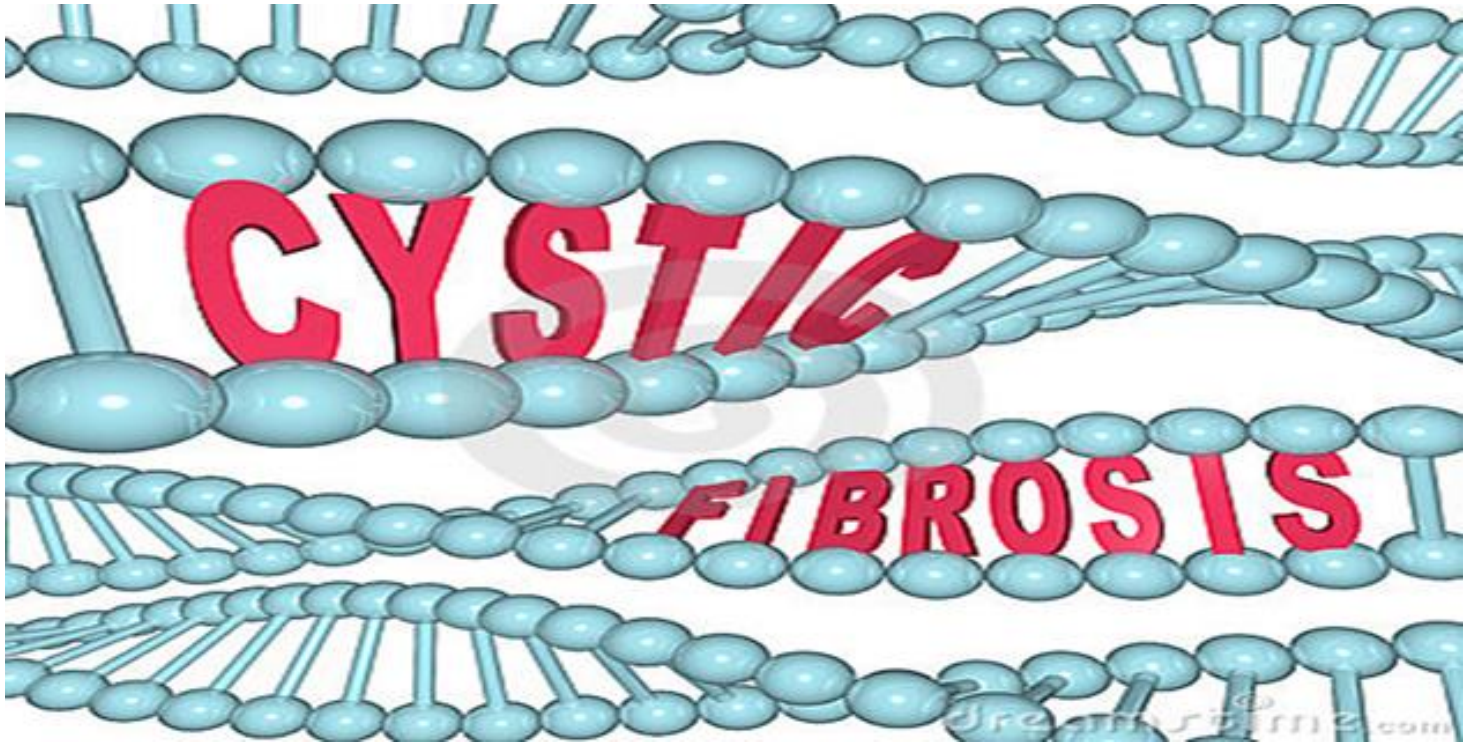


Dr Montaha AL-Iede MD,DCH,FRACP

Paediatric Pulmonologist & Sleep physician

- CF is a life-shortening, multisystem genetic disease.
- First described by Dr. Dorothy Anderson (American Pathologist). provided the first description of the disorder in 1938.
- Mutated CF gene (cystic fibrosis trans-membrane conductance regulator; CFTR) was discovered in 1989.
- The function of CFTR protein discovered in 1992

- 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).

- Median survival has improved steadily from less than 2 years (1938) to 41.1 years currently.

- This results from: early diagnosis
  implementation of therapies to optimize lung health and nutritional status
  treat chronic respiratory infection, and improve quality of life.

Prevalence:

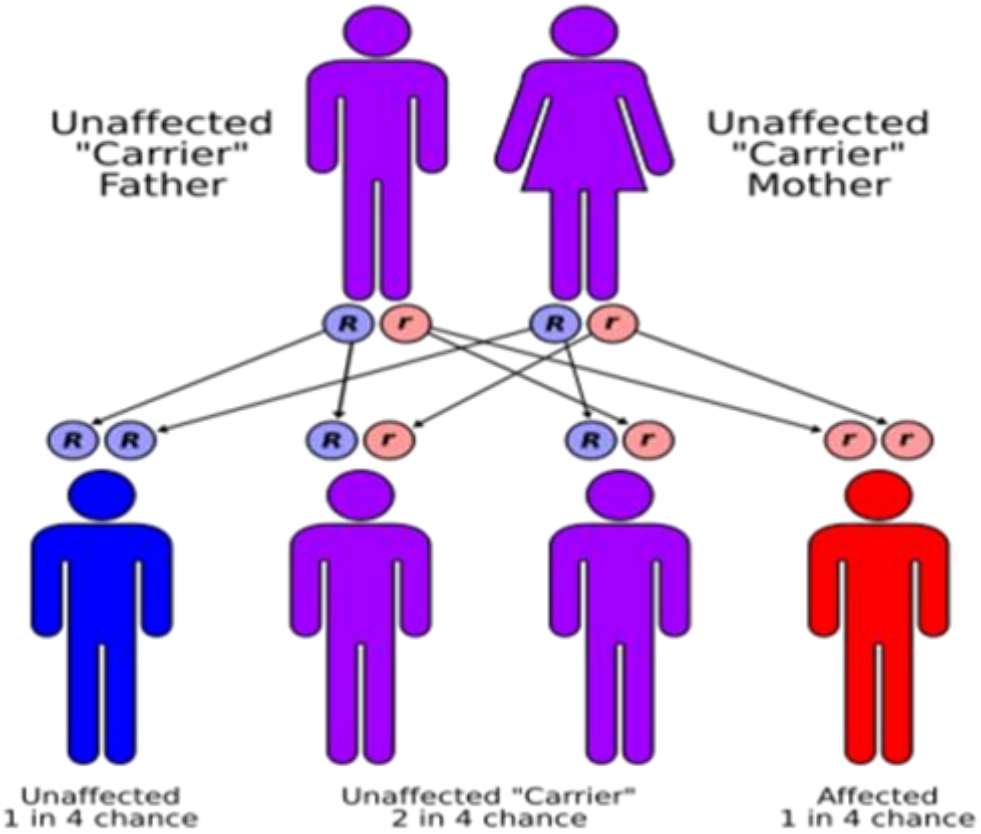
- CF is common in the *Caucasian population* but does occur in all ethnic and racial groups.

- Occurs in approximately 1: 3000 live births. Genet Med. 2008

- M/C gene mutated : delta F508

Genetics

- Autosomal recessive
- 1 in 30 Caucasians are carriers
- 1 in 3300 live births in Caucasians
- US ~30,000 affected individuals
- Other ethnicities - incidences in US
  - Hispanic: 1:9000
  - African American: 1:15,000
  - Asian: 1:32,000



CFF.org. Accessed August 2013.

Rohlfs E, et al. Clin Chem. 2011;57:841-848.

CFTR Gene

Cystic Fibrosis Transmembrane Conductance Regulator(CFTR)

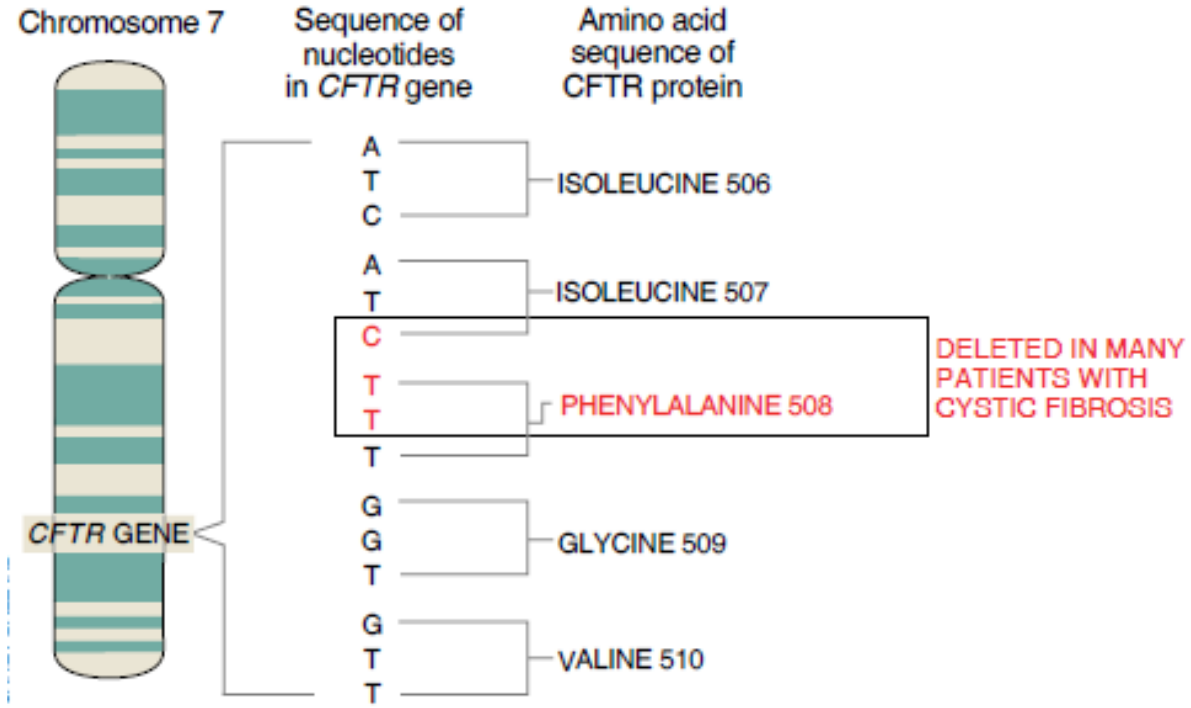
- Long arm chr 7
  (7q31.2)
- Large gene: 189 kilobases, 27 exons
- Transcribed into 6.5 kb mRNA
- Encodes 1480 amino acids

* Regulates chloride movement in and out of a range of epithelial cells.

CF Mutations

Over 1900 CFTR mutations

- **F508del most common**
  - Homozygous – 47%
  - Heterozygous – 40%
- Other mutations
  - G542X – 5%
  - G551D – 4%
  - R117H – 3%
  - N1303K – 2.5%
  - 2789+5G>A – 1.3%

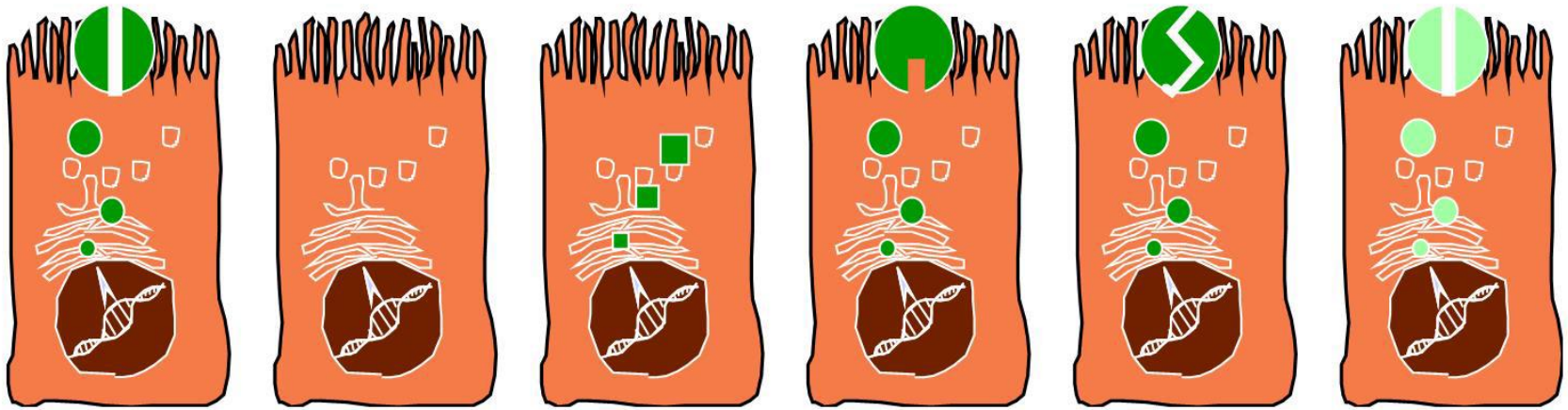


CFF Patient Registry. www.cff.org. Accessed Aug 2013

Mutation	Mutation class	Effect on CFTR protein	Relative frequency [%]
ΔF508	II	Block in protein processing	**66.0**
G542X	I	Reduced or absent synthesis	**2.4**
G551D	III	Block in regulation of CFTR chloride channel	**1.6**
N1303K	II	Block in protein processing	**1.3**
W1282X	I	Reduced or absent synthesis	**1.2**
R553X	I	Reduced or absent synthesis	**0.7**
621 + IG>T	I	Reduced or absent synthesis	**0.7**
1717-IG>A	I	Reduced or absent synthesis	**0.6**
R117H	IV	Altered conductance of CFTR chloride channel	**0.3**
R1162X	II	Block in protein processing	**0.3**

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 D1152H	3849+10kbC→T 5T 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:

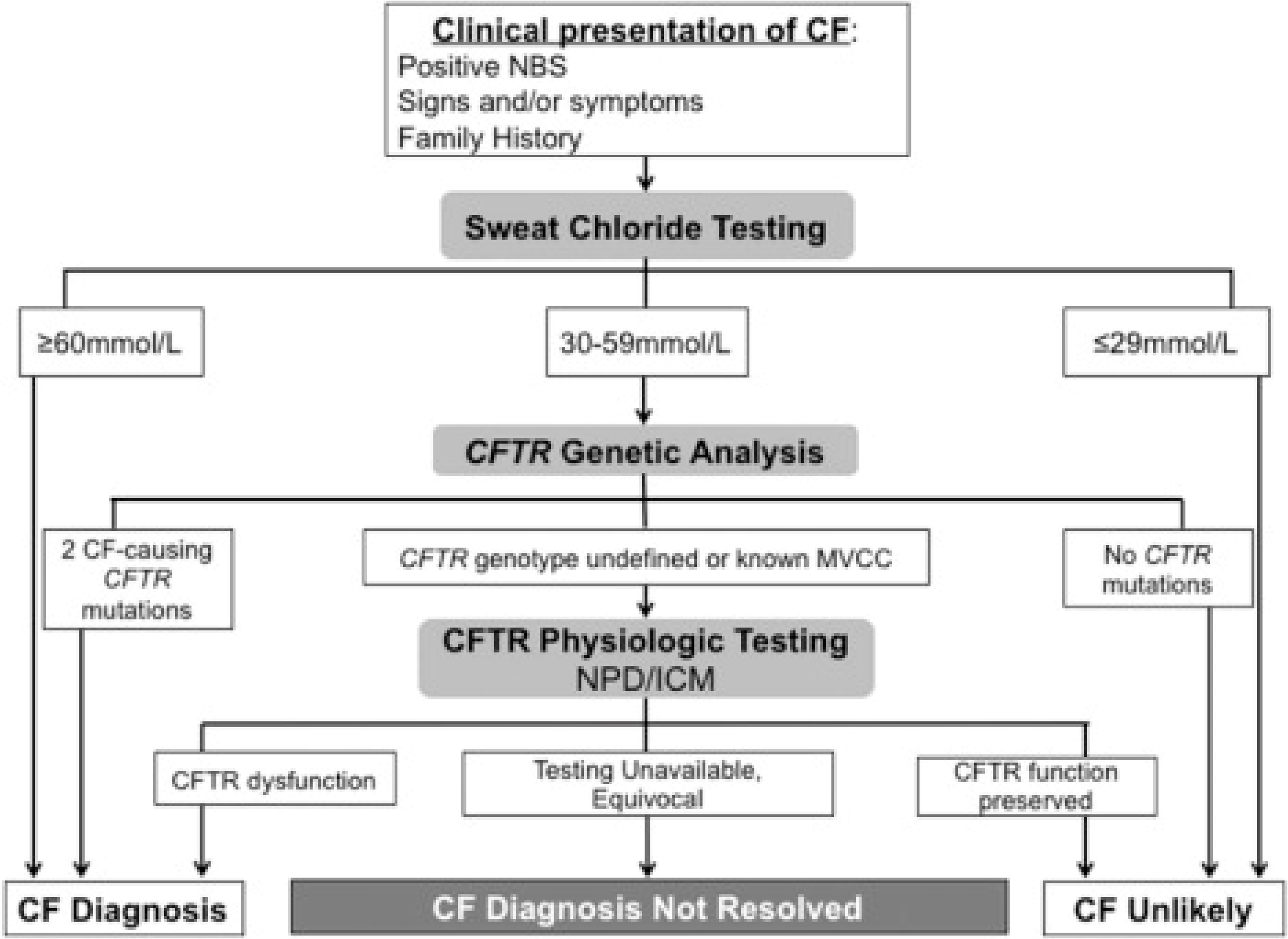
- *Newborn Screening test*: pancreatic derived enzyme immunoreactive trypsinogen [IRT]

- *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.

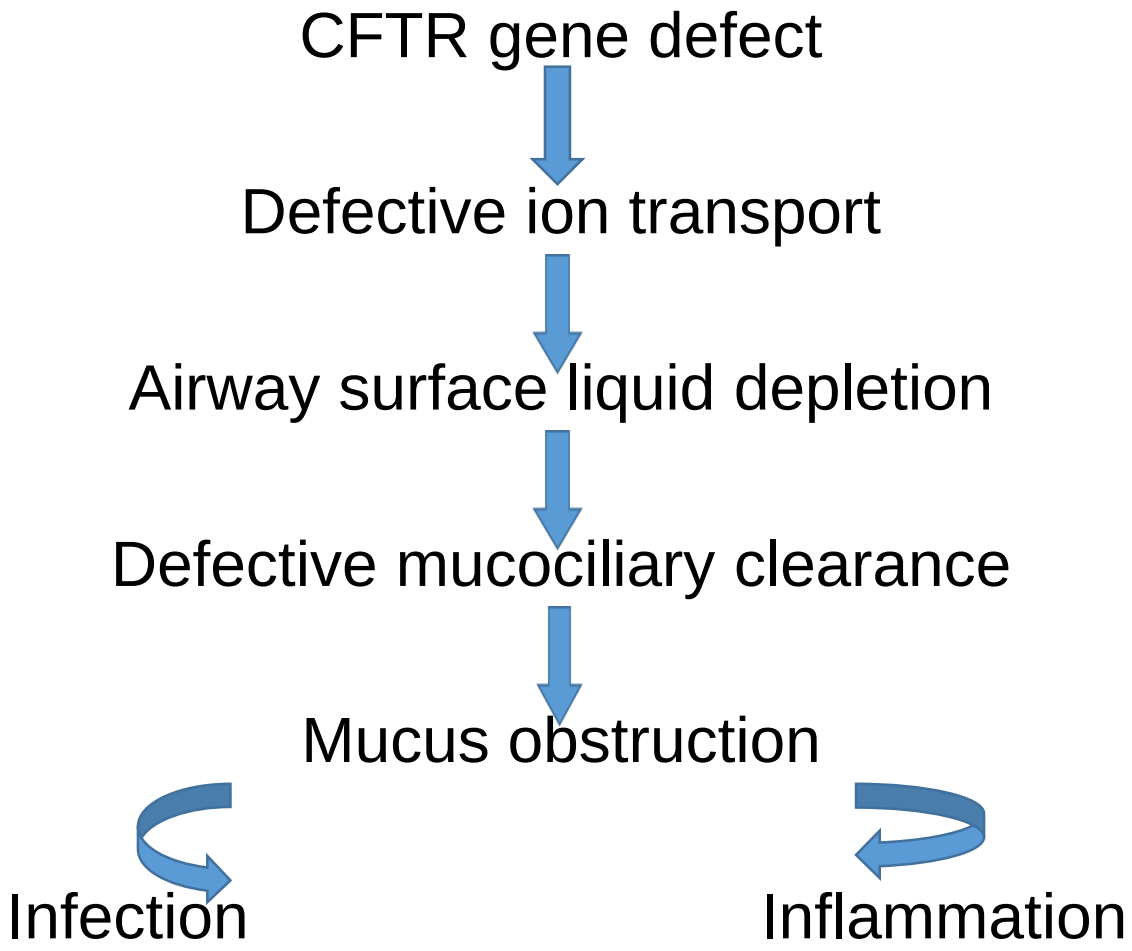
Sweat Chloride testing:

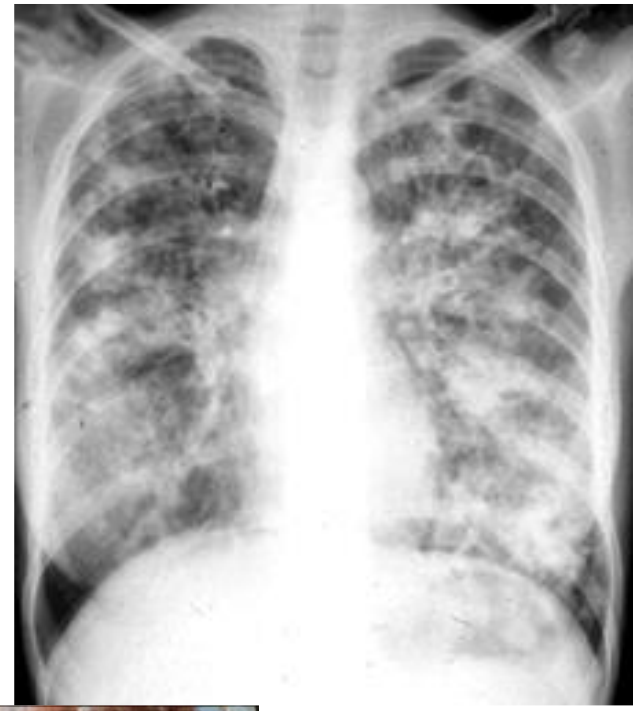
- IF NBS +ve: Sweat Cl testing when the *infant weighs >2 kg*, and is *at least 36 wk of corrected gestational age.*

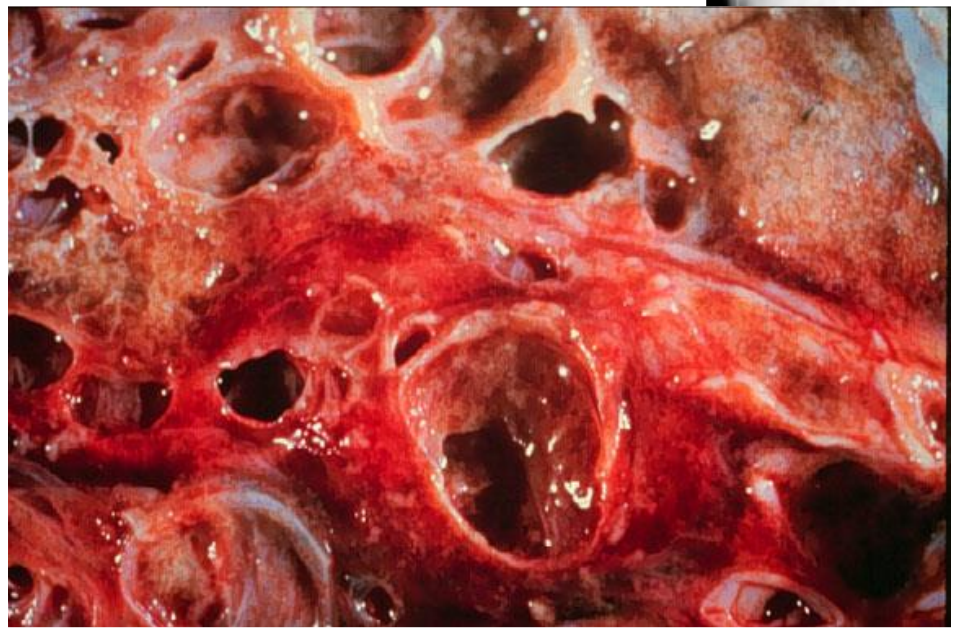
- Newborns greater than *36 wk gestation and >2 kg body weight* with a *positive CF newborn screen, should have sweat chloride testing performed as soon as possible after 10 d of age, ideally by the end of the neonatal period (4 wk of age).*
- *In children </= 6 months: sweat Cl <30 is negative, 30-59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

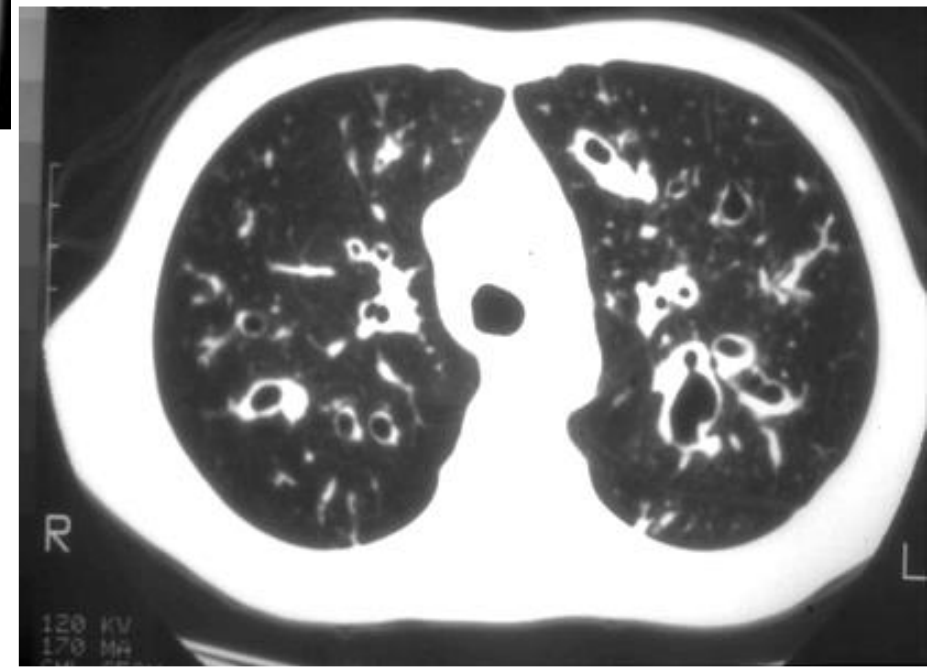

Clinical presentation of CF:
Positive NBS
Signs and/or symptoms
Family History
Sweat Chloride Testing
≥60mmol/L
30-59mmol/L
≤29mmol/L
CFTR Genetic Analysis
2 CF-causing CFTR mutations
CFTR genotype undefined or known MVCC
No CFTR mutations
CFTR Physiologic Testing
NPD/ICM
CFTR dysfunction
Testing Unavailable, Equivocal
CFTR function preserved
CF Diagnosis
CF Diagnosis Not Resolved
CF Unlikely

CF Pathophysiology








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

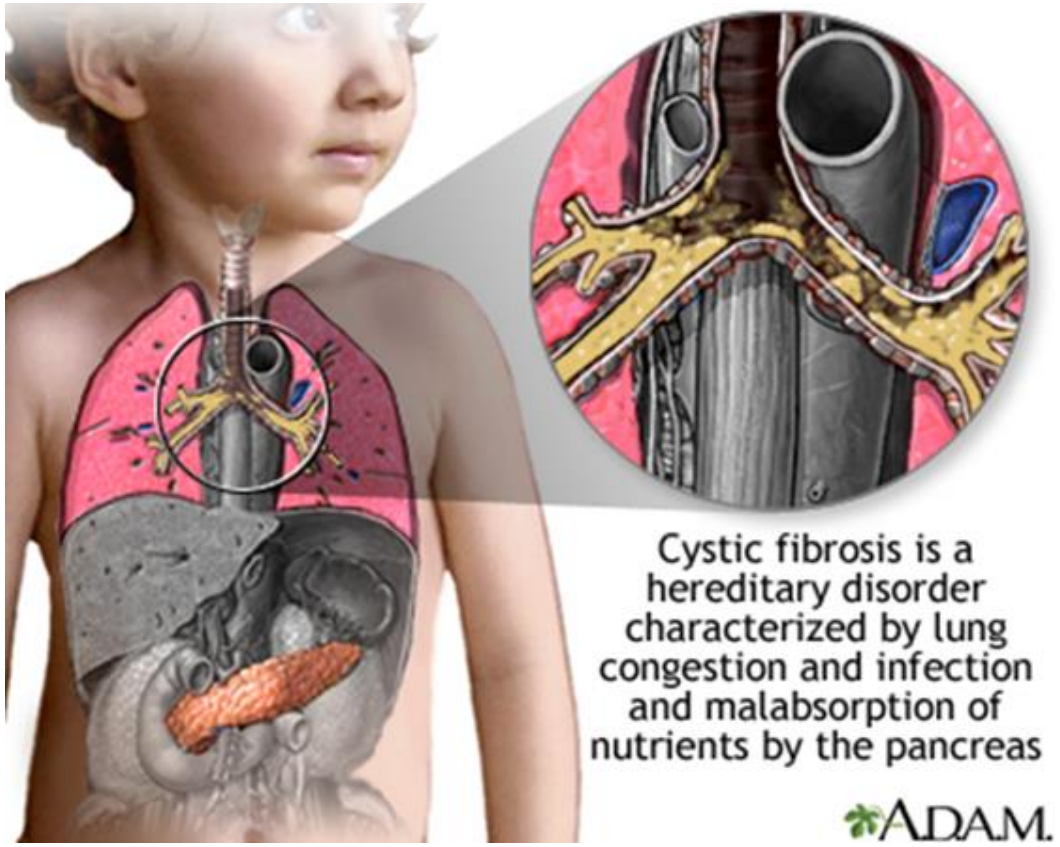
- Decrease in water secretion leads to thickened mucus and desiccated intraluminal contents.
- Obstruction of small and large intestines

-Biliary Tree:

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

Manifestations

- **Common presentation**:
  - Chronic cough
  - Recurrent pulmonary infiltrates
  - Failure to thrive
  - Meconium ileus



Manifestations:

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

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

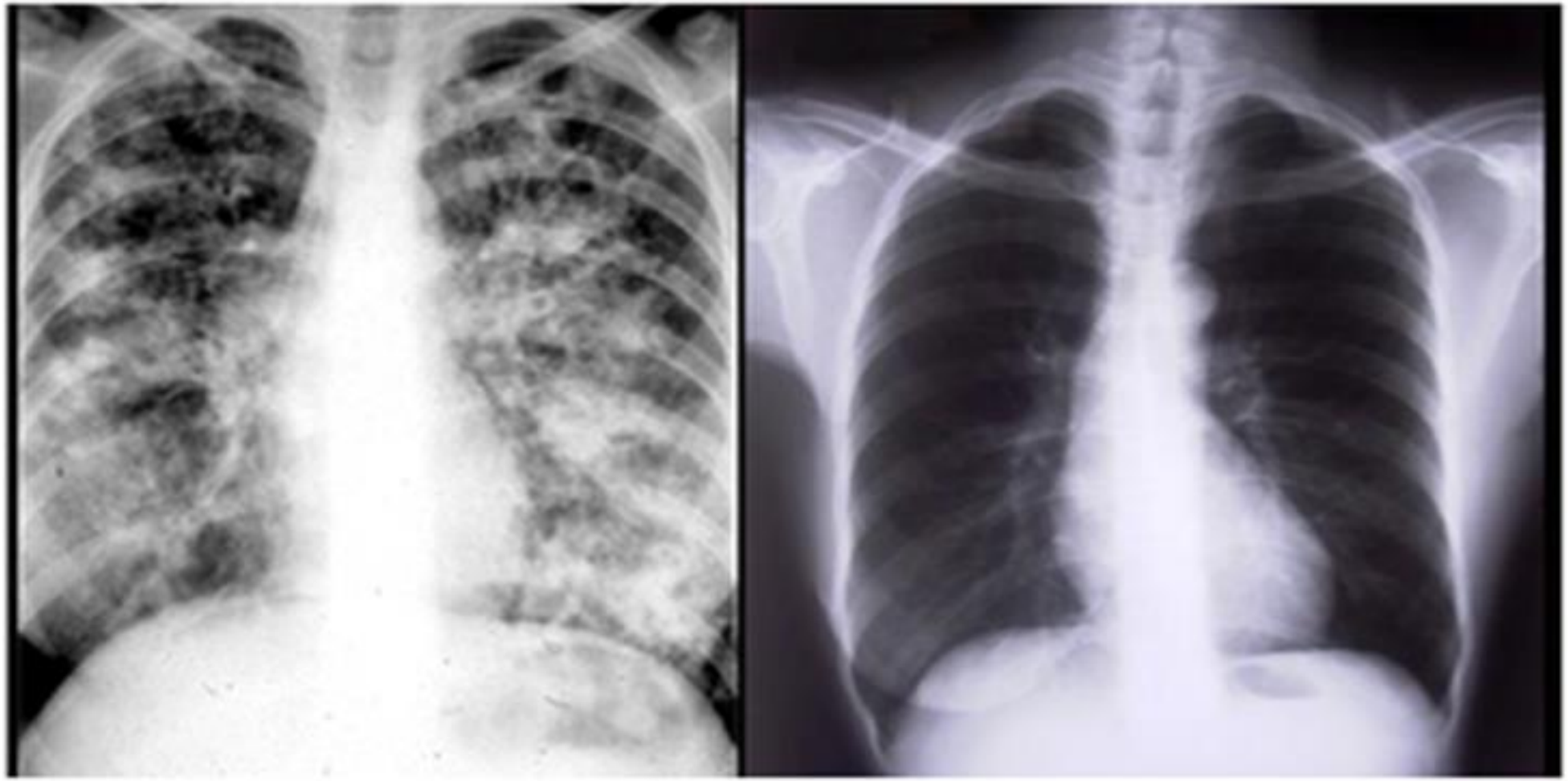
Manifestations

- *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

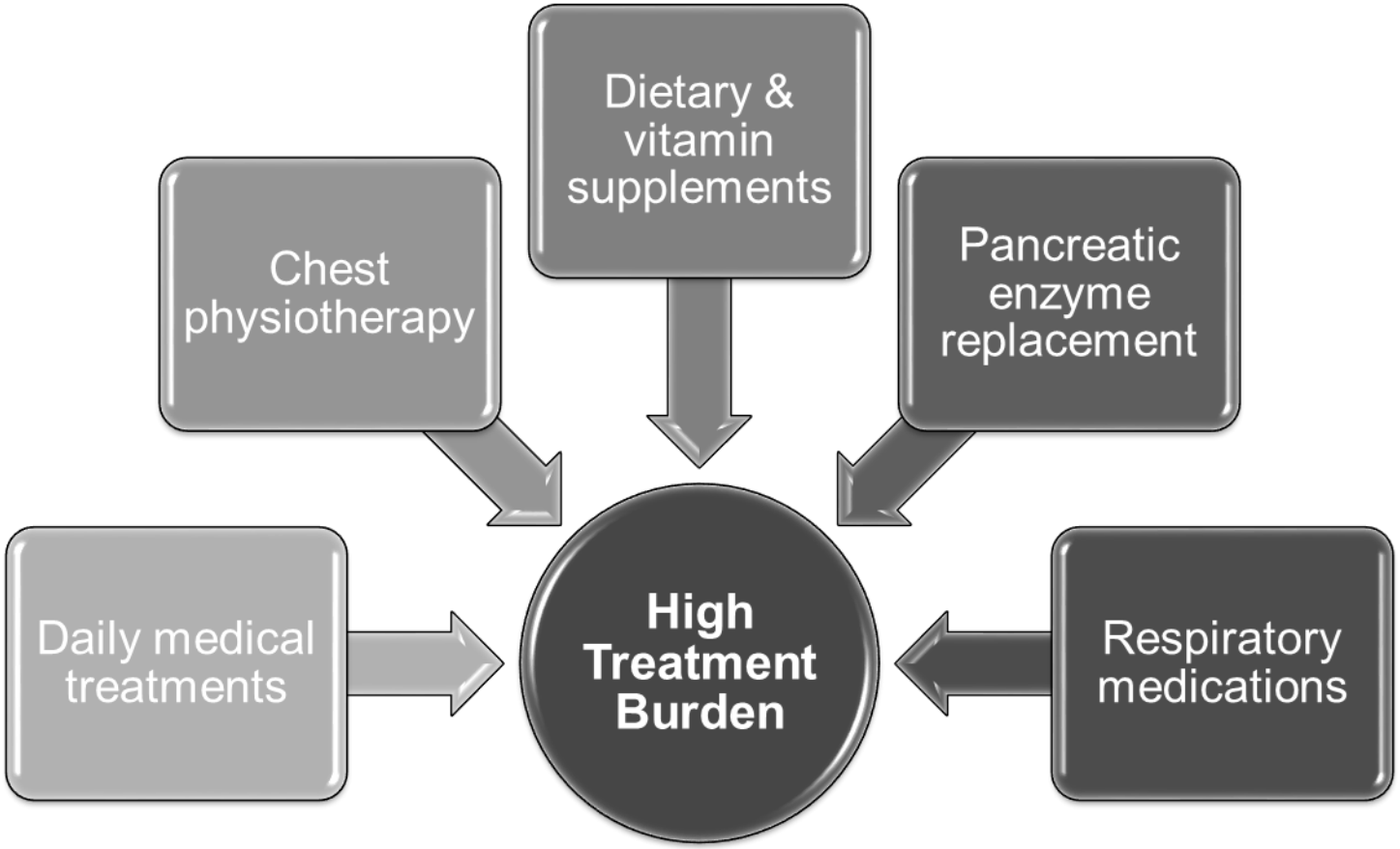
Treatment

- ***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