Cystic Fibrosis

Muna Kilani,MD

- Among the most common life shortening genetic illnesses, median survival is 47years
- Chronic, progressive obstructive lung disease.
- Associated with pancreatic insufficiency, liver disease, CF related diabetes.
- There is no currently no cure for CF

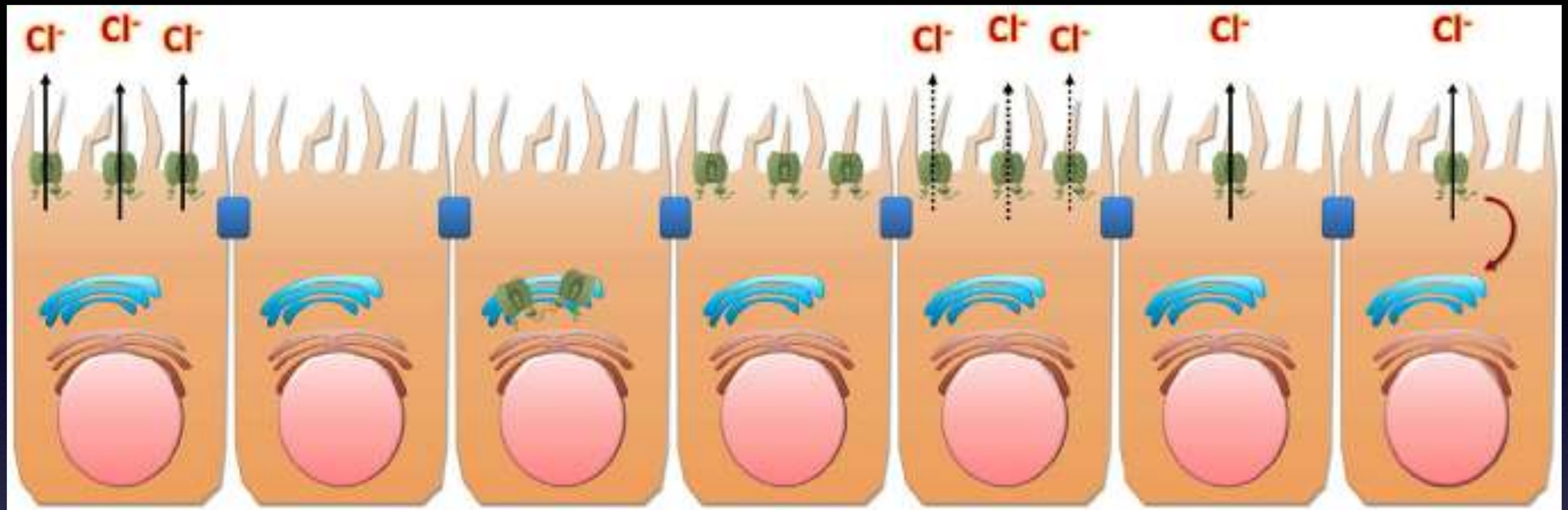
Epidemiology

- 30,000 cases in North America.
- Incidence 1:3200 in whites, 1:15000 in people of African decent.
- Incidence of CF in Jordan???

Pathogenesis

- The disease is caused by a genetic mutation on chromosome 7q31.2, which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein.
- CFTR is an apical epithelial chloride channel.
- 1900 mutations have been identified, all categorized into 6 distinct classes.

- Class 1: Lack of protein production
- Class 2: Defect in protein trafficking with degradation in endoplasmic reticulum
- Class 3:Defective regulation of CFTR
- Class 4: Reduced chloride transport through the apical membrane
- Class 5: Splicing defect with reduced production of CFTR
- Class 6: Decreased CFTR stability



wt-CFTR	I	II	III	IV	V	VI
	No protein	No traffic	No Function	Less Function	Less Protein	Less Stable
	G542X (a)	R1066C	G551D	R117H	A455E	c.120del23
	394delTT (a)	A561E	S549R	R334W	3272-26A>G	rF508del
	1717-1G>A (b)	F508del	G1349D		3849 + 10 kb C >T	

- Most common mutation delta 508, it is a class 2 mutation, 70% have one gene, 50% have 2 genes.
- G551D is a class 3 mutation, that is targeted by Ivacaftor.

- 2 mutations are needed for the disease
- Classes 1-3 are associated with early onset of disease, and pancreatic insufficiency
- Classes 4-5, are associated with later onset lung disease, and pancreatic sufficiency.

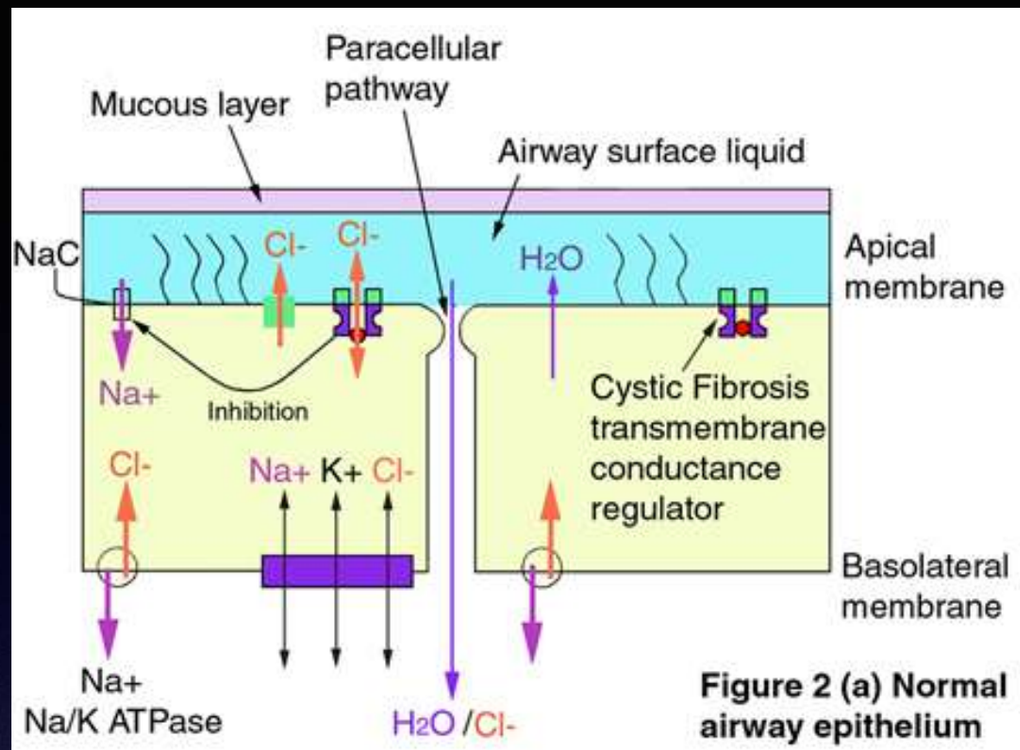


Figure 2 (a) Normal airway epithelium

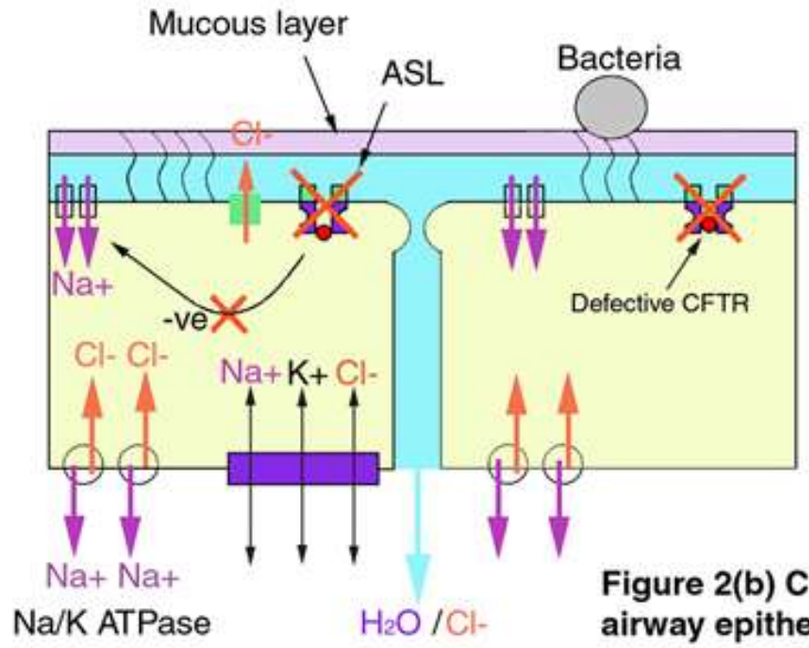
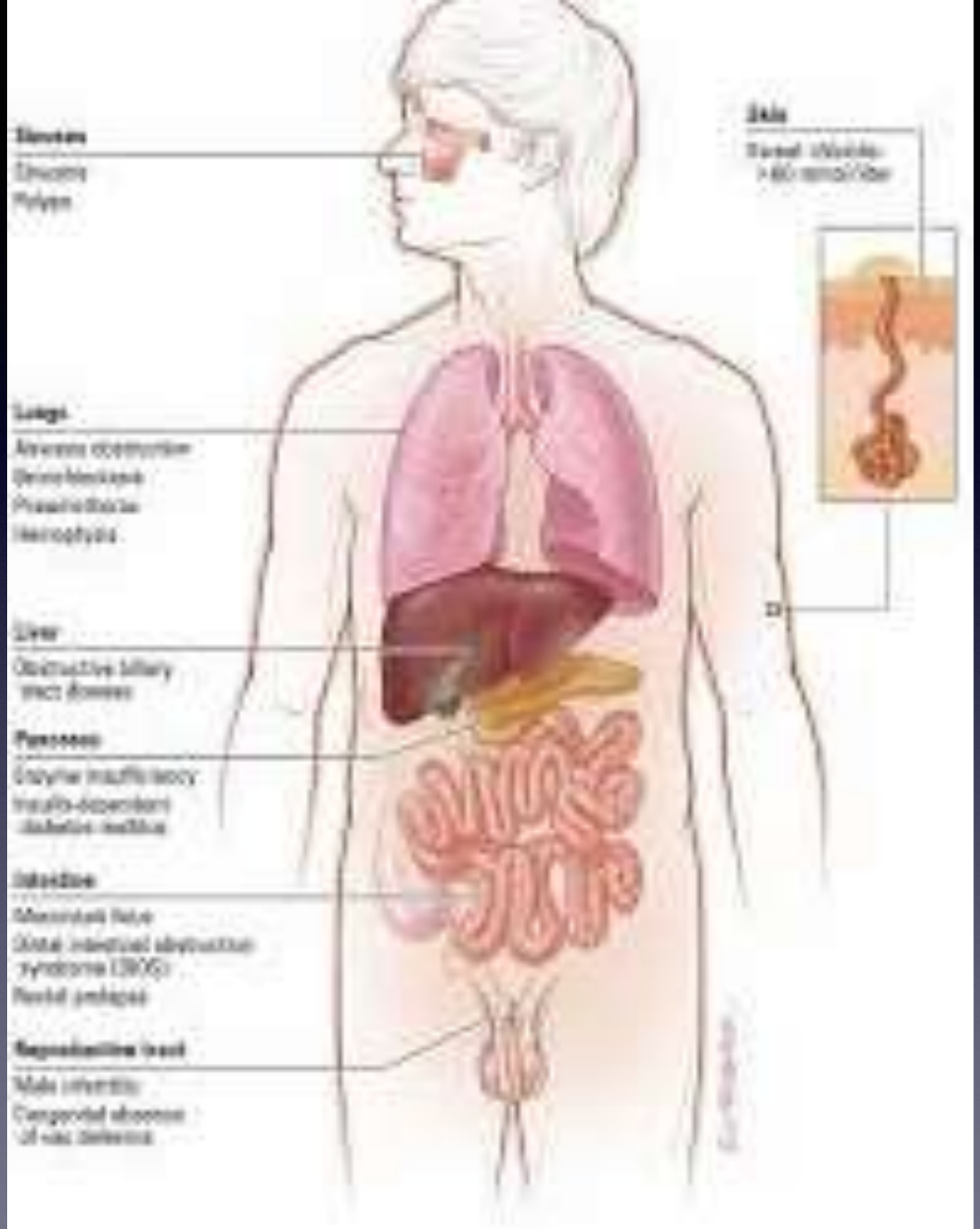


Figure 2(b) Cystic fibrosis airway epithelium


Sinuses
Sinusitis
Polyps
Lungs
Liver
Pancreas
Intestine
Reproductive tract
Skin

Pathophysiology

- Lungs: Mucus plugging==inflammation, chronic infection, small airway obstruction, bronchiectasis
- Exocrine pancreas, intestines and liver: vicid secretions==Pancreatic insufficiency, intestinal obstruction,cholestasis.
- Other systems: Pansinusitis, nasal polyps and infertility, increased salt excretion in the sweat.

Diagnosis

- Cyctic Fibrosis Foundation diagnostic criteria:
  - The presence of 1 or more phenotypic symptoms of CF like, recurrent sinopulmonary disease, nutritional of gastrointestinal symptoms, or absence of vas deference.
  - OR
    - Positive family history of CF in a sibling
    - OR
    - Positive newborn screen,
      - with evidence of chloride transport abnormalitis
        - Abnormal sweat test on 2 separate occasions
        - Abnormal nasal epithelial cell potential
        - The presence of 2 known CF causing mutations on genetic testing

The gold standard for diagnosis of CF remains the pilocarpine iontophoresis sweat test developed by Gibson and Cooke in 1959.

- Chloride concentration mmol/l
- 0-29 CF unlikely
- 30-59 Intermediate/ Borderline
- > 60 Indicative of CF

Diagnosis

- False positive sweat Cl:
  - Eczema, Ectodermal dysplasia, malnutrition, congenital adrenal hyperplasia, Adrenal insufficiency, hypothyroidism.
- False negative sweat Cl:
  - Dilution, edema, inadequate sweat.

Diagnosis

- Abnormal nasal potential difference measurement. (Absence of voltage after pilocarpine administration).
- Fecal elastase to measure exocrine pancreatic junction.
- Genetic testing:
  - usually look for 30-96 mutations.
  - Complete sequencing of the CFTR gene is available for atypical cases
  - List of clinical manifestations associated with the individual CFTR mutations are available on www.cftr2.org

Diagnosis

- Newborn screening was implemented in all states in 2010
- Newborn screening was associated with improved nutritional status, and lung function at age 6.
- It has 90% sensitivity but low specificity.
- Immunoreactive trypsinogen is measured in the newborns blood.
  - a positive test needs referral to a pulmonologist , and the performance of a sweat test.
  - False negative newborn screening can happen especially in infants with meconium ileus.

Clinical Manifestations

- Recurrent sinopulmonary infection
- Stetorrhea
- Failure to thrive.(The triad of symptoms)

Clinical Manifestions by age

- Hyperechoic bowel of fetal US, is suggestive of CF
- Delayed meconium passage, meconium plugging and meconium ileus, are present in 15-20% of infants with CF.
  - Due to high protein in meconium
  - inspissation of meconium is bowel leading to intestinal obstruction…usually needs surgical removal
- Rectal prolapse
  - Seen in patients 6m—3years
  - Due to malnutrition, elimination of large stools

Clinical Manifestions

- Less frequent manifestations in infancy
  - Salt depletion sydrome, results in hyponatremic, hypokalemic, hypochloremic metablolic alkalosis.
  - Prologed neonatal jaundice from intrahepatic biliary stasis, and extra hepatic biliary obstruction.
  - Edema and hypoprotinemia from malabsorbtion
  - Hemorrhagic disease of the newborn from Vit K deficiency.

Clinical Manifestations

- In older children, adolescents and adults.
  - Recurrent lung infection
  - Poorly controlled asthma
  - Bronchiectasis
  - Recurrent sinusitis and nasal polyps
  - Hemoptysis, pneumothorax
  - Respiratory failure

Clinical Manifestations

- Malabsorption
- DIOS…Distal Intestinal obstruction syndrome
- Rectal prolapse
- Liver disease
- Infertility absent vas deference

Management

- The aim of management is to
  - Maintain optimal lung function
    - Antibiotics
    - Lung clearance
    - Anti inflammatory medications
  - Maintain optimal nutritional status

Management

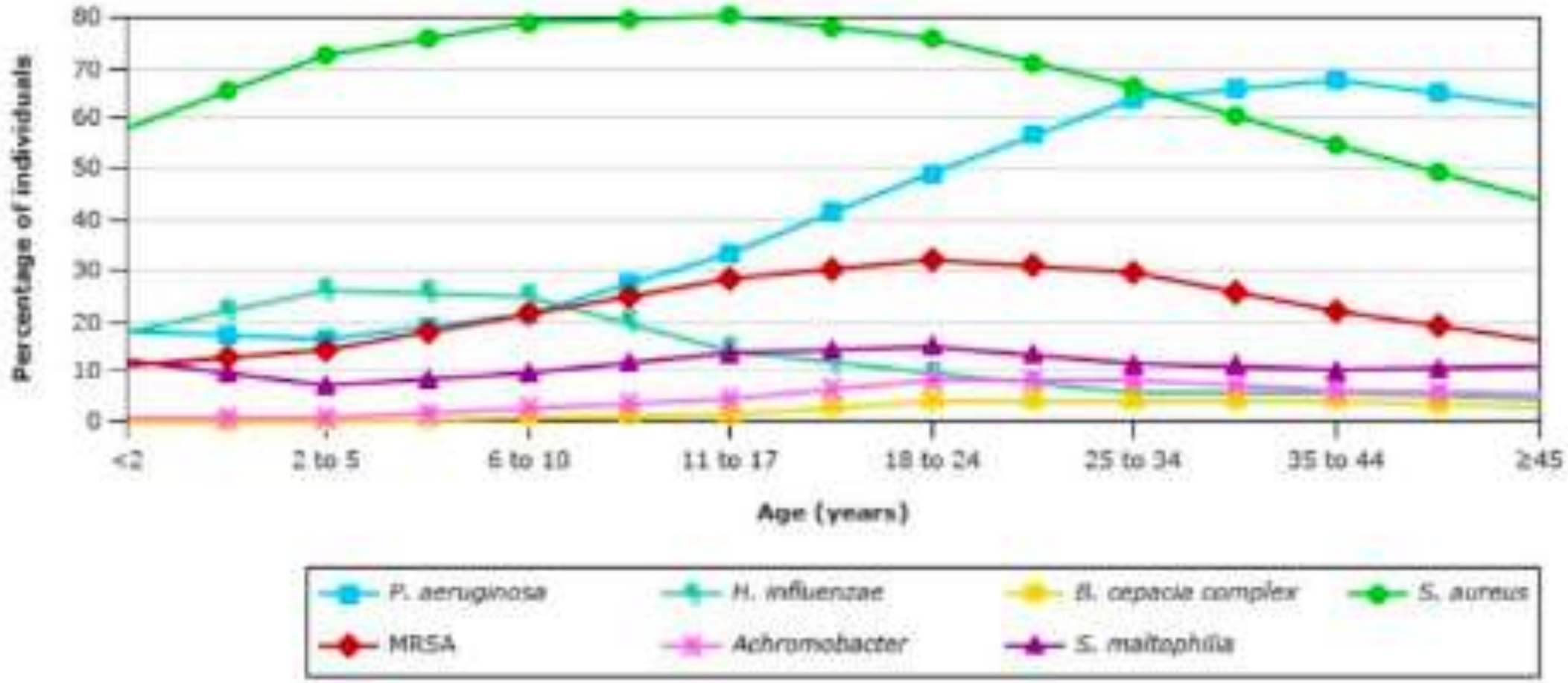
- In the US cystic fibrosis care is provided at CF foundation accredited centers with a multi disciplinary team approach.

Cystic Fibrosis Foundation’s Pulmonary Clinical Practice Guidelines Committee developed recommendations that were based on a systematic review of the literature and assessment of the available evidence based on an established grading scale. These guidelines were updated in 2013

Management

- Chronic airway infection
  - surveillance cultures; pseudomonas, staph aureus, atypical mycobacterial infections, fungal infections
  - First evidence of pseudomona colonization is usually treated with inhaled tobramycin
  - Patients with chronic pseudomonas infection, can benefit from inhaled antibiotics every other month
  - Acute exacerbations are treated with IV antibiotics usually double coverage for pseudomonas and depending on the sensitivities obtained by sputum culture.

Prevalence of bacteria identified in respiratory secretions from patients with cystic fibrosis, by age cohort



The graph shows the proportion of individuals in various age groups who had positive cultures for each of these bacterial species during 2019.

Management

- Airway clearance
  - Percussion, postural drainage, active cycle breathing, positive expiratory pressure, high frequency chest wall oscillation.
  - Usually combined with mucus alternating agents like DNase, and hypertonic saline
  - Usually done twice daily and increased frequency with acute infections.

Management

- Chronic airway infammation
  - Ibuprofen: high doses (blood levels of 50-100microgm/ml) have been associated with decrease neutrophil migration and decreased inflammation
  - Azithromycin: used 3 times/week, improves lung function and lessens exacerbations
  - Sterids: Should not be used routinly

Management

- Pancreatic enzyme replacement therapy
  - Pancreatic enzymes must be taken with every meal and snack
    - The dose is 2000-2500u/kg of lipase/meal
    - Too high of a dose causes fibrosing colonopathy
- Fat soluble vitamines replacement therapy
  - AKED vitamines

Management

- Management of the compilcations
- Pulmonary exacerbation: worsening cough, shortness of breath, fatigue or weight loss, decrease in lung functions
- Treament is with antibiotics, oral,IV or inhaled depending on culture results and sensitivities.

Management

- Hemoptysis 9% of patients:
  - usually from bronchial arteries, in advance disease
  - treatment is antibiotics for mild to moderate, 5-250ml
    - Bronchial artery embolization or lung resection for sever bleeding
- Pneumothorax in 3.4% of patients
  - If small to moderate management depends on degree of respiratory compromise
  - If large a chest tube needs to be inserted
  - if large and recurrent, chemical or surgical pleurodesis

Management

- Chronic rhinosinusitis and nasal polyps
  - Medical therapy with inhaled steroids, saline rinses
  - surgery, functional endoscopic sinus surgery.
- DIOS
  - Vicid fecal matter obstructing distal intestines, risk factors include fat malabsorption secondary to insufficient enzyme replacement, dehydration, a history of meconium ileum
  - Treatment is hydration, and osmotic laxatives, in cases of complete obstruction gastrografin enema

Management

- CF liver disease
  - Patient get biliary fibrosis that leads to biliary cirrhosis and liver cirrhosis
  - Hepatomegaly, abnormal liver functions and abnormal liver US and and an abnormal liver biopsy
  - Treatment is ursodeoxycholic acid

Management

- Cystic Fibrosis Related Diabetes Mellitus
  - CFRD has been associated with decreased body mass index, lung functions and mortality
  - Early control improves outcome and mortality
  - Microvascular complications of DM can happen
  - Incidence increase 5% per year after 10 years of age, and 10% per year after 20 years of age
  - Recommended to perform a glucose tolerace test yearly after 1 year of age, HA1C is not recommended as in underestimates the glycemic load
  - Treatment is with Insulin, oral hypoglycemic agents are not recommended
  - Caloric restriction is not recommended, intake of carbohydrates is not discouraged.

Management

- Disease-Modifying Therapies
  - Ivacaftor is an oral pharmacologic potentiator
    - Activates defective CFTR in patients with class 3 mutation G511D
    - Approved for patients with at least one G511D mutation

Management

- CFTR modulator therapies
- Ivacaftor
- Ivacaftor and lumacaftor (Orkambi)
- Ivacaftor, Tezacaftor, Elexacaftor (TriKafta)

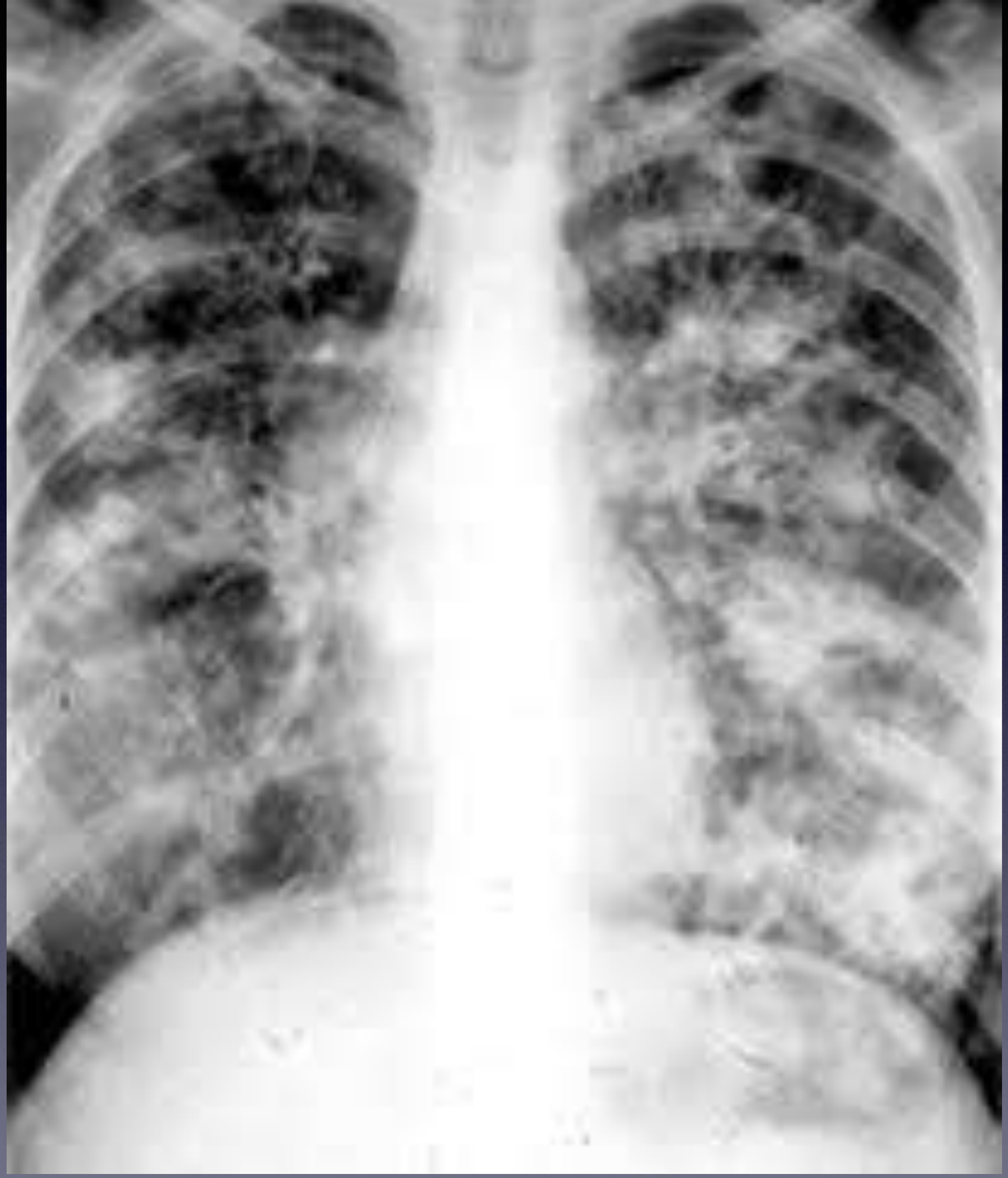
Table 1. Most common CFTR mutations causing CF in 2013

Mutation	Prevalence (%)
F508del	86.4
One copy	39.9
Two copies	46.5
G542X	4.6
G551D	4.4

Abbreviations used: CFTR, cystic fibrosis transmembrane conductance regulator; CF, cystic fibrosis.

Management

- Lung transplantation
  - 5 year survival about 70%



Non-CF Bronchiectasis

- Incidence unknown and varies between 4/100.000 (children) – 52/100.000 (adults)
- It is still an important cause of chronic suppurative lung disease in low-income countries
- Decline in prevalence since 1950’s in high-income countries

- **Definition:** dilatation of the airways, supported by radiological and clinical evidence
- **Pathophysiology:**
  - ▪ Infection
  - ▪ Inflammation ▪ Tissue damage

- Etilogy

- Idiopathic 17-40%
  - Aetiology depends on region: primary immunodeficiency/

- infections

Al Subie et al. J Paediatr Child 2012.

Table 1 Factors predisposing to bronchiectasis

- Cystic fibrosis
- Immunodeficiency
  - Primary immune defects
    - Common variable immunodeficiency
    - Hyper immunoglobulin E/Job syndrome
    - Panhypogammaglobulinaemia
  - Secondary immune defects
    - HIV/AIDS
- Infection
- Recurrent pulmonary aspiration
  - Impaired airway protection (e.g. cerebral palsy)
  - Structural proximal airway abnormalities
    - Cleft larynx
    - H-type tracheo-oesophageal fistula
- Congenital structural lung malformation
  - Congenital lobar emphysema
  - Bronchomalacia
  - Tracheobronchomegaly (Mounier–Kuhn syndrome)
  - Cartilage deficiency (Williams–Campbell syndrome)
- Primary ciliary dyskinesia
- Retained foreign body
- Miscellaneous
  - Post-chemotherapy
  - Post-irradiation
- Allergic bronchopulmonary aspergillosis
- Smoke inhalation
- Autoimmune conditions
  - Inflammatory bowel disease
  - Rheumatoid arthritis
- Yellow nail syndrome

Table 3 Summary of associations with non-CF bronchiectasis of childhood by disease category (989 patients with 994 associations)

	Total number	% of total
No association	308	34%
Infectious	174	19%
Primary immunodeficiency	158	17%
Aspiration/foreign body	91	10%
Primary ciliary dyskinesia	66	7%
Congenital malformation	34	4%
Secondary immunodeficiency	29	3%
Asthma	16	2%
Bronchiolitis obliterans	12	1%
Skeletal diseases	11	1%
Others	7	1%

Brower et al. BMC Pediatr 2014

Symptoms

- Chronic cough > 8 weeks
- Asthma not responding to treatment
- Pneumonia with incomplete resolution or recurrent pneumonia
- Hemoptysis
- Persistent lung crackles on exam

Investigations

- **Imaging**
  HRCT gold standard, sensitivity 97% ,MRI ?

- **Differential diagnosis** Sweat test, screening for PCD

- CRP, WBC, **Immunological screening**
  • IgG, IgA, IgM, specific antibodies, HIV, IgE, aspergillus IgE, aspergillus allergy skin test, response to vaccinations

- • Lymphocytes subsets, proliferation tests, NK cells
  • Phagocyte function, complement levels.

Treatment

- Treatment of the etiology if possible
- Antibiotics, inhaled and oral
- Chest physiotherapy
- Azithromycin

Thank you!