias
- Neutrophilic dysfunction

# Etiology

**Exaggerated immune response**

- Allergic Bronchopulmonary Aspergillosis (ABPA)
- Graft versus Host disease
- Inflammatory Bowel Disease (Crohn's, UC)

**Inhalation/obstruction**

- Aspiration/GERD
- Smoke inhalation
- Foreign body
- Tumor/endobronchial lesion
- Extrinsic compression

# Etiology

**Fibrosis/Traction/Inflammation**

- Sarcoidosis
- Idiopathic pulmonary fibrosis (IPF)
- Rheumatoid Arthritis
- Sjögren Syndrome
- Systemic Lupus Erythematosus
- Ankylosing spondylitis

# Etiology

**Miscellaneous**

- Alpha 1-Antitrypsin deficiency
- Yellow nail syndrome (lymphedema +pleural effusion)
- Nontuberculous mycobacterial infection ("Lady Windermere syndrome")
- Pulmonary sequestration
- Radiation injury

- **Congenital**: Williams-Campbell syndrome, Marfan syndrome,Mounier-Kuhn syndrome

## Does it matter to know underlying medical condition?

- **Yes**, it changed specific management in **40-50% of patients**
- Target therapy (ABPA,CVID, NTM,IBD, A1-AT)
- Prognostic implications

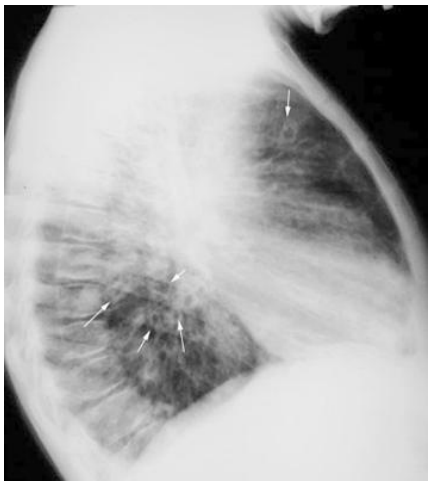
## Diagnosis

- Suspicious in chronic cough + sputum
- **PFT**: obstructive pattern
- **CXR shows** fewer than 50% of cases
- **High Resolution CT chest (HRCT)**

## Radiologic Manifestations

- **Parallel line opacities** (tram tracks)
- **Tubular opacities**
- **Ring opacities or cystic spaces**
- **Increase in size and loss of definition of pulmonary markings in specific segmental areas of the lungs**

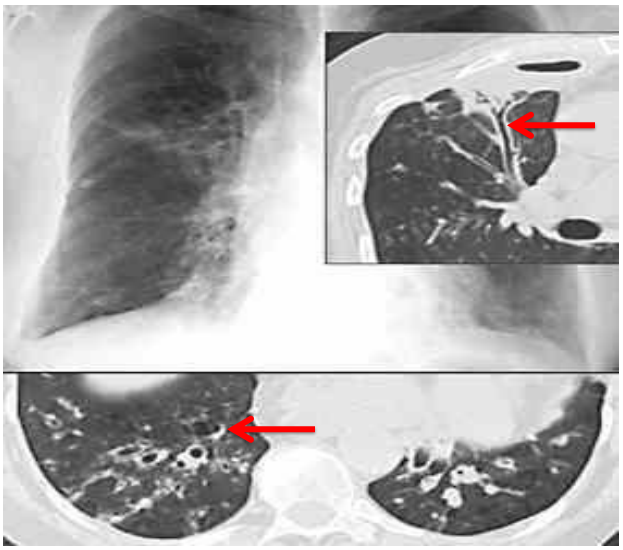
## Radiologic Manifestations



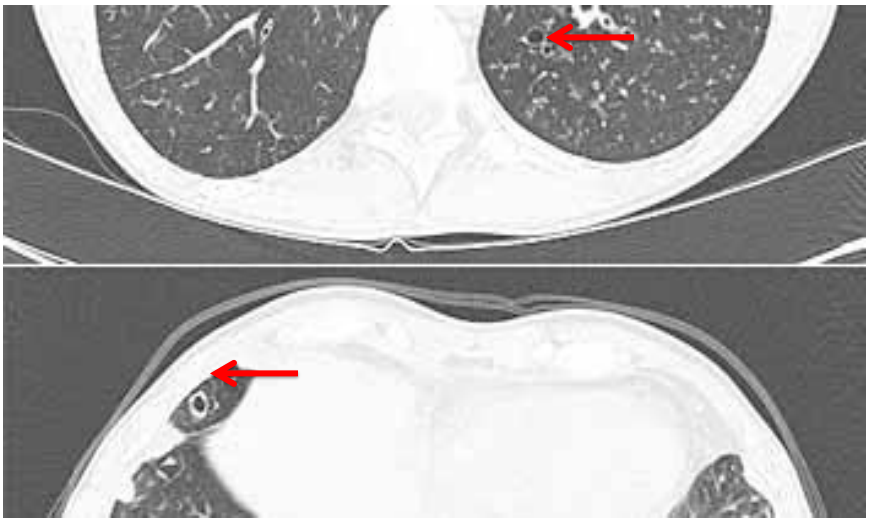
# HRCT findings

- Internal diameter of airway wider than adjacent pulmonary artery
- Failure of bronchi to taper
- Visualization of airway in the outer 1-2 cm of lung field
- Bronchial wall thickening

# Radiologic Manifestations



# Radiologic Manifestations



# Work up

- CXR - HR CT chest
- Pulmonary function test
- Sputum cultures
- Sputum smear for acid fast bacilli
- Skin allergy testing (mold)
- Sweat test
- Barium swallow evaluation

**Labs:**

- CBC with differential
- Immunoglobulins + IgG subtypes
- Mold radioallergosorbent (RAST)
- Aspergillus precipitins
- Rheumatoid factor
- ANA
- Alpha1 AT
- CRP/ESR
- HIV
- Genetic testing

# Treatment Goals

- Limit the cycle of infection-inflammation
- Improve symptoms
- Reduce exacerbations
- Improve quality of life

**Vaccinations:**

- **Pneumovax** (reduction in exacerbations?)
- **Flu shot**

# Treatment

- **Mobilize airway secretions** (chest PT, postural drainage, PEP devices-flutter, high frequency chest vest, accapella)

  ➡ Exercise

- **Mucolytics** (bromhexine, N-acetylcystein )
- **Nebulized hypertonic saline** (3%,7%, 10%)
- **Bronchodilators**
- **Inhaled corticosteroids** (+/-)

- Dornase alpha (DNAse) → **not beneficial**

# Treatment- Antibiotics

- **Antibiotics prophylaxis**: decreases burden bacteria

Pseudomonas Aeruginosa, Staph Aureus, Haemophilus Influenza, anaerobes

- Inhaled gentamicin, tobramycin, aztreonam

- **Antibitotics therapeutic**: for acute exacerbations (culture driven vs empirical)

# Treatment- Azithromycin

- **Azithromycin** 3 times weekly reduced exacerbation rate

**EMBRACE** trial, RCT, New Zealand, 3 centers, 141 patients

Placebo vs Azithromycin for 6 months

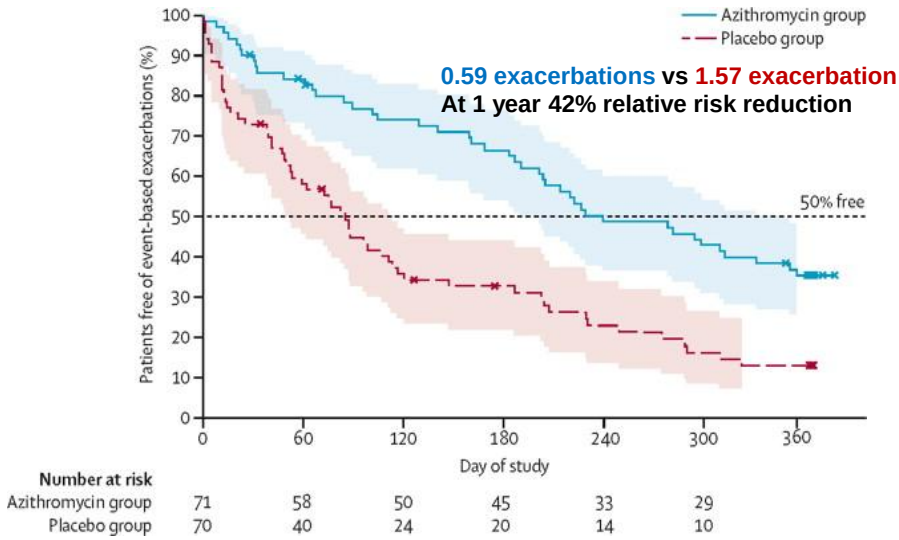
(**Excluded** CF patients, Ig deficiency, ABPA, colonized with nontuberculous mycobacteria, unstable arrhythmias)

**Main endpoint** → exacerbation requiring antibiotics

**Secondary points** → changes in FEV1, quality of life

*Wang et al. Lancet* 2012 August 18th ;380:660-667

# Azithromycin




*Wang et al. Lancet* 2012 August 18th ;380:660-667

# Further Treatment

- **Surgery** (unresponsive to medical therapy localized bronchiectasis, life threatening hemoptysis)
- **Lung Transplant :** end stage disease

# Cystic Fibrosis

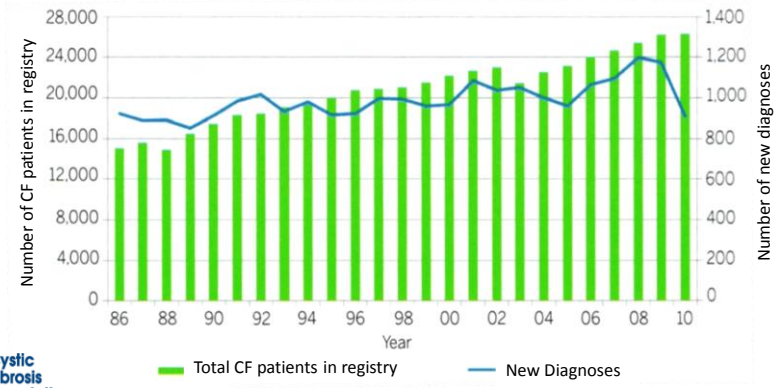
## CF Epidemiology

- Most common lethal autosomic recessive disease in Caucasians
- Single mutation in gene encoding **CFTR** (CF transmembrane regulator protein) long arm of chromosome 7 (>2000 mutations known)

ΔF508 the most common , 90% of US CF patients

# Cystic Fibrosis epidemiology

- 30.000 patients with CF in the US
- Over 900 new diagnosis every year
- **57%** detected by newborn screening

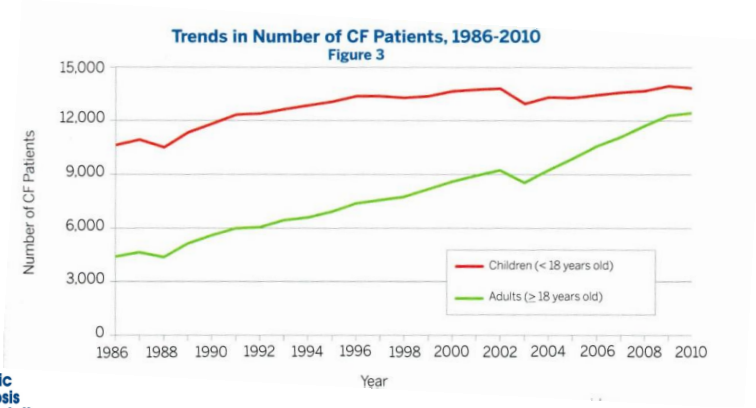



Cystic Fibrosis Foundation

*Patient registry* CFF 2010

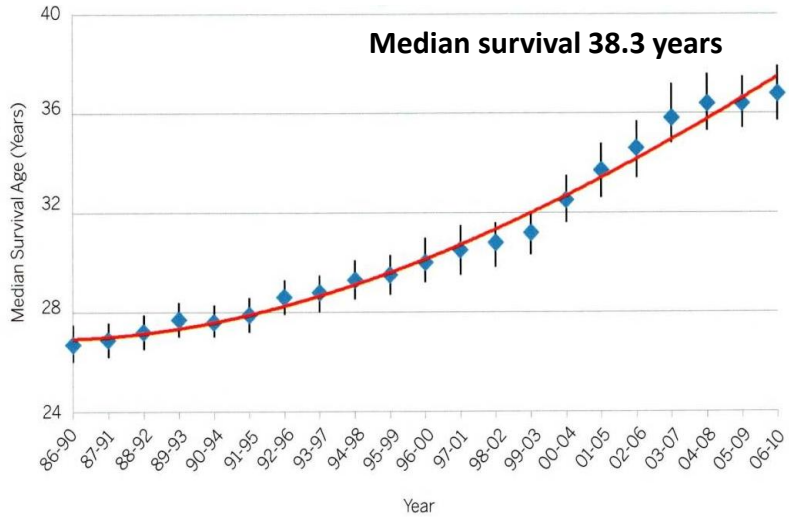
# Cystic Fibrosis epidemiology

- 1 every 3500 newborns
- Adults comprise **47 %**



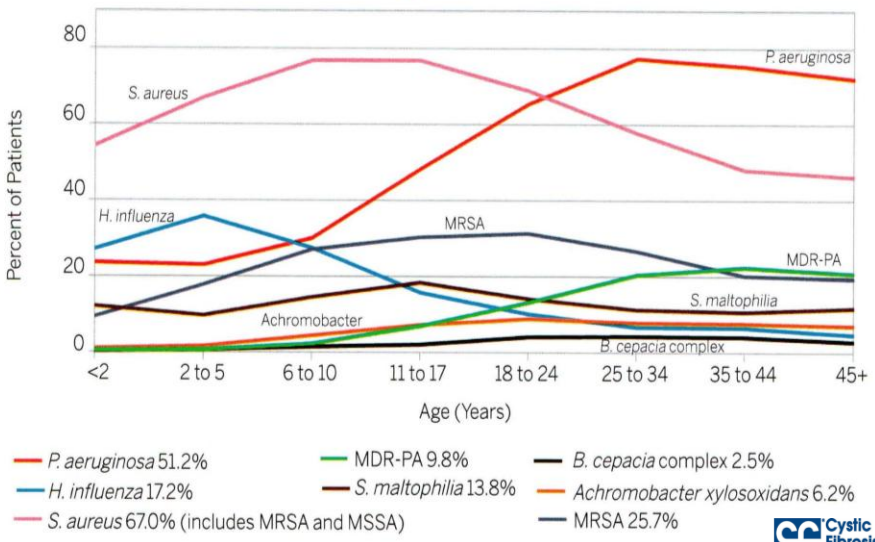

Cystic Fibrosis Foundation

# Cystic Fibrosis Survival




Cystic Fibrosis Foundation

# Respiratory microbiology



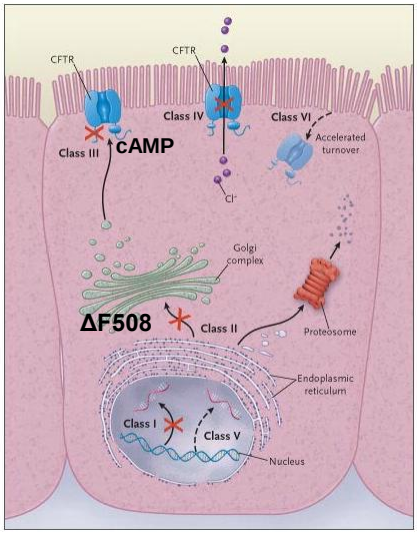

**Data report 2010**

Cystic Fibrosis Foundation

# What is CFTR?

- **Ion channel**
  - Regulates liquid interface on epithelial surfaces – influences chloride secretion
  - Location: all epithelial cells
    - Lung
    - Pancreas
    - Sweat gland
    - Liver/gall bladder
    - Intestine
    - Reproductive system

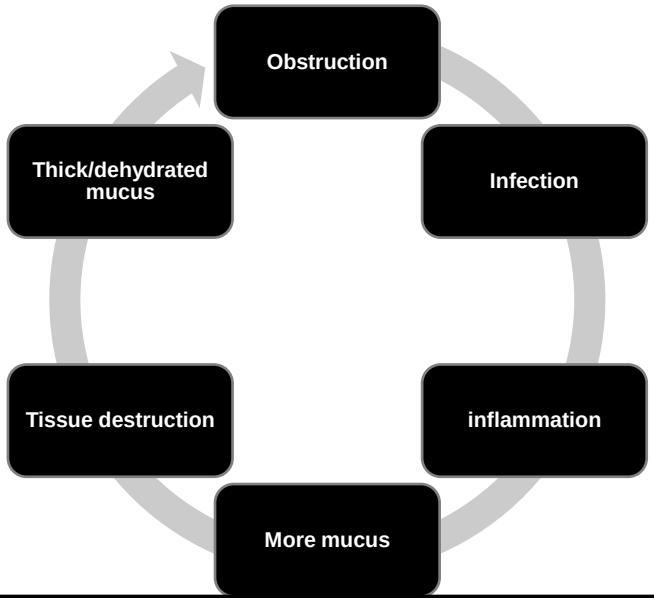
# CFTR mutations




- **Class 1** Defective protein synthesis (G542X)
- **Class 2** Little-no protein, trafficking problem (ΔF508)
- **Class 3** gating problem (G551D)
- **Class 4** Cl-conductance (R117H)
- **Class 5** rapid turnover

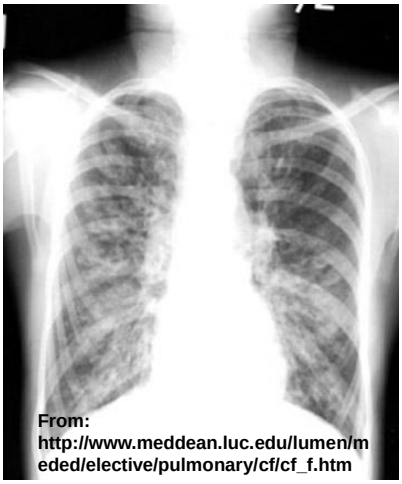
*NEJM* 2005

# Clinical manifestations




# Common Sinopulmonary Issues

- Colonization and infection by multiple organisms
- Cough, sputum
- Airway obstruction
- Hyperinflation
- Bronchiectasis
- ABPA
- Nasal polyposis
- Chronic rhinosinusitis
- Pulmonary fibrosis
- Respiratory failure



# Pancreatic Insufficiency

## Exocrine function

- Protease
- Lipase
- Abnormal absorption leads to deficiency of lipid vitamins (A, D, E, K)
  - Coagulopathy
  - Stunted growth
  - Osteoporosis

➡ Replace enzymes

# Pancreatic Insufficiency

## Endocrine function

Decrease B cell mass with insulin deficit

- **Glucose intolerance:** 50-70% of the adult CF
- **Diabetes:** 50% by adulthood
- Difficulty in treating diabetes in CF
  - Diabetic adults without CF: need calorie/carbs restriction
  - Malnutrition/malabsorption in CF
    - They need high calorie and unlimited carbs
  - Need tight BG control with insulin replacement and nutritionist input

## Liver Disease

- **Location of CFTR channel**
  - Bile ducts
  - Gall bladder
- "Dried up" bile
  - Focal biliary cirrhosis
- Some develop portal HTN
- **Ursodeoxycholic acid** to treat biliary disease

## GI Motility

- **Meconium ileus**
  - Thick stool found in amniotic fluid
  - 10-20% of the newborns with CF
- **Distal Intestinal Obstruction Syndrome (DIOS)**
  - Starts at ileocecal region (RLQ pain)→colon
  - Seen in pancreatic sufficient or insufficient patients
  - 18% of the adults
  - Stool softeners (PEG), gastrografin, hydration

# Infertility

- **Male**
  - **98 %** CF males are **infertile** due to obstructive azoospermia
  - Congenital bilateral absence of vas deferens (CBAVD)
- **Female**
  - Better fertility, hard to determine %
  - Amenorrhea from malnutrition
  - Thick cervical mucus, not thinning at ovulation

  → Pregnancy does not have negative impact on CF prognosis

# Osteoporosis

- Reduced vitamin D absorption
- Reduced bone mineral content
- CF adults have higher risk of fracture
- Monitor 25-OH-Vitamin D yearly
- **Calcium supplementation**
- **Bisphosphonates** may be helpful

# CFRD (CF related DM)

- 50% adults
- Correlates with nutrition and lung function
- Insulin deficiency from decreases B cell mass

- 75gr OGTT used for screening
- **Insulin** is the treatment of choice
- **No** caloric or carbohydrate limitations!!

# CF (Classic vs Non-classic)

- **Classic CF**
  - Abnormal sweat chloride **+** CFTR dysfunction in one or more organs systems
    - Chronic respiratory infection, malnutrition, infertility
- **Non-classic CF**
  - Normal or intermediate sweat chloride: partially function CFTR
  - One organ involved
  - Requires DNA sequence analysis
  - In general preserved pancreatic exocrine function
  - Not uncommon to diagnose in adulthood

# Diagnosis

- Classic manifestations of CFTR dysfunction in several organs

**+**

- Sweat chloride test > 60 mmol/L (concentration of salt in sweat)

**or**

- Mutation genetic analysis (2 CFTR mutations detected)

**or**

- Nasal potential difference measurement (abnormal ion transport measured in nasal epithelium)

- **Newborn screening in every state**

(immunoreactive trypsinogen test (IRT) )

# Treatment Goals

- **Major goals**
  - Control infection in the lung
  - Keep airway clean, open
  - Prevent intestinal obstruction
  - Prevent complications due to lack of endocrine and exocrine pancreatic functions
    - Lack of pancreatic enzyme: malnutrition
  - Infertility and social issues
  - Treat complications (CFRD and Osteoporosis)

# Treatment

**Diet:**

- High caloric intake (usually twice as much as normal kids)
- Fat soluble vitamin supplementation (A, D, E, K)
- Pancreatic enzyme supplementation:

  May need anti-acid to keep enzymes active

  Excess pancreatic enzymes passed to colon

  →May cause Fibrosing colonopathy

**Endocrine:**

– Tight glucose control with insulin

# Chronic respiratory therapy

- **Airway clearance/Chest PT**/Aerobic exercise
- **Bronchodilators** (albuterol)
- Inhaled antibiotics (maintenance)
- Anti inflammatory

## Mucolytic: hrDNAse- Dornase alpha

- Extracellular DNA (high molecular weight) from leukocytes accumulates and makes mucus viscous
- Decreases exacerbations
- Increases lung function 5-6%

*N Engl J Med* 1994; 331:637-642

## Hypertonic saline

- **Restores airway surface liquid (moisturizes mucus)**

→ Decreases exacerbation

→ Increases lung function

- Careful since it causes bronchospasm

## Anti inflammatory

- **Azithromycin** (3 times weekly)
  decreases airway inflammation
- Immunomodulation properties

- Works well in airway colonized by Pseudomonas (oxygen depleted environment)
- Decreases exacerbations

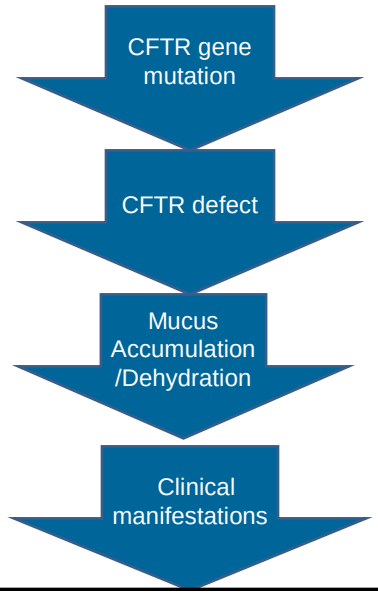
## Inhaled antibiotics

- Tobramycin solution (TOBI)

- Aztreonam (Cayston)

- Colisthemate (Colistin)

# Therapeutic targets




Gene therapy

CFTR modulators

Osmotic agents/mucus alteration agents

Pulmonary toilette
Antibiotics

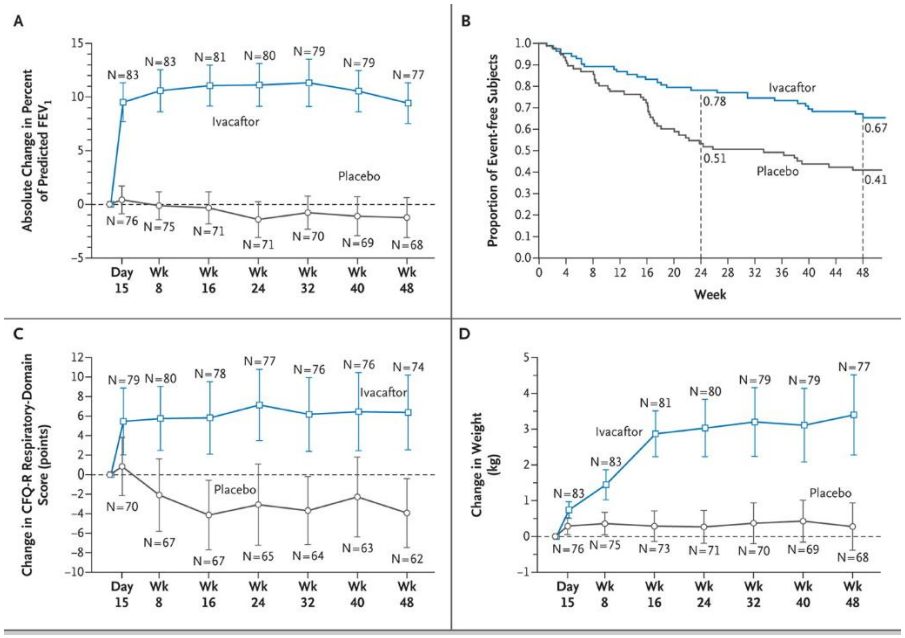
# G551D mutation

- **4%** CF patient carrying G551D mutation (gating mutation)

- **Ivacaftor** is a potentiator that opens CFTR that is already in the cell surface

Increases lung function by **15%**

***N Engl J Med*** 2011; 365:1663-1672




***N Engl J Med*** 2011; 365:1663-1672

# Major Factors to Consider

- Quality of Life
  - Frequent sickness and contact with healthcare systems
  - Need to abide by strict maintenance therapy which requires serious commitment
  - High morbidity and mortality
  - Difficult to mature socially and emotionally from childhood
- Family planning
- End of life

# Take home points

- Bronchiectasis are the end injury results of multiple underlying diseases
- Etiology is important since it might change prognosis and management
- HRCT gold standard for diagnosis
- CF is still seen and diagnosed in adults