# Cystic Fibrosis

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# CF

- Multisystem genetic disease Characterized by*: chronic, progressive obstructive lung disease*
- Other systemic manifestations, such as:

  *nutrient malabsorption and malnutrition due to pancreatic insufficiency.*

  *liver disease and cirrhosis, and CF-related diabetes mellitus (CFRD).*

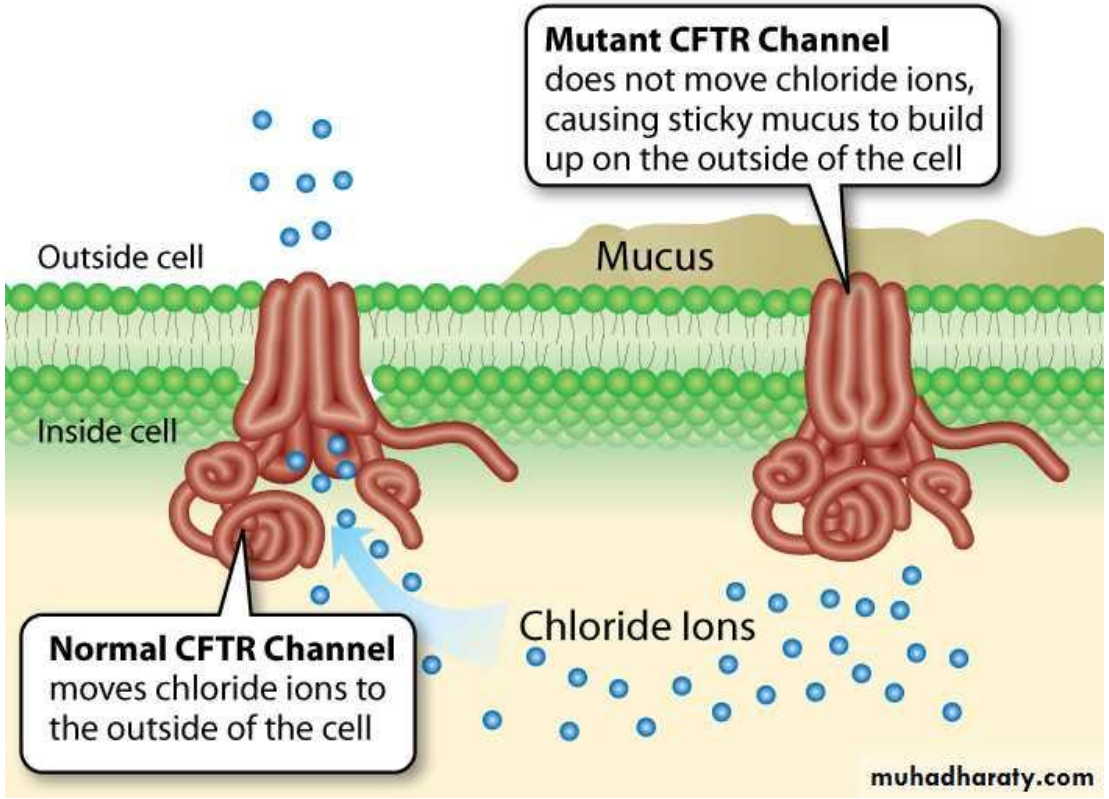
- CF is common in the *Caucasian population* but does occur in all ethnic and racial groups.

- M/C gene mutated: delta F508

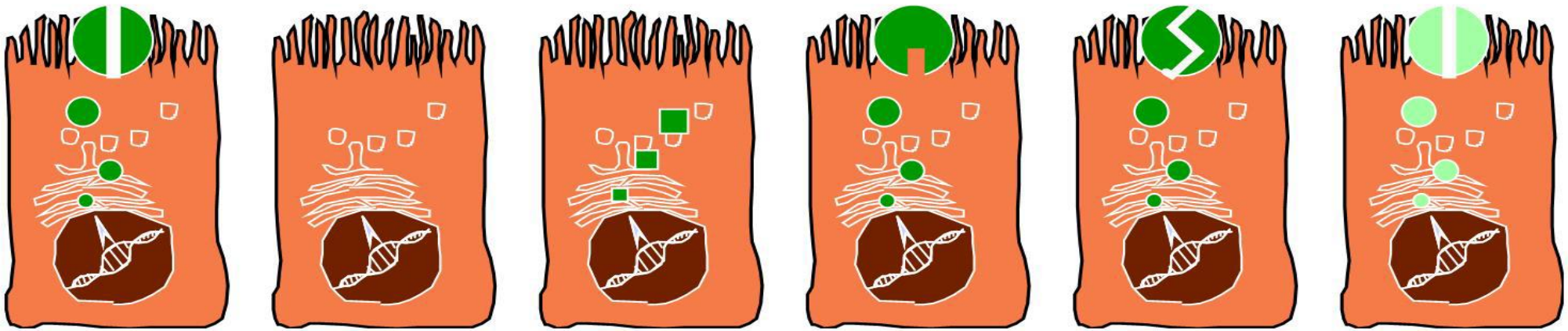
**Cystic Fibrosis Transmembrane Conductance Regulator(CFTR)**

- Long arm chr 7

  (7q31.2)



# CFTR
## *Classes of Mutations*



| Normal | I | II | III | IV | V |
|---|---|---|---|---|---|
| | No synthesis | Block in processing | Block in regulation | Altered conductance | Reduced synthesis |
| | G542X | F508del | G551D | R117H<br>D1152H | 3849+10kbC→T<br>5T<br><br>A455E |
| | 12% | 87% | 5% | 5% | 5% |

Scriver CR, et al. *The Metabolic and Molecular Bases of Inherited Disease*. 2001:5121-5188.[8]

# Diagnosis

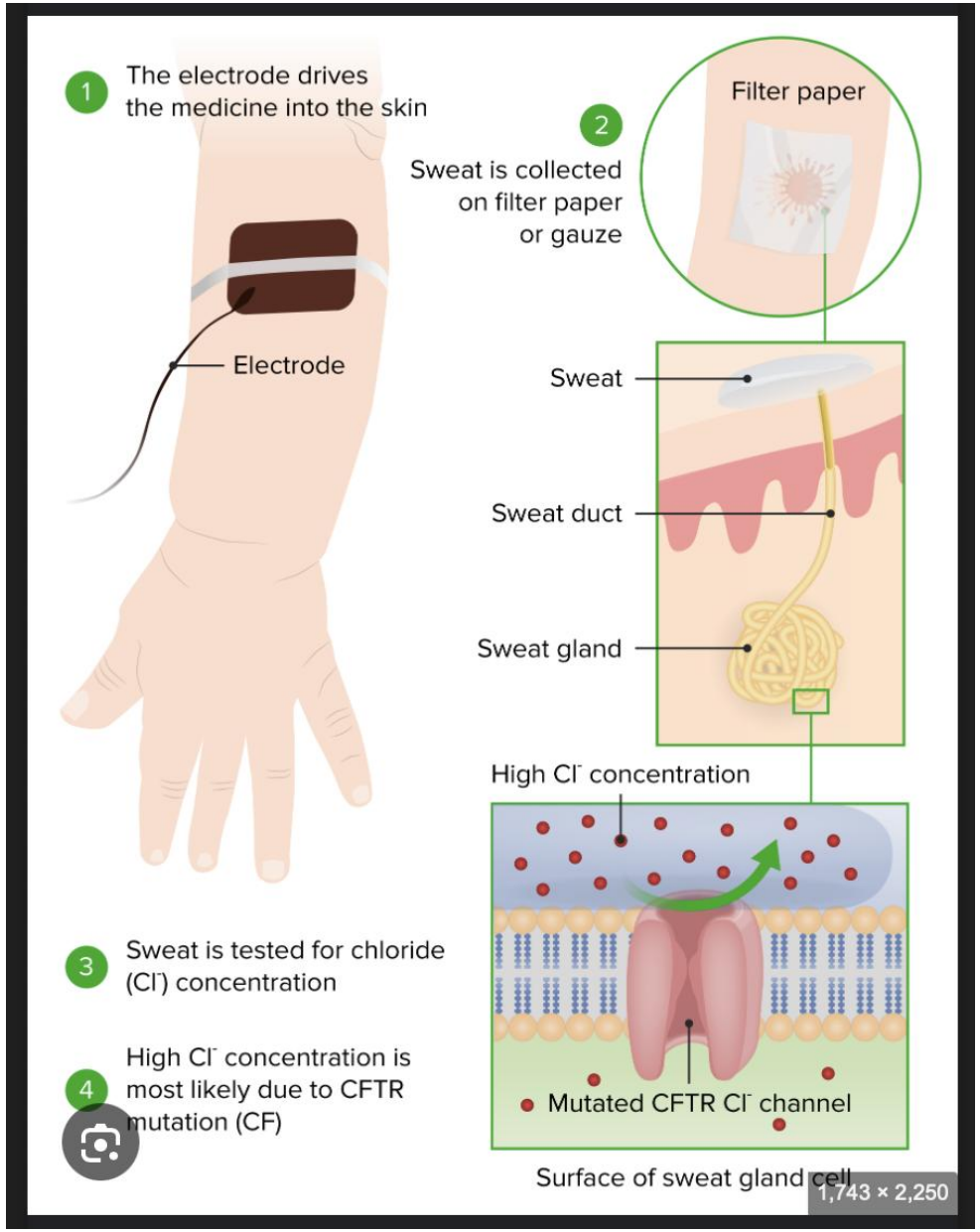
- Criteria
  - One of the following
    - . Presence of typical clinical features
    - . History of CF in a sibling
    - . Positive newborn screening test

  - Plus laboratory evidence for CFTR dysfunction
    - . Two elevated sweat chloride concentration on 2 separate days
    - . Identification of 2 CF mutations
    - . Abnormal nasal potential difference measurement

# Diagnostic testing

- *Newborn Screening test*:
- pancreatic derived enzyme immunoreactive trypsinogen [IRT]

- *Sweat Chloride:* the most useful test for diagnosing CF. ≥60 mmol/L
- Genetic testing
  The standard diagnostic test for pancreatic insufficiency has been the three day fat collection.

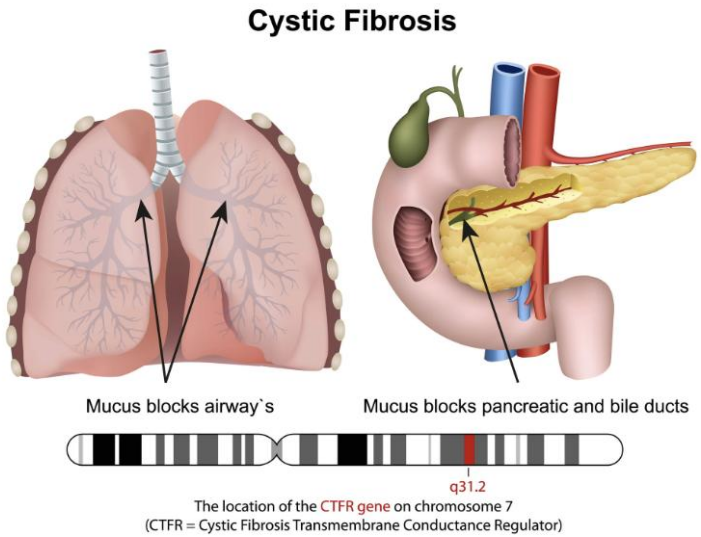


# Sweat Chloride testing

- IF NBS +ve: Sweat Cl testing when the *infant weighs >2 kg*, and is *at least 36 wk of corrected gestational age.*

- Newborns greater than *36 wk gestation and >2 kg body weight* with a *positive CF newborn screen, should have sweat chloride testing performed as soon as possible after 10 d of age, ideally by the end of the neonatal period (4 wk of age).*
- *In children </= 6 months: sweat Cl <30 is negative, 30-59 is An intermediate sweat chloride value ( consider extended CFTR gene analysis), >/= 60 mmol/l …CF*

# CF Pathophysiology




CFTR gene defect

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Defective ion transport

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Airway surface liquid depletion

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Defective mucociliary clearance

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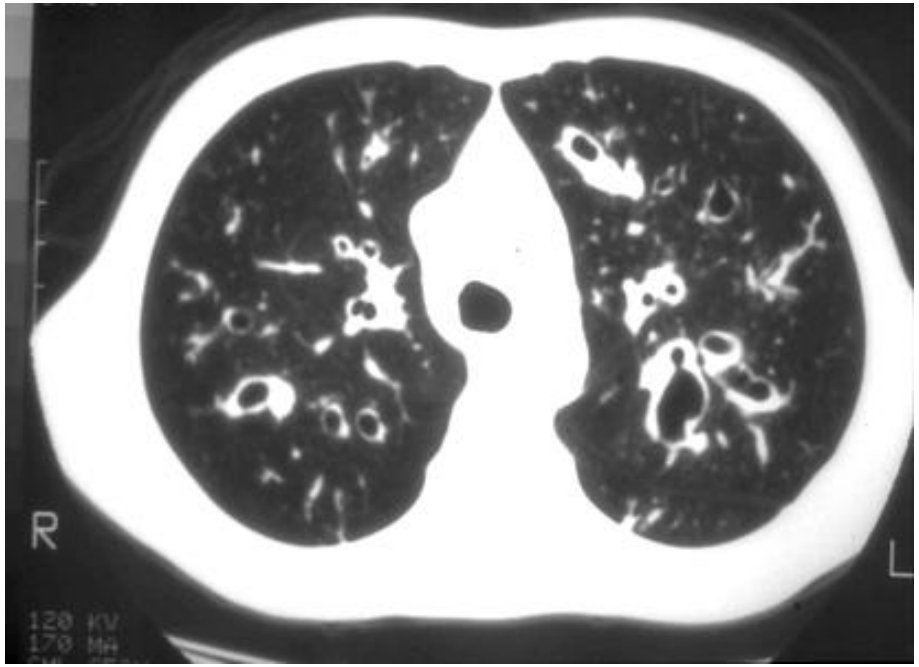
Mucus obstruction

↻ Infection

↻ Inflammation


R
L
120 KV
170 MA

# Pathophysiology

- **Gastrointestinal:**
  - *Pancreas*
    - Absence of CFTR limits function of chloride-bicarbonate exchanger to secrete bicarbonate.
    - Leads to retention of enzymes in the pancreas, destruction of pancreatic tissues.

# Pathophysiology

**- Intestine**

- Decrease in water secretion leads to thickened mucus and desiccated intraluminal contents.
- Obstruction of small and large intestines

**-Biliary Tree:**

- Retention of biliary secretion
- Focal biliary cirrhosis
- Bile duct proliferation.
- Chronic cholecystitis, cholelithiasis

# Manifestations:

- **Respiratory tract:**
  - *Chronic sinusitis.*
    . Nasal obstruction
    . Rhinorrhea
    . Nasal polyps in 25%; often requires surgery

  - *Chronic Cough:*
    . Persistent
    . Viscous, purulent, green sputum

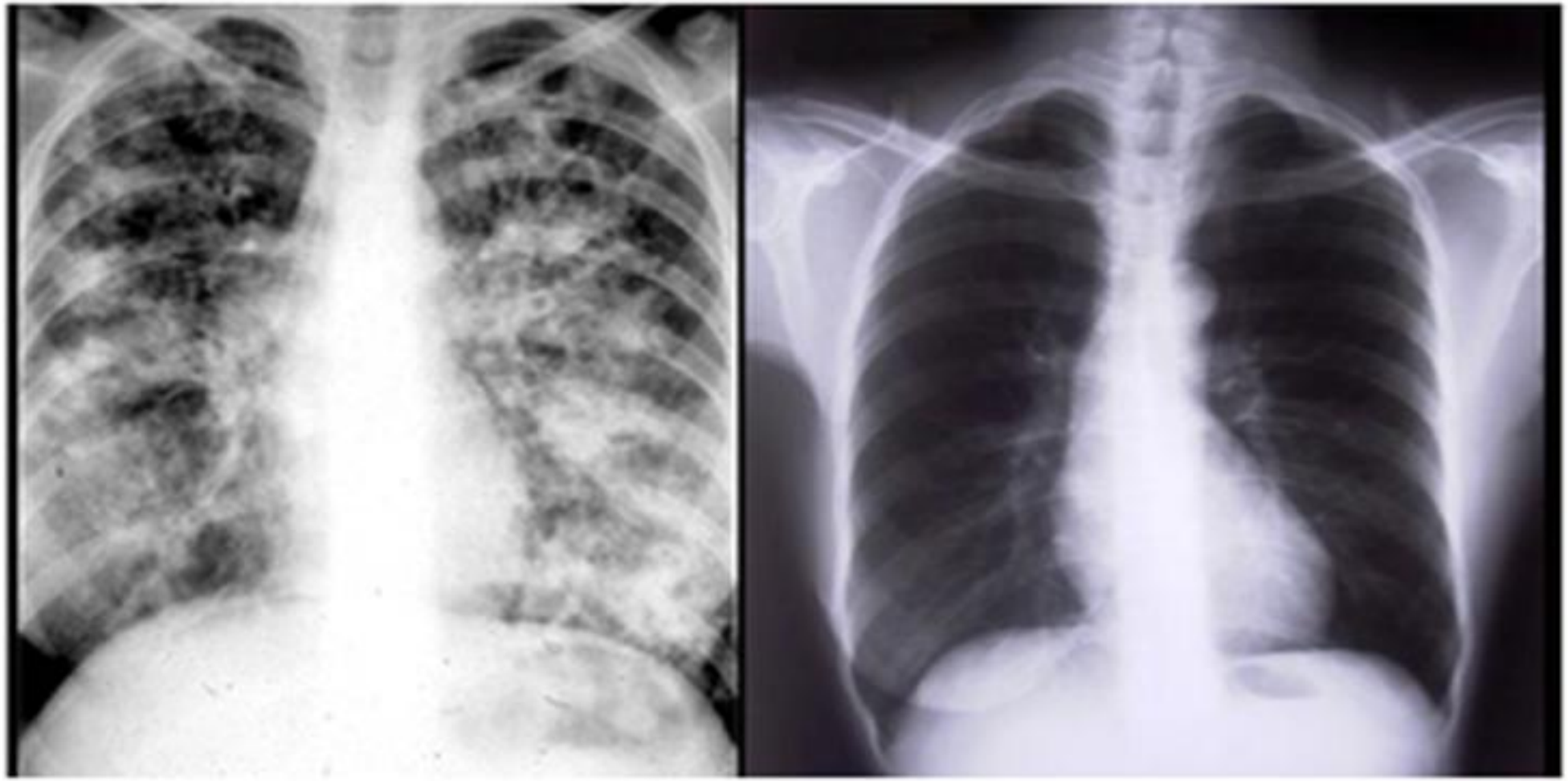
# Manifestations

- *Infection:*
  . Initially with H. influenza and S. aureus
  . Subsequently P aeruginosa
  . Occassionally, Burkholderia gladioli, proteus, E. coli, klebsiella.

- *Lung Function:*
  . Small airway disease is first functional lung abnormality
  . Progresses to reversible as well as irreversible changes in FEV1
  . Chest x-ray may show hyperinflation, mucus impaction, bronchial cuffing, bronchiectasis

# Complications

- ***Respiratory Tract:***
  - . Pneumothorax : 10% of CF pts
  - . Hemoptysis
  - . Digital clubbing
  - . Cor pulmonale
  - . Respiratory failure



Cystic Fibrosis Lung

Healthy Lung

# Complications

- **Gastrointestinal:**
  - *Meconium ileus*
    . Abdominal distention
    . Failure to pass stool
    . Emesis

  - *DIOS: distal intestinal obstruction syndrome*
    . RLQ pain
    . Loss of appetite
    . Emesis
    . Palpable mass
    . May be confused with appendicitis

# Gastrointestinal complications

- Exocrine pancreatic insufficiency
    . Found in > 90% of CFpts
    . Protein and fat malabsorption
    . Frequent bulky, foul-smelling stools
    . Vitamins A,K,E,D malabsorption

- Increased incidence of GI malignancy

# Genitourinary

- Late onset puberty
    . Due to CLD and inadequate nutrition.

- >95% of male pts with CF have azospermia due to obliteration of the vas dererens
- 20% of female pts with CF are infertile

# Treatment

- ***Major objectives:***
  - Promote clearance of secretions
  - Control Lung infection
  - Provide adequate nutrition.
  - Prevent intestinal obstruction

# TTT: Lung

- > 90% of CF pts die from complications of lung infection
- ***Antibiotics:***
  - Early intervention, long course, high dose
  - Staphylococcus-anti staph: fluclox

  - Pseudomonas-treated with two drugs with different mechanisms to prevent resistance- e.g: cephalosporin (ceftazidime) + aminoglycoside(amikacin, gentamicin)

  - Use of aerosolized antibiotics

# Lung

- ***Increasing mucus clearance***
  . Long-term DNAse treatment increase time between pulmonary exacerbations
  . Inhaled beta-adrenergic agonists to control airway constriction
  . Oral glucocorticoids for allergic Bronchopulmonary aspergillosis (ABPA)

# Lung:

- ***Atelectasis***
  . Chest PT + antibiotic
- ***Respiratory Failure and cor pulmonary***
  . Vigorous medical management
  . Oxygen supplementation
  . NIV
  . Lung transplantation

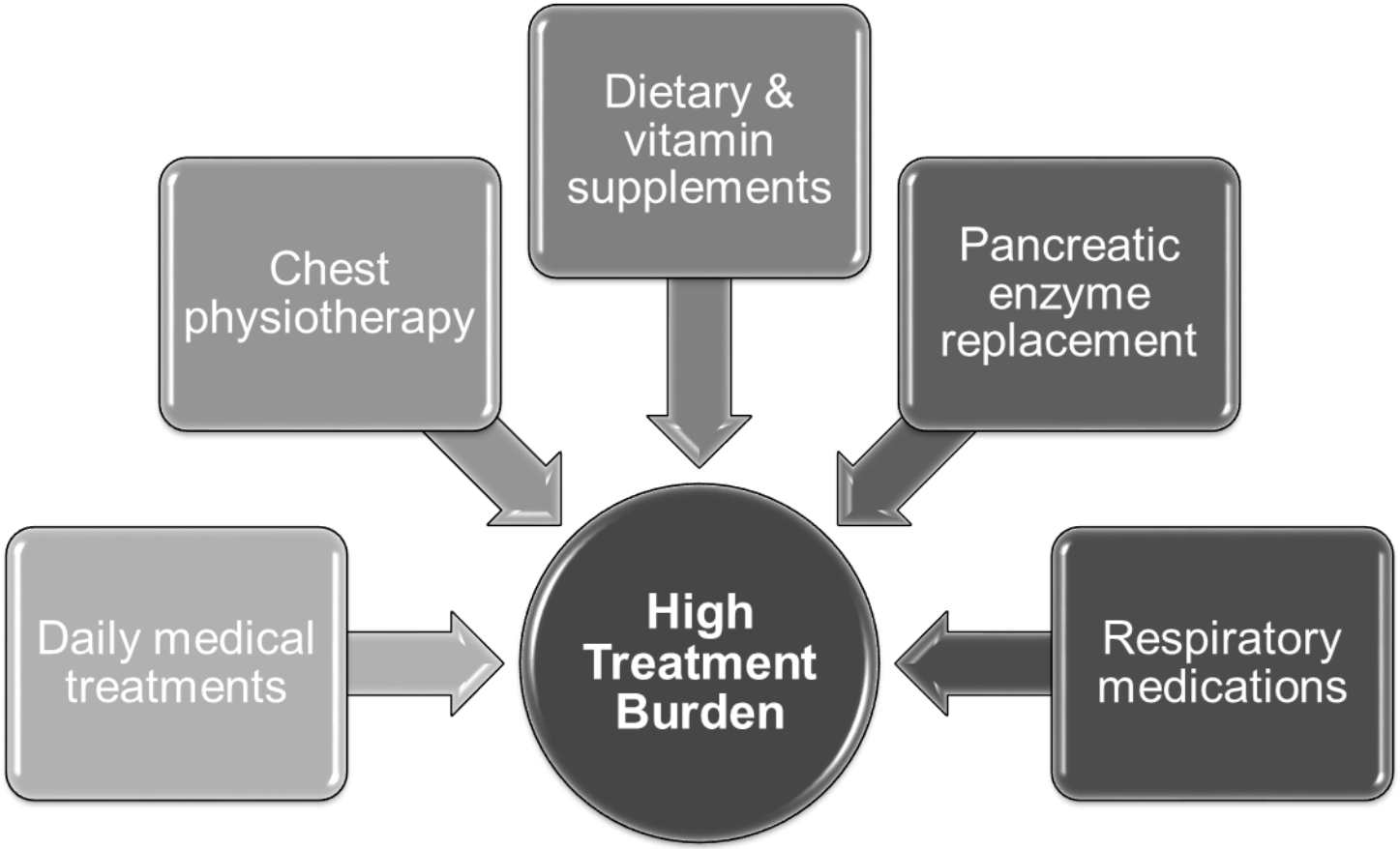
# Treatment

- ***Gastrointestinal:***
  - Pancreatic enzyme replacement
  - Replacement of fat-soluble vitamins- especially Vitamin E & K
  - insulin for hyperglycemia
  - Intestinal obstruction
    - . Pancreatic enzymes (creon) +osmotically active agents
    - . Distal-hypertonic radio contrast material via enema

# TTT: Gastrointestinal

- End-stage liver disease- transplantation
  . 2 year survival rate >50%

# Complexity of CF Treatment




Bregnballe, et al. Patient Prefer Adherence. 2011;5:507-15.
Sawicki, et al. Pediatr Pulmonol. 2012;47(6):523-33

# Summary

- CF is an inherited monogenic disorder presenting as a multisystem disease
- Pathophysiology is related to abnormal ion transportation across epithelia
- Respiratory, GI and GU manifestations
- Treatment is currently preventative and supportive

# THANK YOU