Cystic Fibrosis

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Introduction

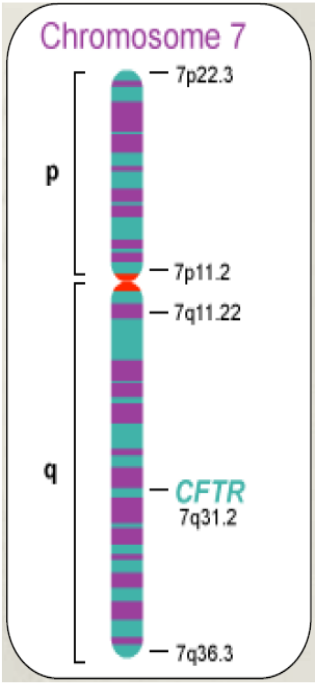
- Cystic fibrosis (CF) is a chronic, progressive **(start with normal lung then due to chronic inflammation airway obstruction occurs),** multisystem, life-shortening autosomal-recessive disorder resulting from defective epithelial ion transport with primary manifestations in the respiratory, digestive, and reproductive systems.
- The predominant morbidity in CF is progressive obstructive lung disease, but additional problems include pancreatic malabsorption, chronic sinusitis, elevated sweat electrolytes, infertility, diabetes and hepatobiliary disease.

Introduction

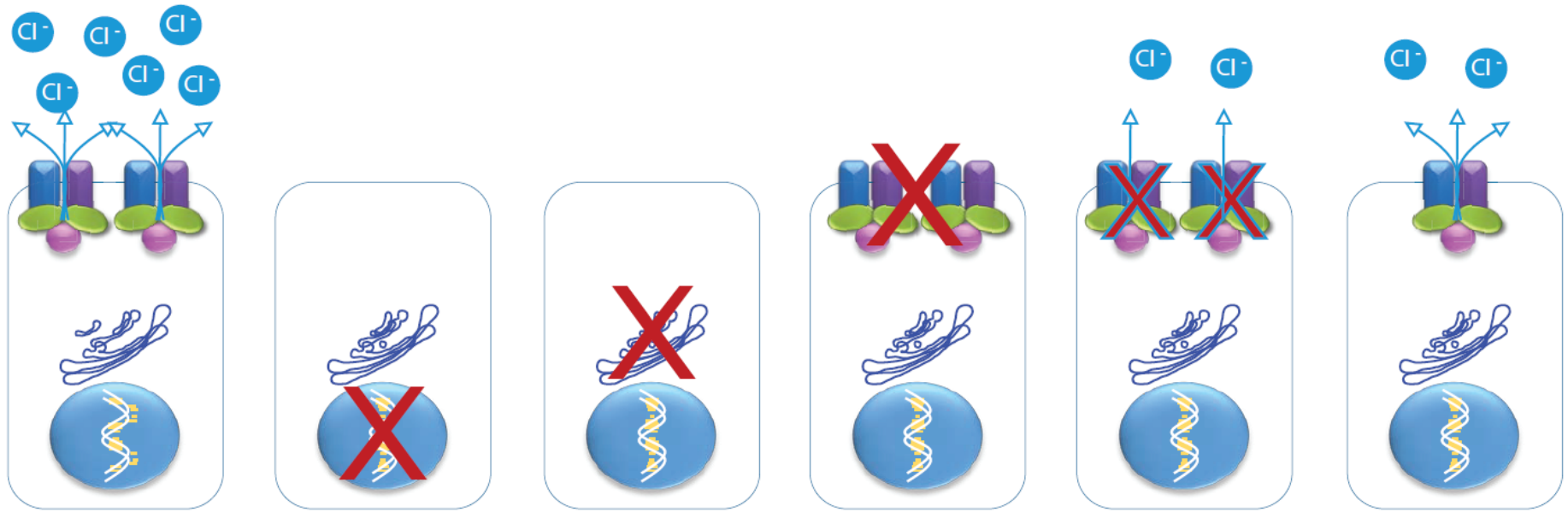
- Cystic fibrosis (CF) is the most common autosomal recessive disease in the Caucasian population, occurring in approximately 1/3500 births.
- Usual pulmonary course is chronic lung infections with specific pathogens and excessive inflammation that leads to bronchiectasis, declining lung function and eventually respiratory insufficiency
- >95% of mortality in CF patients is due to respiratory failure, which is the end-result of progressive pulmonary infections

Introduction

- In 1989, it was discovered that CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (on long arm of chromosome 7) that encodes the CFTR protein **(controls the traffic electrolytes across cell membrane : maintain the usual flow of CL ions and water into and out the cells)**
- Over 2000 mutations have been described
- The most common mutation worldwide is caused by deletion of phenylalanine at position 508 (ΔF508del), 70-80% of CF patients have this mutation globally. Yet, its frequency varies between ethnic groups, e.g. 82% in Denmark versus 32% in Turkey, 4-30% in Jordan in various studies



One Way of Classifying CFTR Mutations



	Normal	Class I	Class II	Class III	Class IV	Class V
DESCRIPTION	CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.	No functional CFTR created.	CFTR protein is created, but misfolded, keeping it from reaching the cell surface.	CFTR protein is created and reaches cell surface, but the gate does not function properly.	The opening in the CFTR protein ion channel is faulty.	CFTR is created in insufficient quantities.
EXAMPLES		G542X W1282X R553X	F508del N1303K I507del	G551D S549N V520F R117H	R117H D1152H R347P	3849+10kbC->T 2789+5G->A A455E

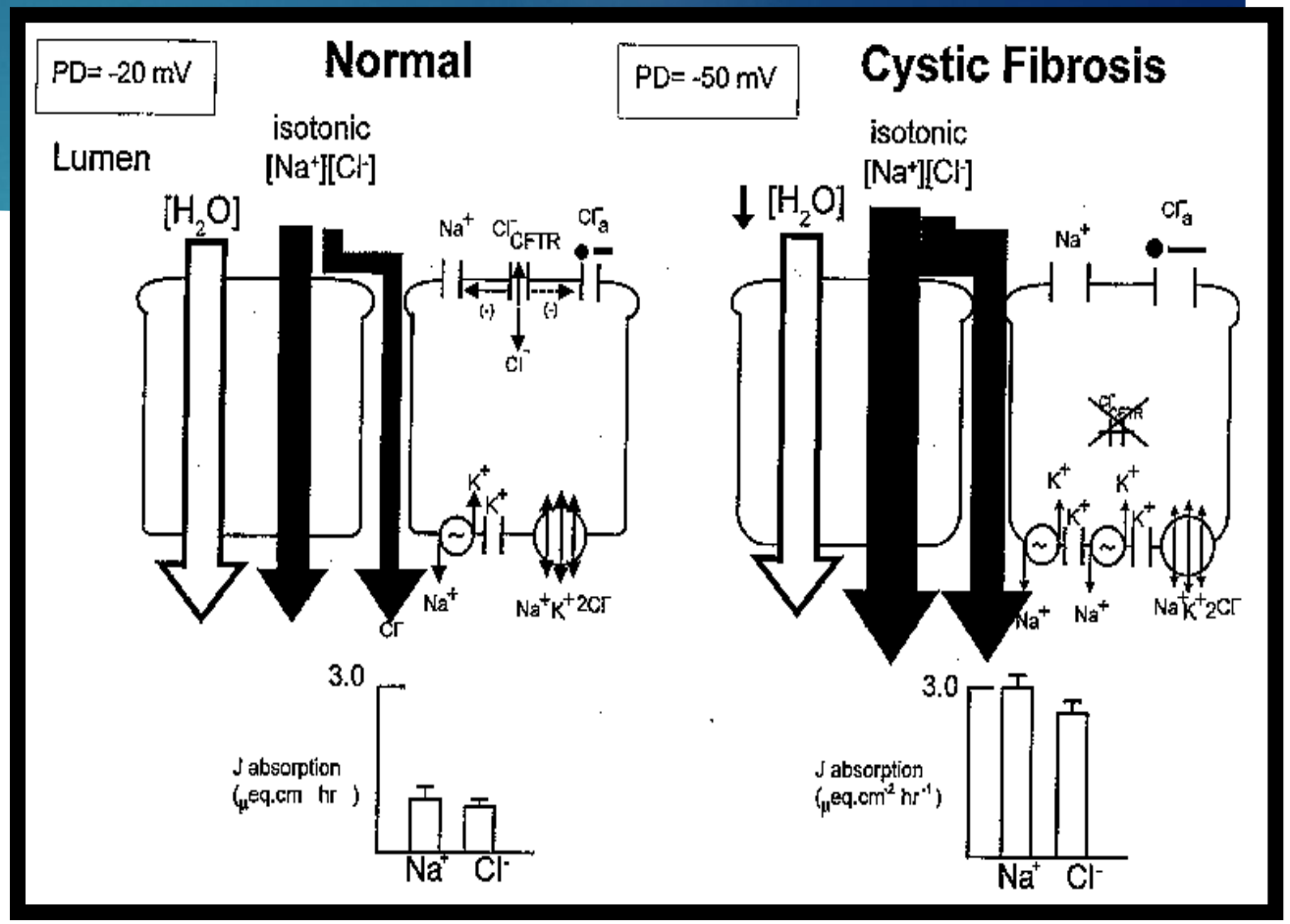
Pathophysiology

- Cystic fibrosis leads to pathological changes in organs that express *CFTR*, including secretory cells, lungs, pancreas, sinuses, liver, and reproductive tract **(affects all ducts / all tubes / all secretions)**

Pathophysiology

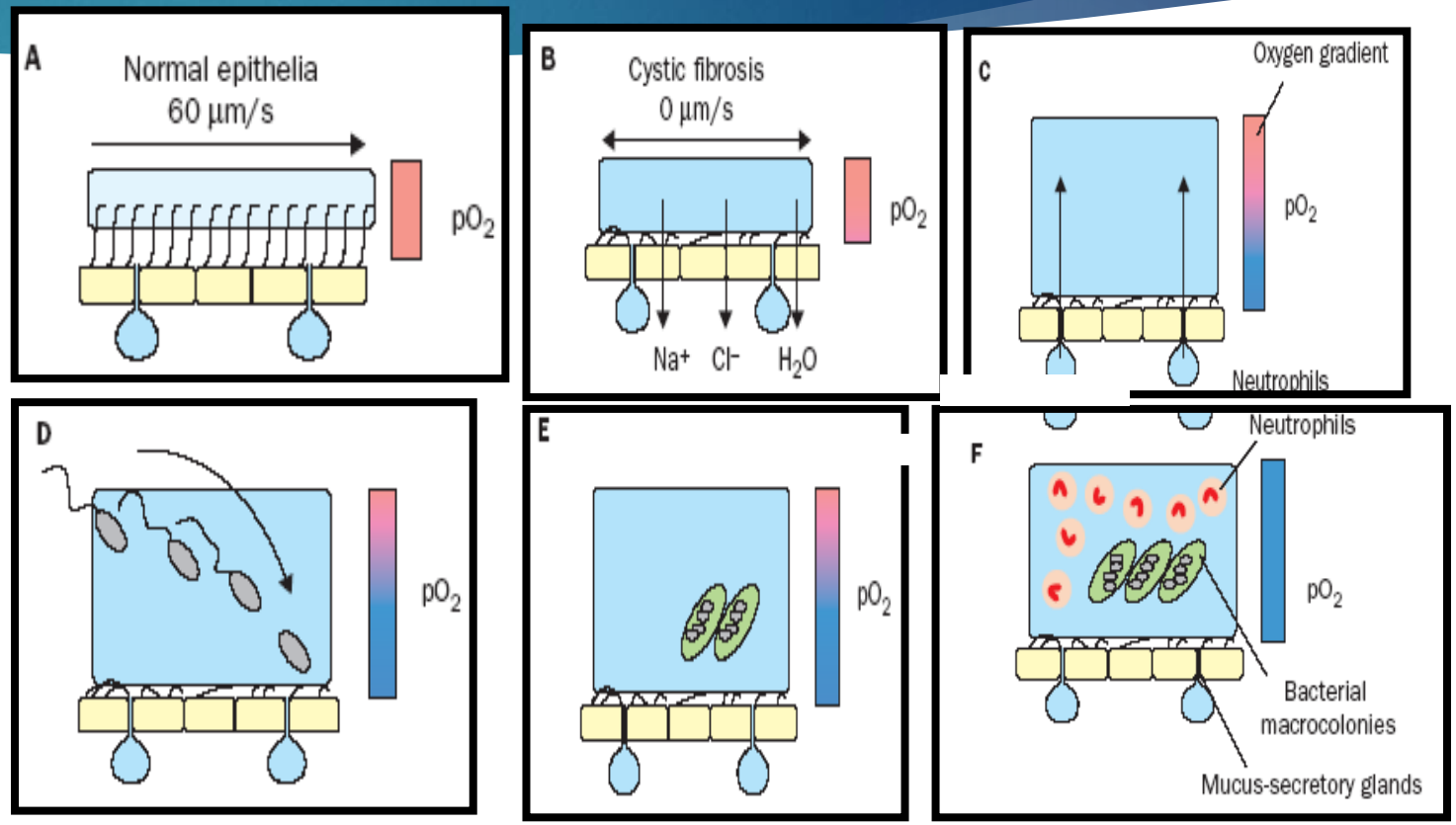
CFTR channel maintains fluid layer at the airway lining ; by moves CL ions outside the cell then attracts water .

On CF : NA ions keeps intracellular and CL ions follows it paracellularly : NACL attracts water inside lumen keeps the airway lining dehydrated : which makes the mucus sticky .



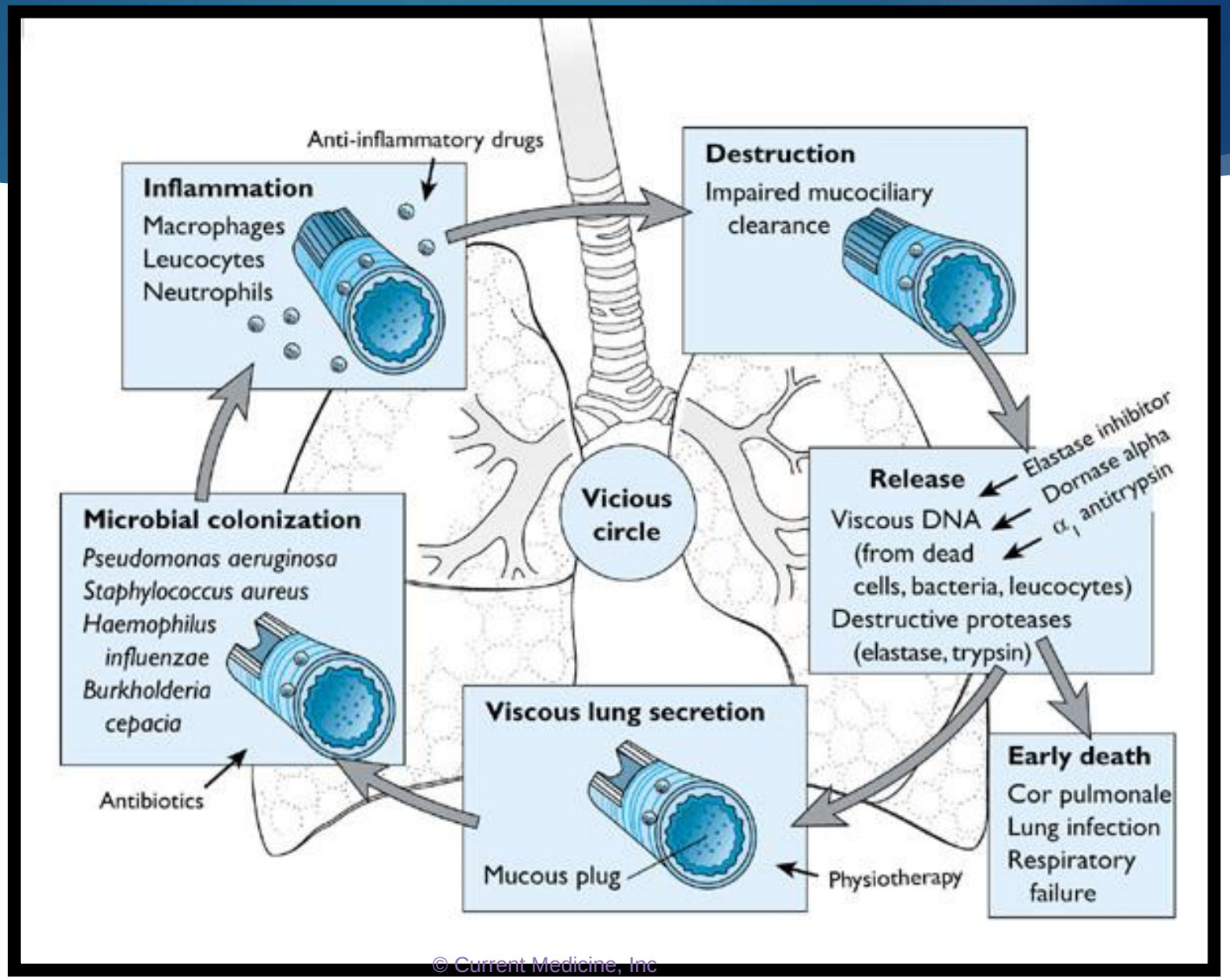
Pathophysiology / airways

Cilia needs fluid to move freely and to clear the mucus which prevents the infection and obstruction.



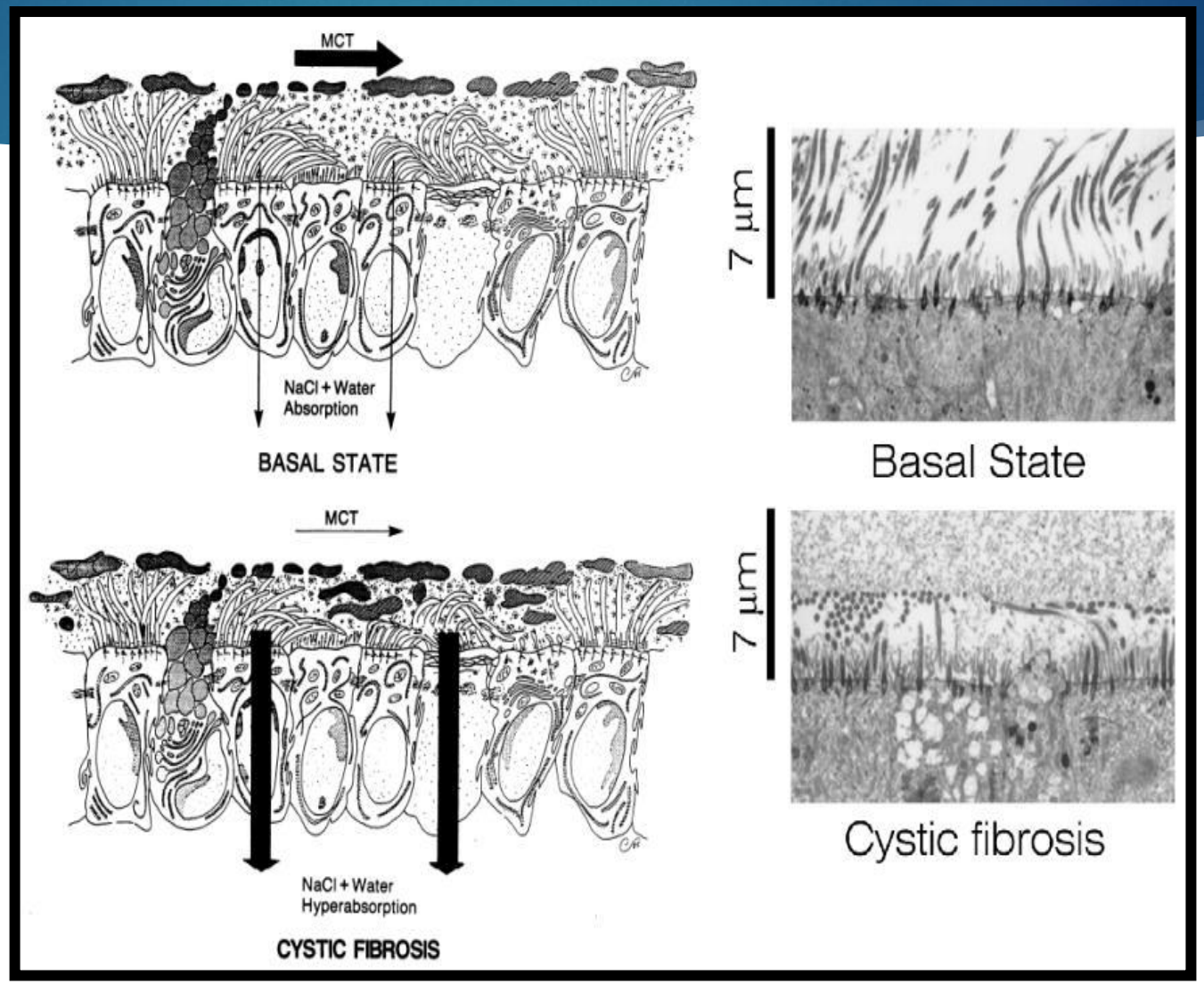
The "Vicious Circle" of Lung Disease in CF

Hypoxia is a perfect media for pseudomonas to colonize



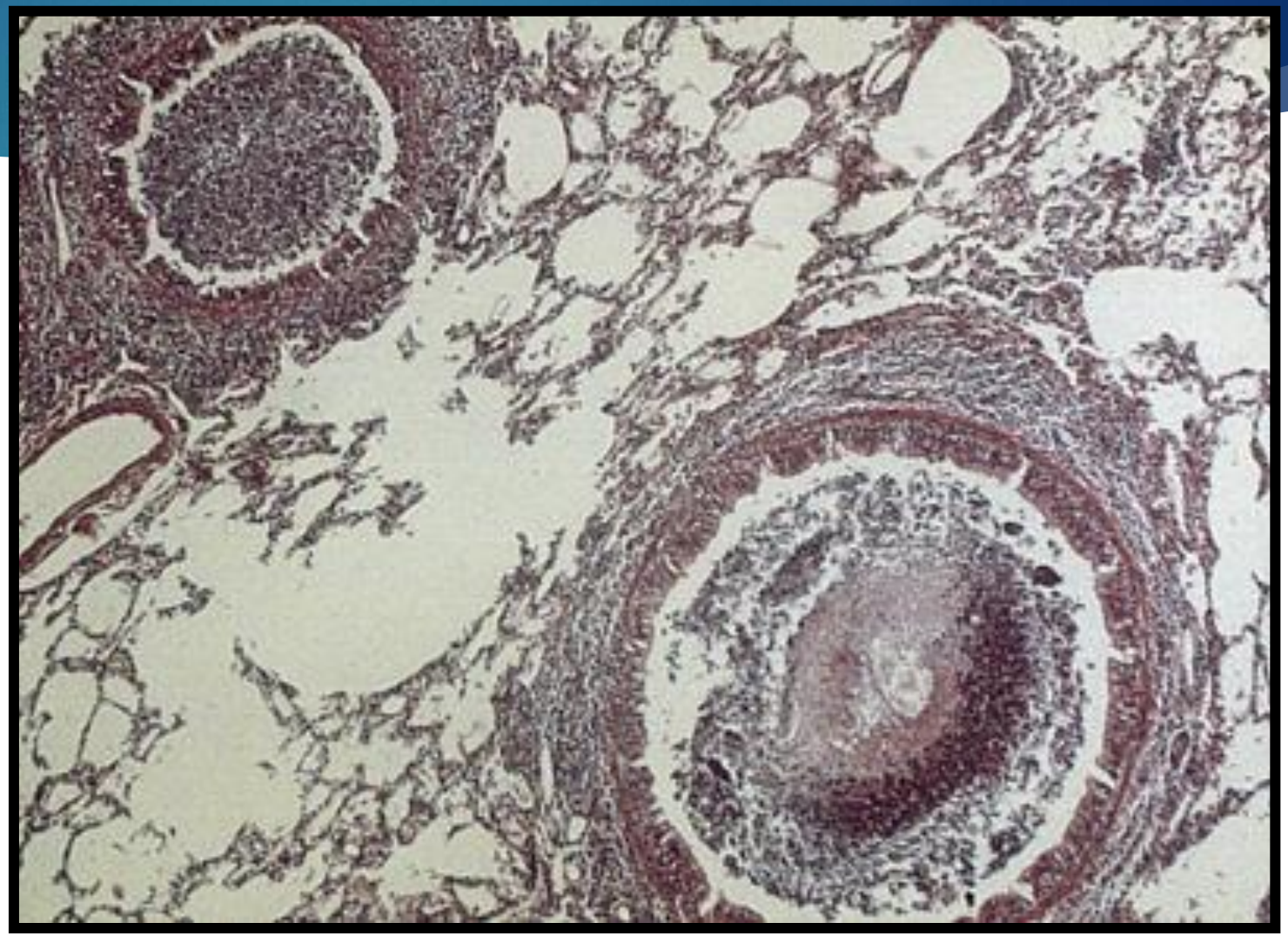
Pathophysiology / airways

Electro microscopic picture shows the fluid layer becomes 3 micrometer in CF



Airway Obstruction

Autopsy for patient dies from CF shows a lot of inflammatory debris and mucus and bacteria.



Pathophysiology

- **Pancreatic insufficiency and diabetes:**
- Exocrine pancreatic insufficiency is present in about 90% of patients with cystic fibrosis. it results from a reduced volume of pancreatic secretion with low concentrations of HCO_3 Leading to digestive proenzymes being retained in pancreatic ducts and prematurely activated, ultimately leading to tissue destruction and fibrosis.

Pathophysiology

- The effect of the resulting malabsorption is further augmented by raised energy demands caused by the hypermetabolic state associated with endobronchial infection.
- Also, since lung infections can lead to reduced appetite **(don’t eat well)** and vomiting, malnutrition **(more malnutrion more infection)**is further enhanced.
- These factors might exacerbate lung infection, leading to a vicious cycle of malnutrition and infection.

Pathophysiology

- Langerhans cells are initially spared from pancreatic fibrosis, and diabetes mellitus is rare in the first decade of the patient's life; prevalence of this disease rises constantly with age.
- **Endocrine function of pancreas affected lately after 10-15 years.**
- Diabetes in patients with cystic fibrosis shares features of the type 1 and 2 disorder, thus called CFRD (CF-related diabetes)

Pathophysiology

- **Biliary disorders**
- CFTR is expressed in cells of the biliary tract, and at least a third of patients have abnormal results of liver function tests. Fatty infiltration is reported in up to 70% of older patients; in fewer than 10% of these, this infiltration progresses to biliary cirrhosis.
- A small, poorly functioning gallbladder is present in up to 30% of patients and gallstones in up to 10%.
- Infants can present with cholestasis from bile that is sticky.
- **CF and hypothyroidism maybe the cause of Prolonged neonatal jaundice.**

Pathophysiology

- **Fertility**
- 98% of men with cystic fibrosis are infertile, with aspermia secondary to atretic or absent vasa deferentia, sexual potency and spermatogenesis are normal **(aspermia maybe the only manifestation).**
- **The testis Produce sperms but the vas deferens cant deliver it.**
- Female reproductive function is normal, although cervical mucus can be dehydrated, which might impair fertility **(maybe the vaginal secretion is sticky and fallopian tubes are obstructs) but still she can become pregnant.**

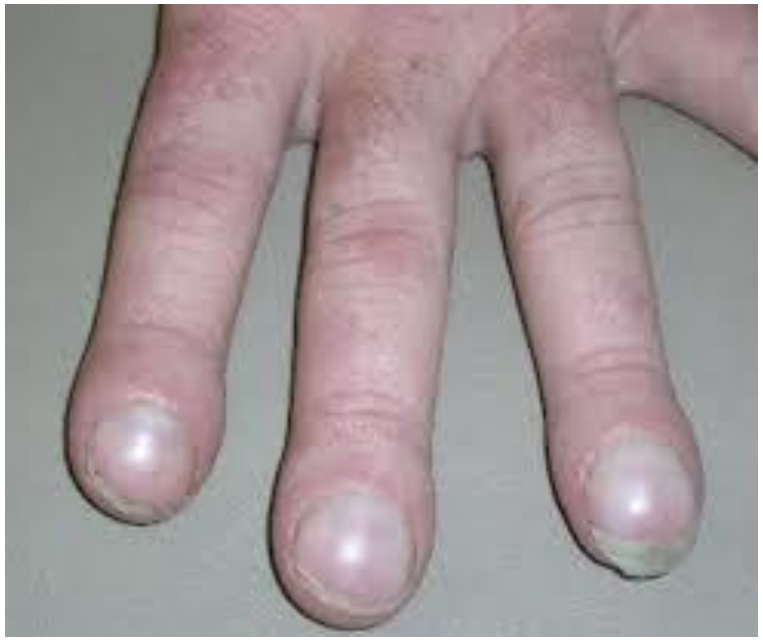
Respiratory Manifestations

- Chronic productive cough **before age of 1y** & increasing obstruction **(wheezy chest later crackles , sob , hypoxia , sever limitation of activity , loss of lung function)**
- with progressive decline in lung function till respiratory failure is the usual course
- Usually no or few respiratory symptoms in neonatal period **(obstruction takes time to happen)**
- Wheezing is common early in the disease
- Hyperinflation **barrel chest**, progressive bronchiectasis, clubbing & recurrent "exacerbations" **(with viral infection mainly comes with bad cough , sob ,increased sputum , decreased saturation)** then occur **with age exacerbations will be longer , worse and shorter periods between them ; ends by one longer exacerbation.**

Respiratory Manifestations

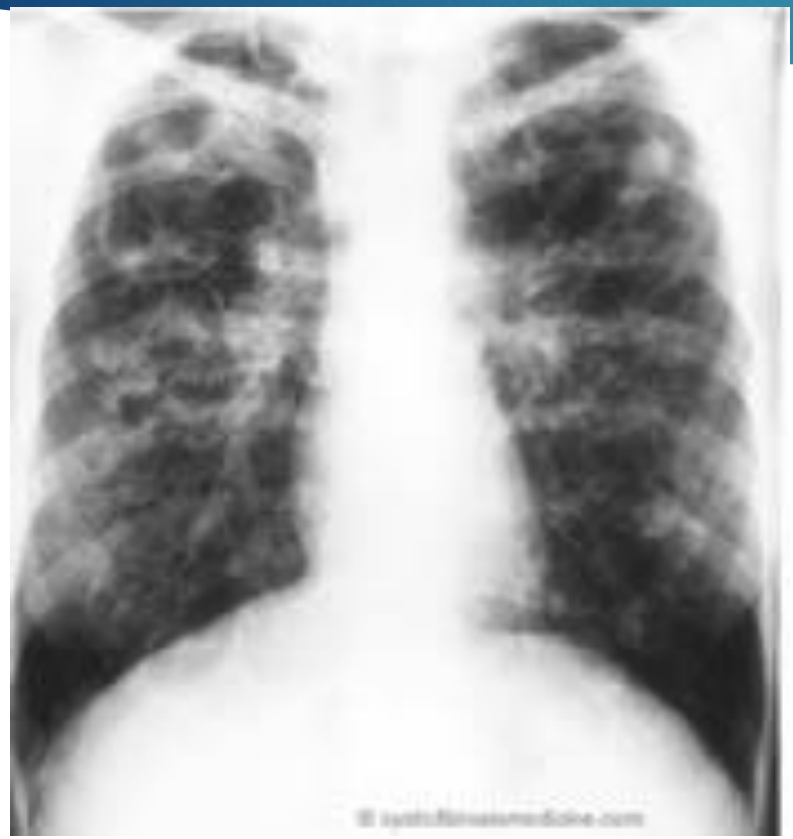
- ~ 50% have airway hyperreactivity **(asthma medication can be helpful)**
- Hemoptysis **(due to airway erosion by infection and vitamin k deficiency Bec of malabsorption),** pneumothorax **is common due to hyperinflation but tension one is rare Bec the lung is stiff** & ABPA **(allergic bronchopulmonary aspergillosis)** are common complications
- FEV1 is a good marker of health status & prognosis , usually ↓ 2-3% yearly (**the treatment slow the lung function decline but doesn't stop it).**
- > 90% of cases of CF die of pulmonary disease

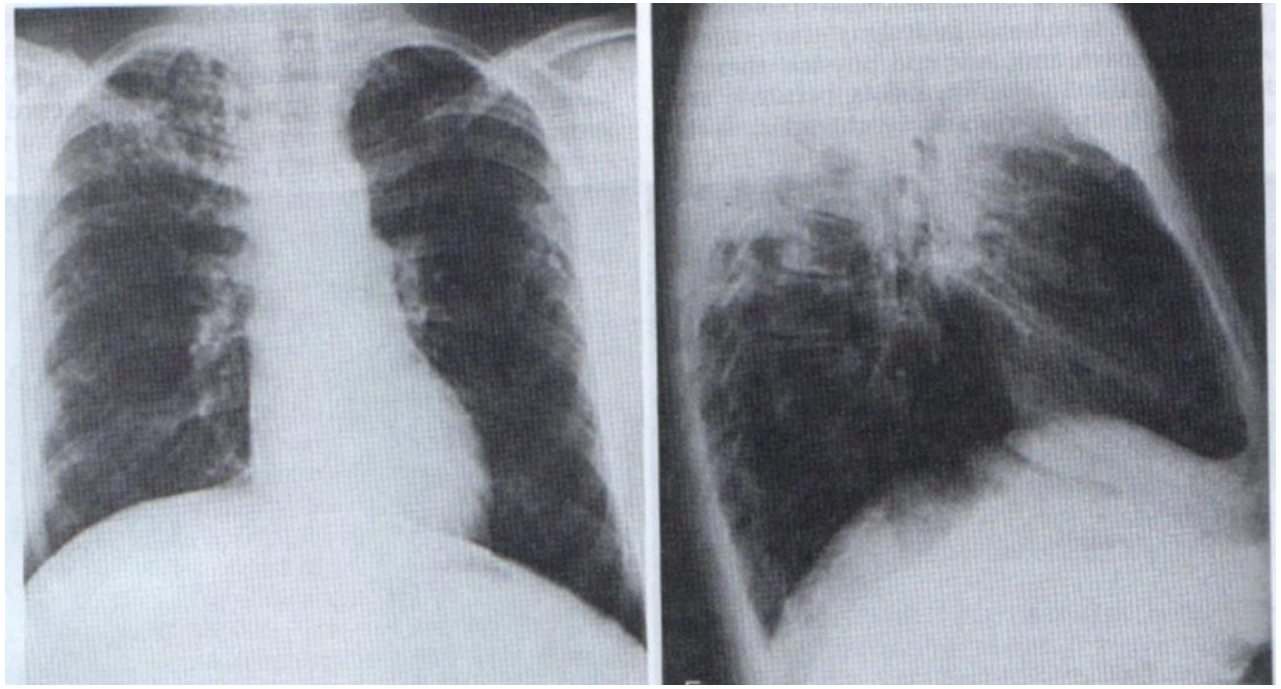
Finger clubbing



X -ray

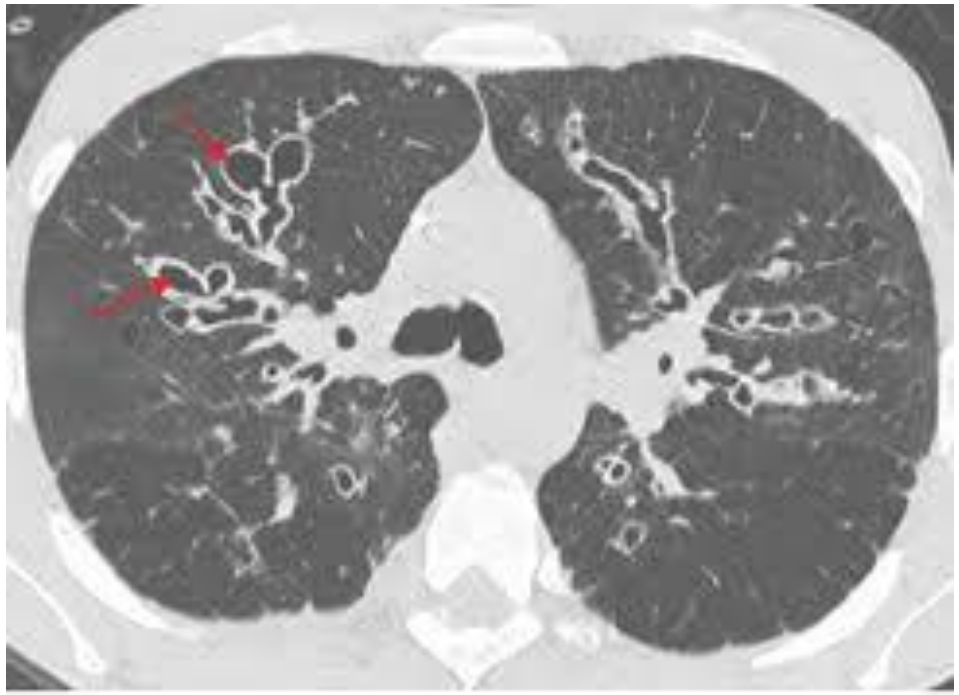
Bilateral infiltration
Usually start at upper lobes
Hyperinflation

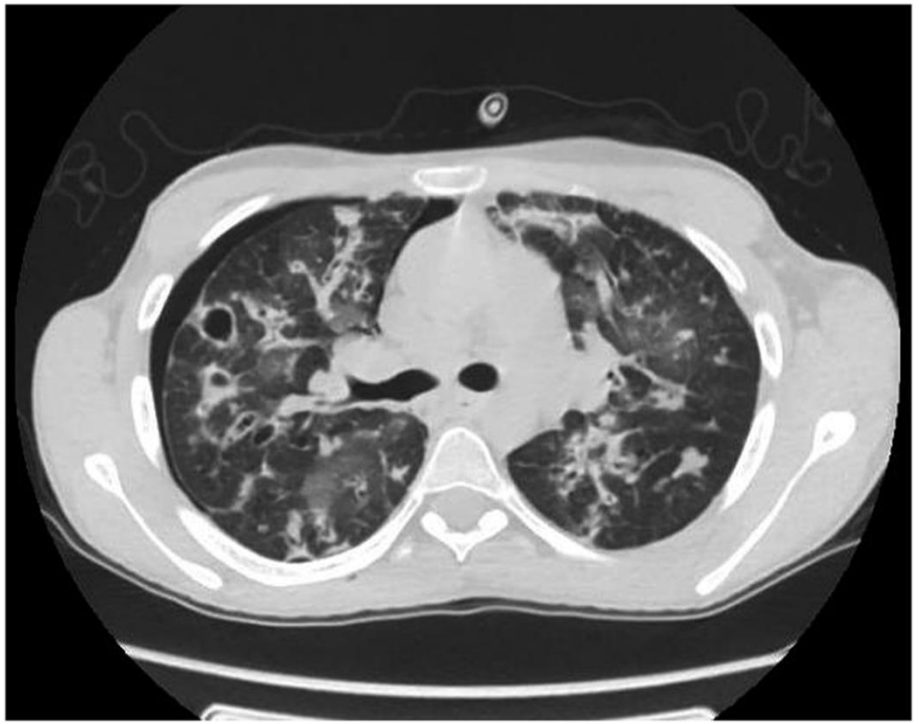


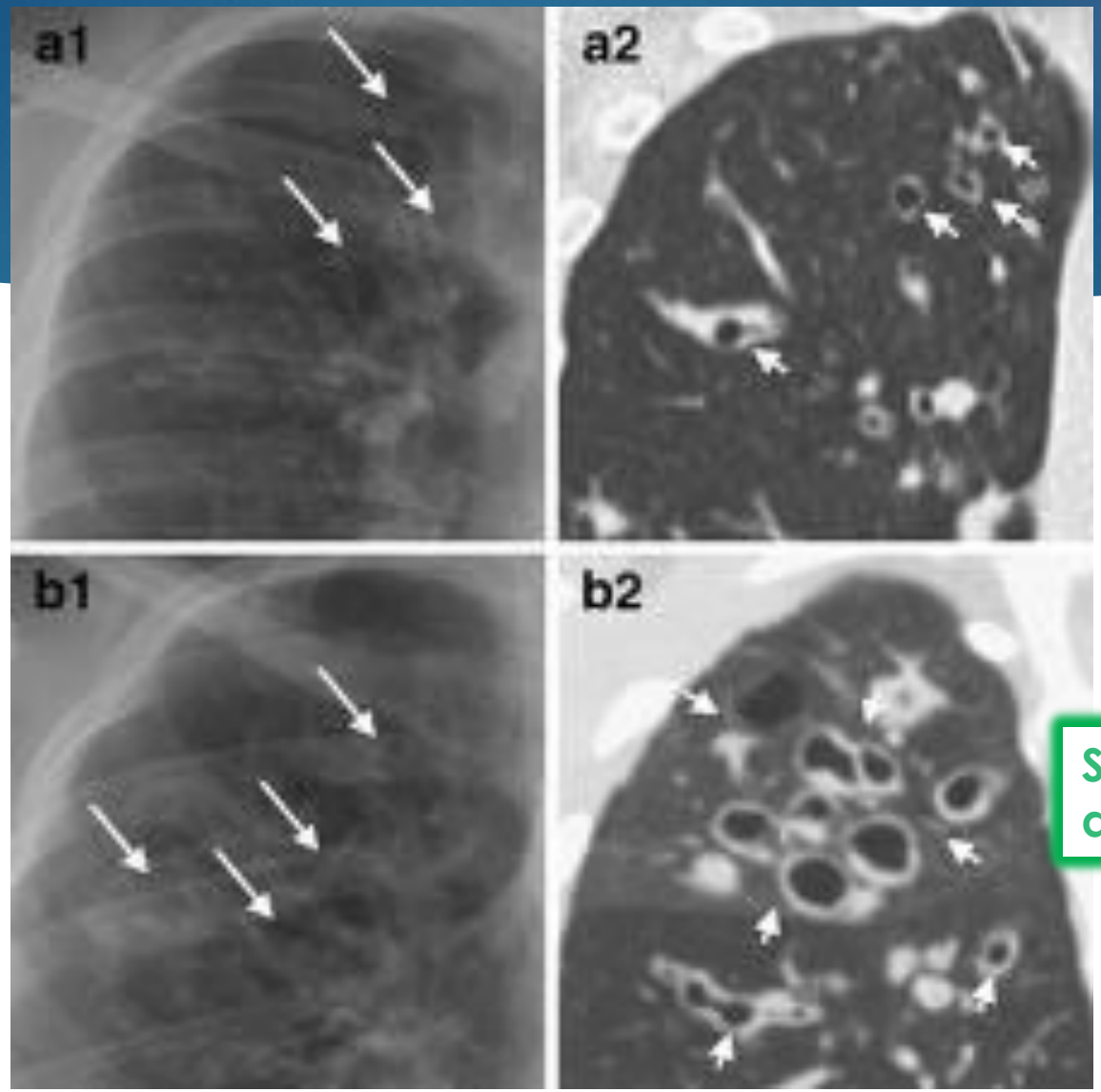


CT chest

Show bronchiectasis







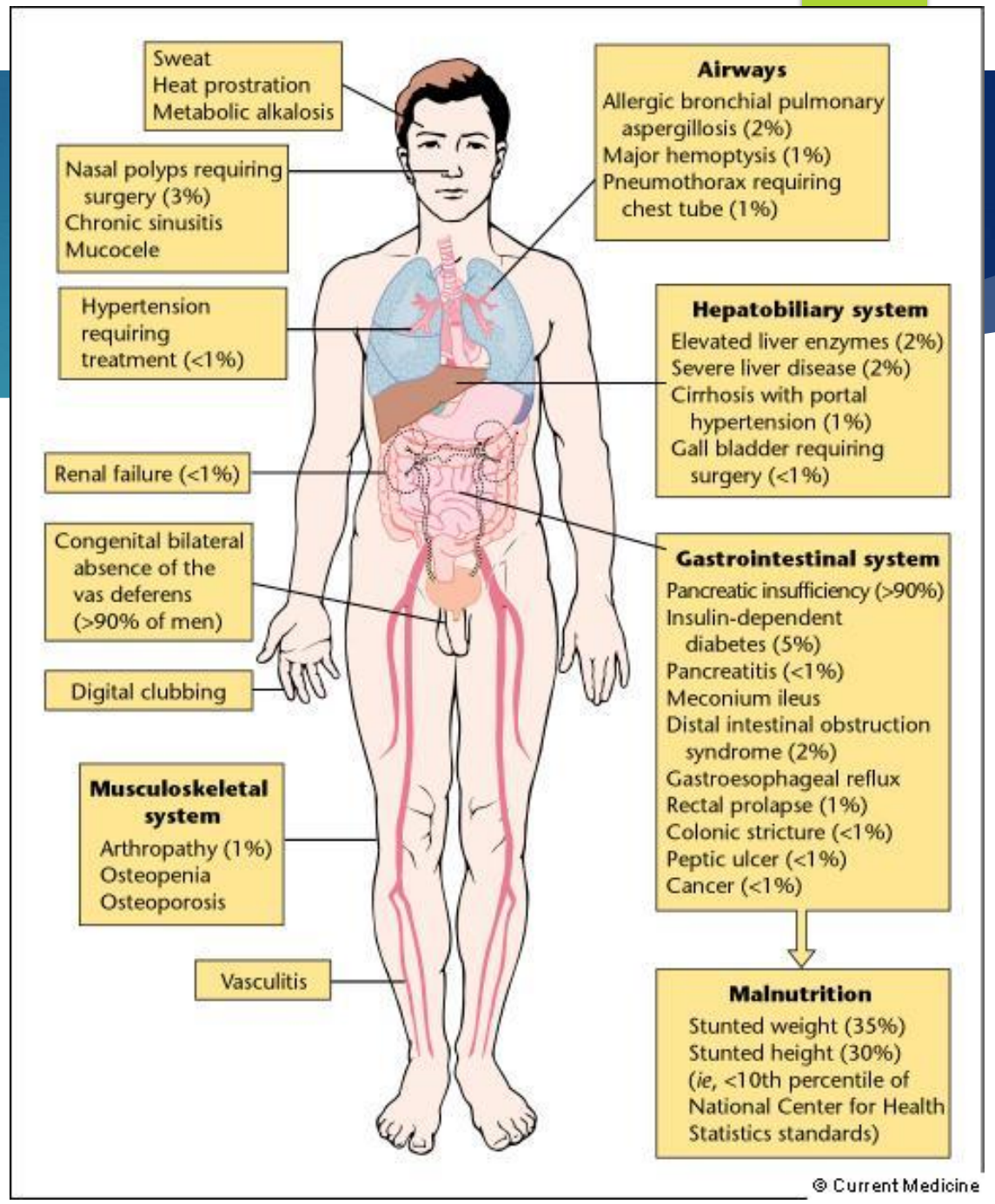
Severe case ;
advanced cysts

GI Manifestations

- 85 – 90% have pancreatic insufficiency
- 10 – 20% have meconium ileus **(not passing stool within 48 h) its pathognomic ; he is CF until proven otherwise**
- Malabsorption can manifest with persistent diarrhea, steatorrhea, FTT **not significant early in the disease Bec increasing in appetite due to malabsorption** , hypoprotinemia, vitamin deficiencies
- DIOS (Distal Intestinal Obstruction Syndrome) in older patients **thick secretion in the gut , constipation , abdominal distension**
- GER in ~ 15%

Clinical Manifestations

Recurrent nasal polyps which isn't common in children



Clinical signs of cystic fibrosis

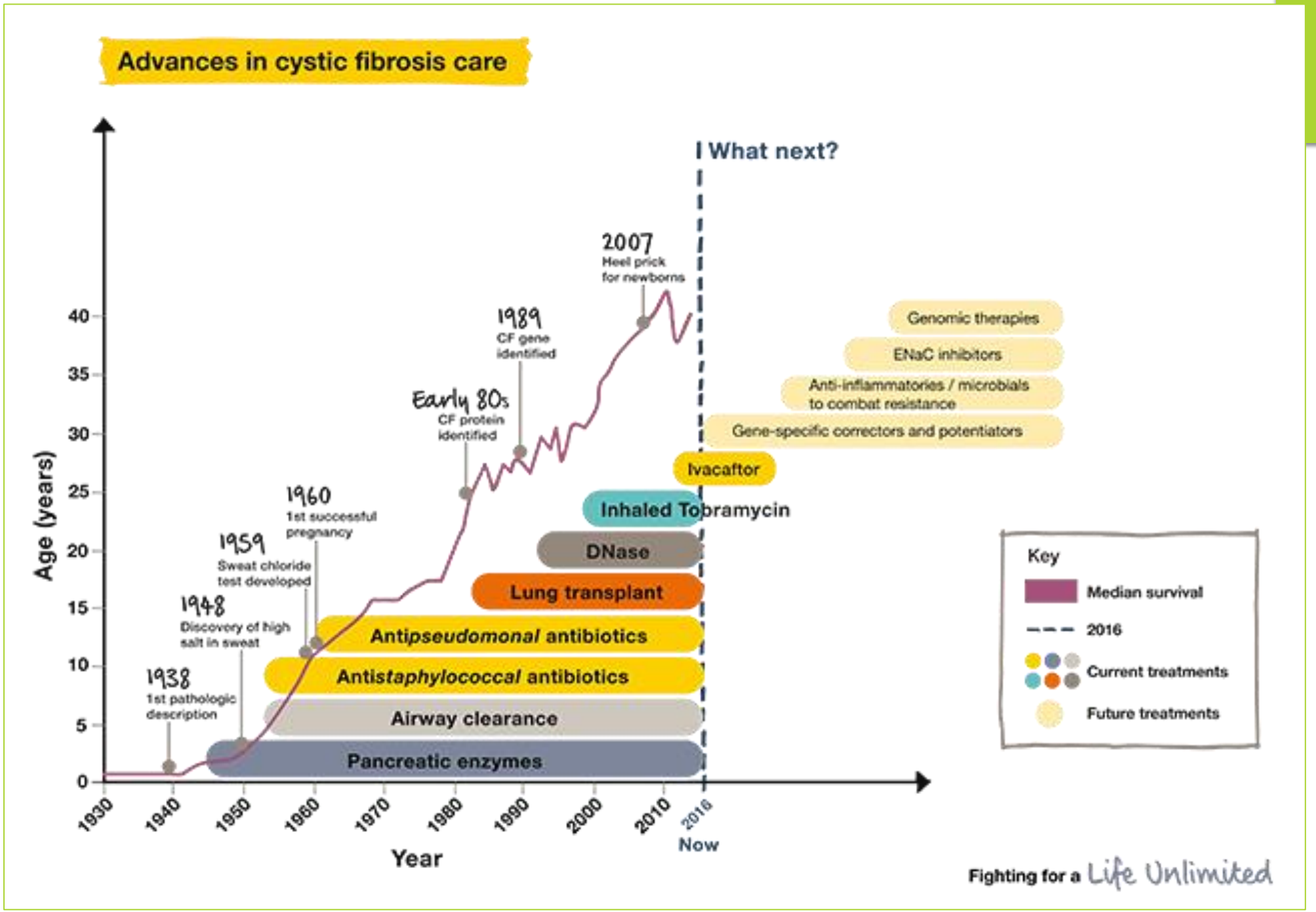
Chronic airway disease
Chronic productive cough
Airway colonisation with pathogens (*S aureus*, mucoid *P aeruginosa*)
Persistent abnormalities on chest radiograph
Airway obstruction
Clubbing
Pansinusitis
Nasal polyps
Gastrointestinal disease
Meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
Pancreatic insufficiency, pancreatitis
Biliary cirrhosis
Failure to thrive, oedema with hypoproteinaemia, deficiency of fat-soluble vitamins
Pseudo-Bartter's syndrome (salt wasting with metabolic alkalosis)
Infertility due to obstructive azoospermia

Kidney can affected later by the aminoglyc oside treatment

when Sweating a lot : loss of NA and Cl ; dehydration : kidney try to compensate by HCO3 absorption ;which leads to metabolic alkalosis (like barters syndrome but the kidney is normal

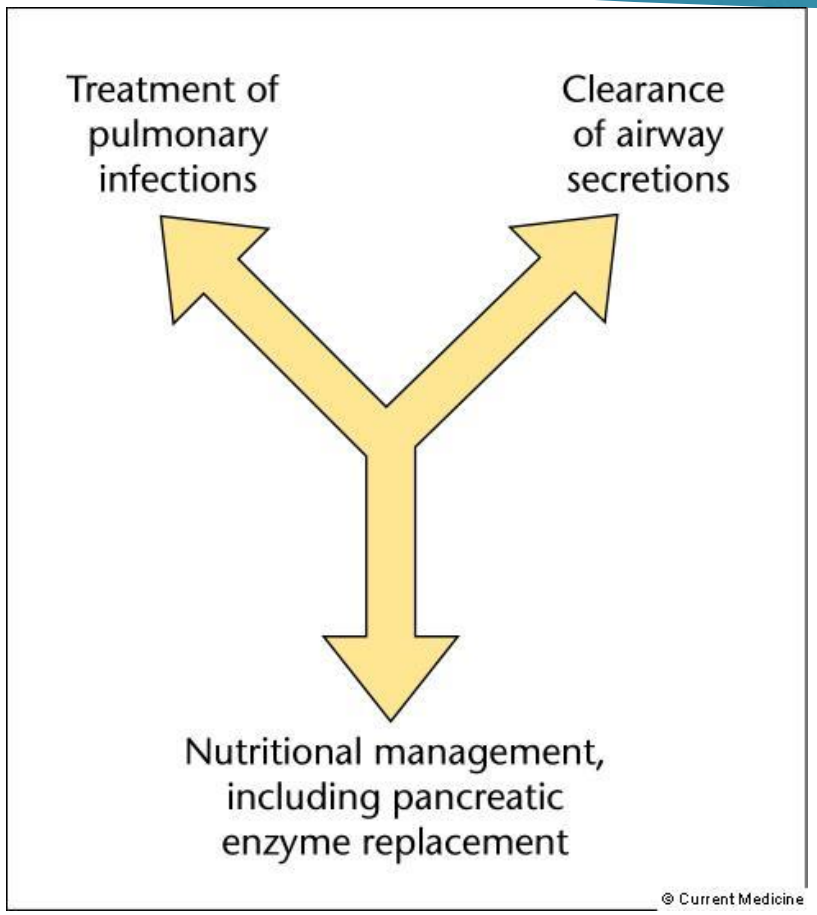
Diagnosis

- Clinical characteristics + 2 sweat chloride results ≥ 60 mEq/L, ***in a reliable lab,*** is diagnostic of CF
- Sweat test not reliable 1st 2 days of life or in patients with edema
- False +ve in adrenal insufficiency, G6PD, nephrogenic DI, ectodermal dysplasia, MPS, malnutrition, hypothyroidism, hypoparathyroidism & other rare disorders
- Result of ***30 – 59*** is borderline (changed in 2015)
- Gene testing: presence of 2 CF mutations is diagnostic , **1 mutation is carrier**
- Newborn screening: IRT (immunoreactive trypsinogen), mutations
- Stool elastase to assess pancreatic insufficiency **pancreas produce stool elastase which excrete unchanged in stool that's means if its low in stool there is pancreatic insufficiency**


Advances in cystic fibrosis care
What next?
2007
Heel prick for newborns
1989
CF gene identified
Early 80s
CF protein identified
1960
1st successful pregnancy
1959
Sweat chloride test developed
1948
Discovery of high salt in sweat
1938
1st pathologic description
Genomic therapies
ENaC inhibitors
Anti-inflammatories / microbials to combat resistance
Gene-specific correctors and potentiators
Ivacaftor
Inhaled Tobramycin
DNase
Lung transplant
Antipseudomonal antibiotics
Antistaphylococcal antibiotics
Airway clearance
Pancreatic enzymes
Age (years)
0
5
10
15
20
25
30
35
40
1930
1940
1950
1960
1970
1980
1990
2000
2010
2016
Now
Year
Key
Median survival
2016
Current treatments
Future treatments
Fighting for a Life Unlimited

Treatment strategies

"Classical" therapy



"New" therapies

- Directed at repairing the CFTR function, potentially finding a cure for CF
- CFTR modulators
- Gene therapy

Treatment

Infection:

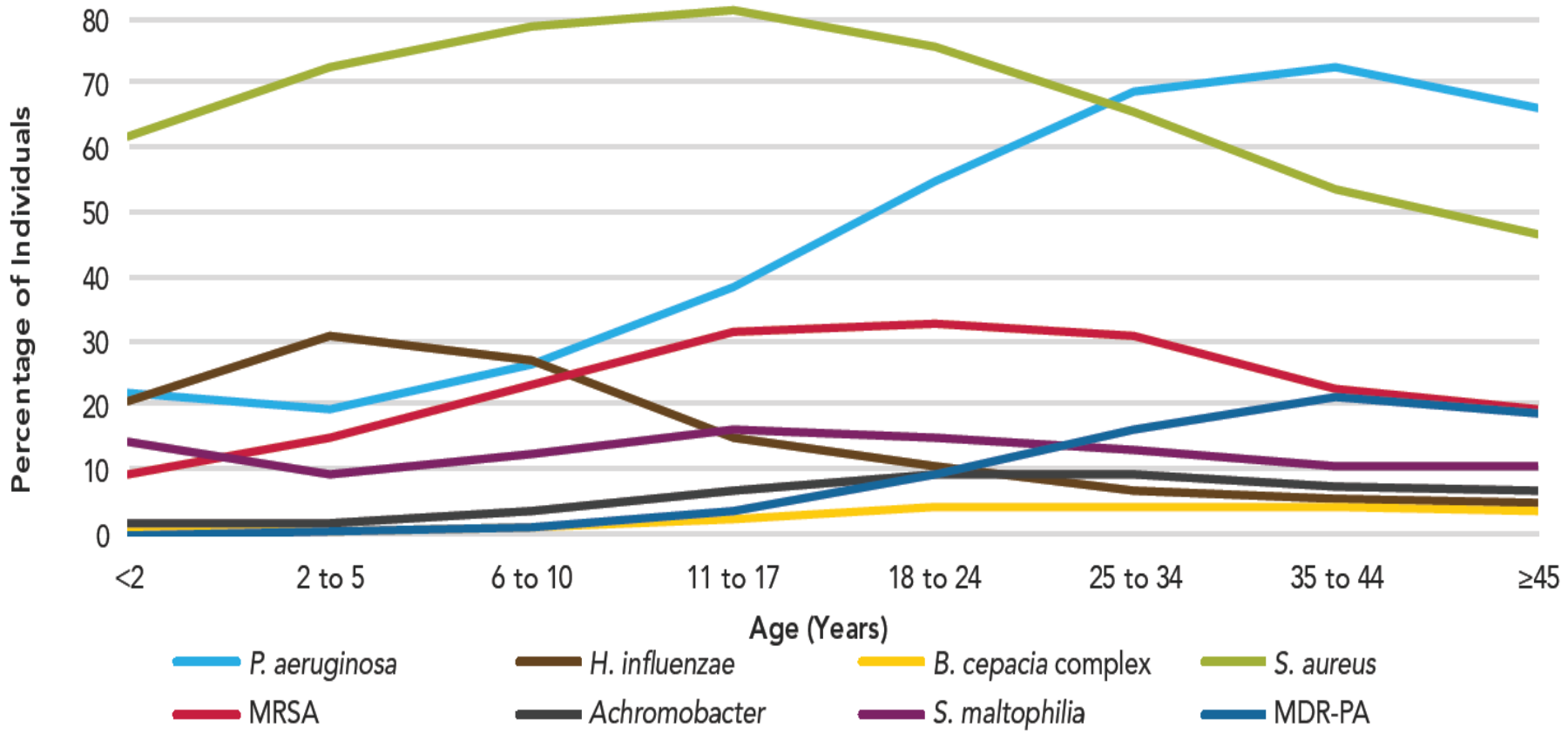
- Aggressive treatment to control resp infections is essential, by oral, IV or inhaled antibiotics. Either routinely or only for exacerbations
- Accurate C/S data is essential **proper sputum culture and sensitivity for bacteria**
- On the long run, side effects & resistance are major concerns
- Eradication of **early** Pseudomonas colonization is a beneficial approach, but not S. aureus

Eradication of Pseudomonas

- Acquisition of *P. aeruginosa* in CF airways is associated with clinical worsening, delaying it leads to better lung function and less exacerbations
- A widely accepted approach is to do surveillance cultures **sputum culture every 6m – 1y** and to treat Pseudomonas as soon as it appears, the most common method is by inhaled Tobramycin, often given as “4 weeks on, 4 weeks off”

*Staph mc organism , dominant until adolescence.
*Pseudomonas becomes dominant at 25y.
*S melophilia very bad , very resistant to drugs.
*B cepacian rare 2-3% the worst one die within 2y.

Prevalence of Respiratory Microorganisms by Age Cohort, 2016



Treatment

- Introduction of inhaled Tobramycin solution 300mg (TOBI) showed good resuls in both Pseudomonas eradication or ↓ colonization density as well as improved lung function
- Inhaled Colistin **against pseudomonas** (??and gentamicin) may have similar effect
- Inhaled Aztreonam is also very effective **but expensive.**
- Azithromycin 3 times/week showed improvement in Pseudomonas infection and in lung function but less than TOBI **long time treatment**
- Inhaled Ciprofloxacin, Levofloxacin & Amikacin has been studied as well

Eradication of Staph. aureus

- For individuals with CF, the CF Foundation recommends **<u>against</u> the prophylactic use** of oral antistaphylococcal antibiotics

Treatment

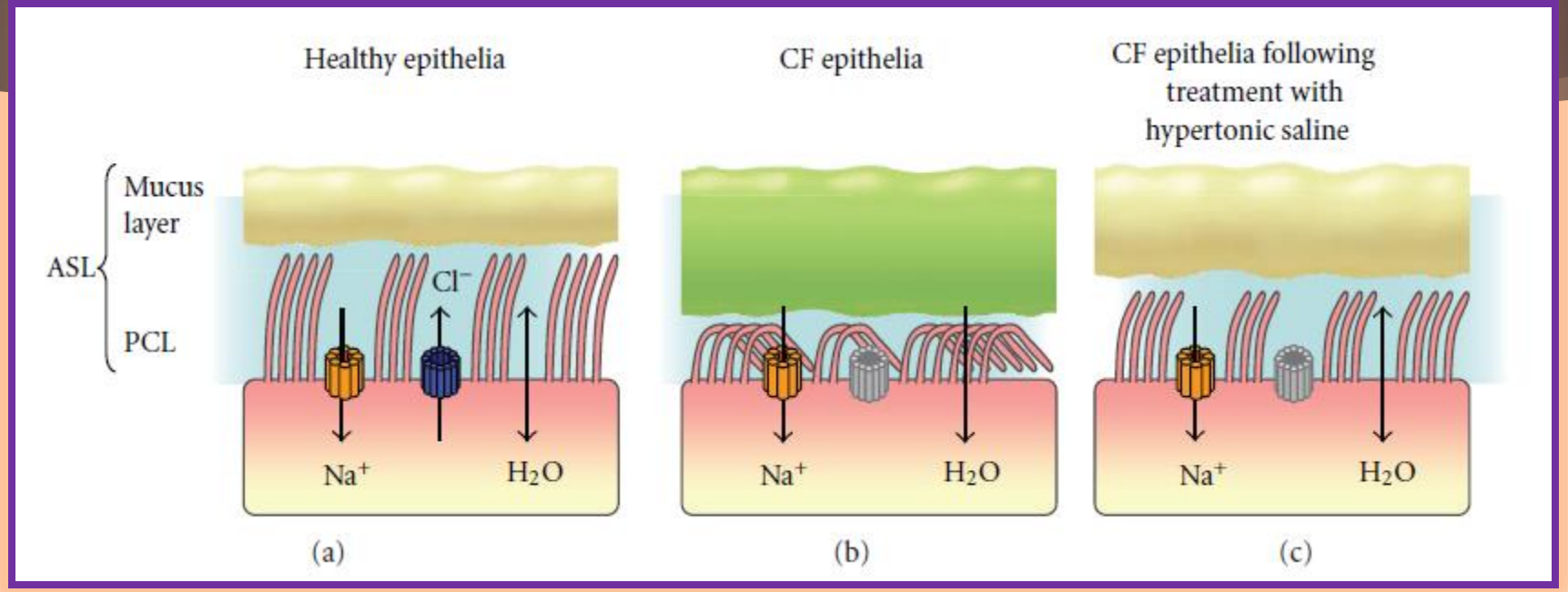
Airway clearance:

- **Daily** chest physiotherapy is important
- Usually done after a bronchodilator nebulizer treatment
- Several devices exist to aid clearance
- Inhaled DNAse (Dornase alpha) is proven helpful, mucolytics are **NOT**
- Hypertonic saline neb's (**7%**) are of proven efficacy in CF airway clearance
- Mannitol via nebulizer or dry powder inhalation could be helpful

Chest physiotherapy vest

Produce vibration
Better than manual

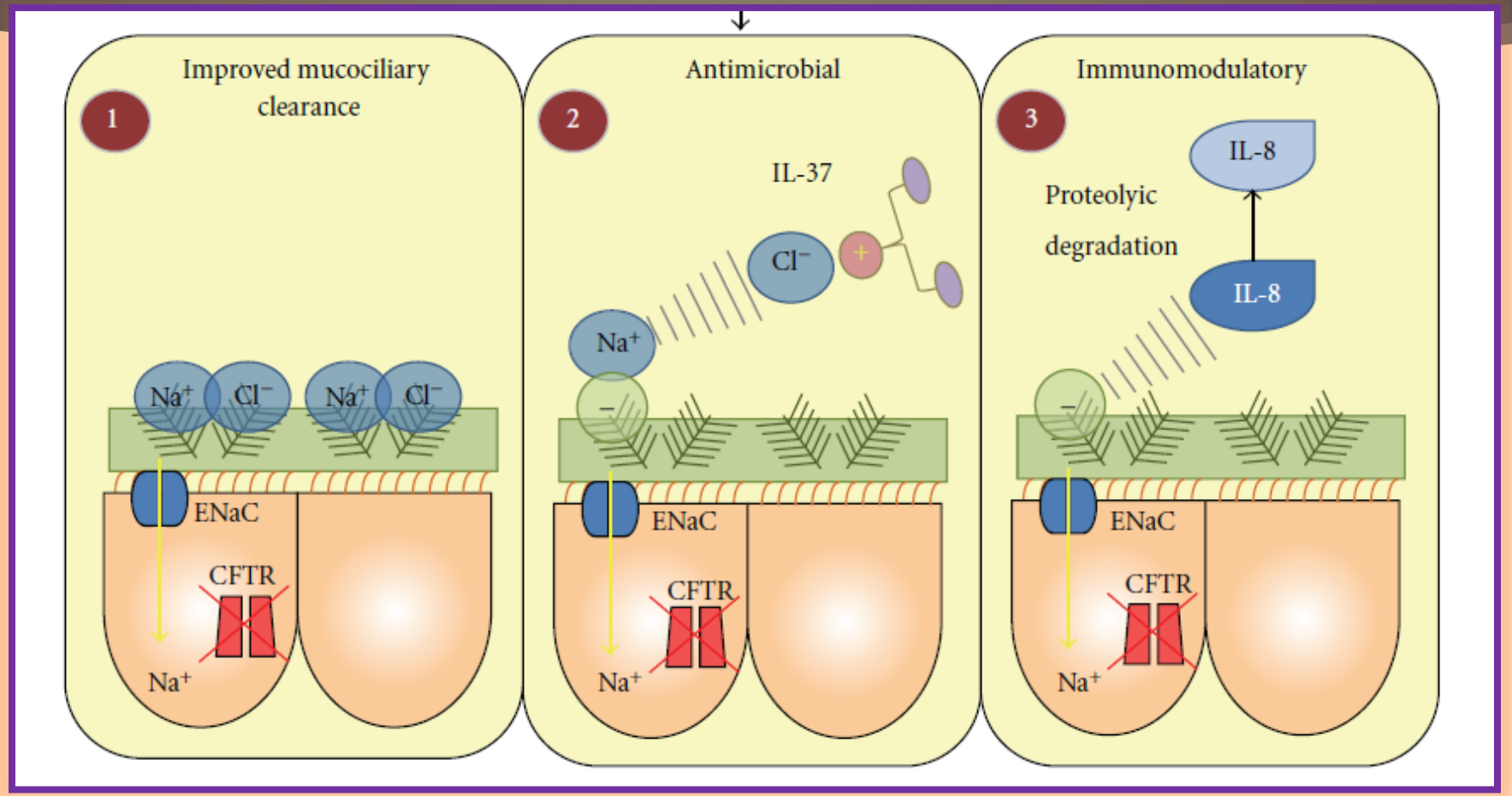
Hypertonic saline



Hypertonic Saline in Treatment of Pulmonary Disease in Cystic Fibrosis

The Scientific World Journal
Volume 2012, Article ID 465230, 11 pages
doi:10.1100/2012/465230

Hypertonic saline



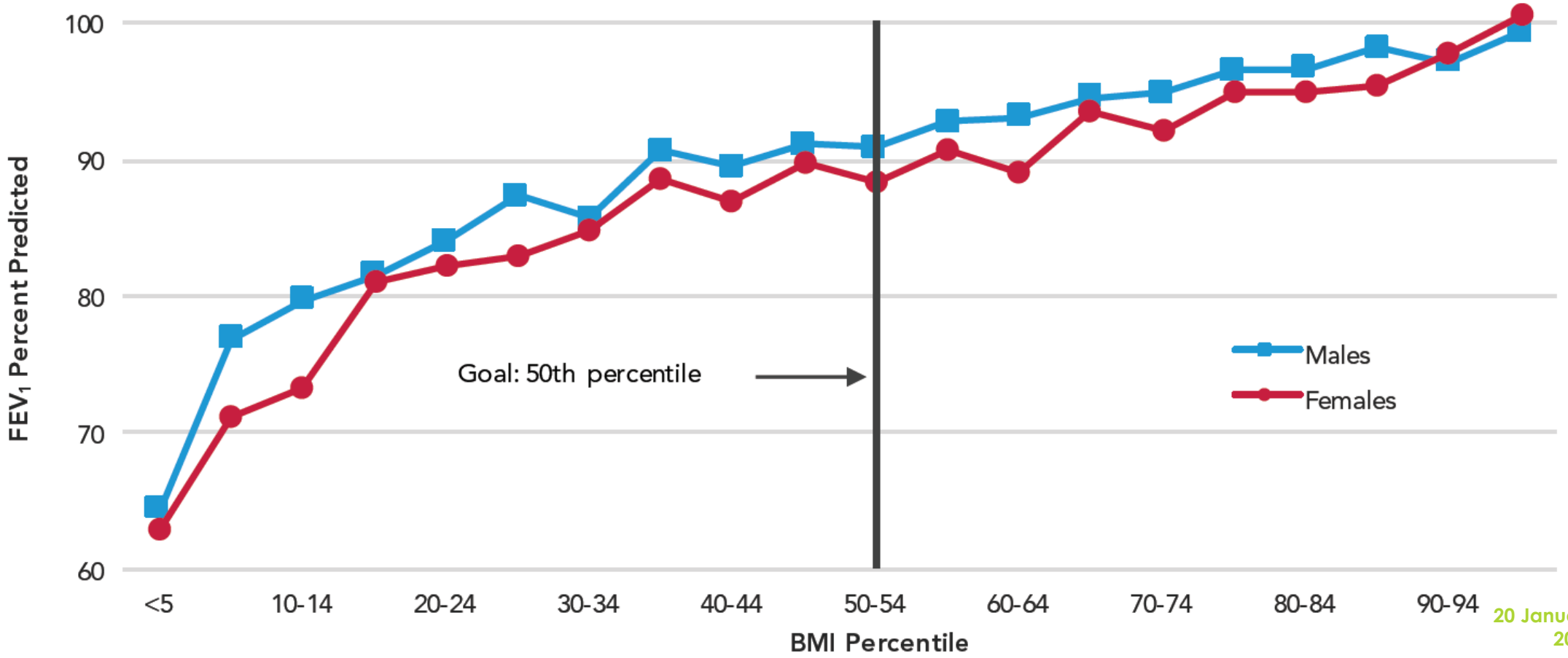
Treatment

GI problems:

- Pancreatic replacement enzymes *in pancreatic-deficient patients* ***(CREON)***
- Good nutrition is essential, patients with normal weight have better morbidity & prognosis
- Supplements of fat-soluble vitamins ADEK
- Screen for CF-related Diabetes (CFRD) **after 10y** , LFT **yearly**
- Treat GER
- Tube feeds sometimes necessary

Good BMI : good lung function

FEV_1 Percent Predicted vs. BMI Percentile for Children 6 to 19 Years in 2016



20 January 2024

New Therapies

- Since the CFTR gene was identified in 1989, research was directed towards trying to correct the genetic defect itself or trying to correct or repair the dysfunctional CFTR molecule, with the great hope of finding a “cure” for CF
- In this regard two areas were extensively researched:
  - gene therapy: no clinical success yet
  - CFTR modulators: impressive results

CFTR modulators

- The last 10 yrs have seen success in the management of CF using small molecules called CFTR modulators.
- This method focuses on targeting certain mutations with specific molecules
- CFTR modulators can be categorized into three main classes: potentiators, correctors and premature stop codon suppressors or read-through agents.

CFTR modulators

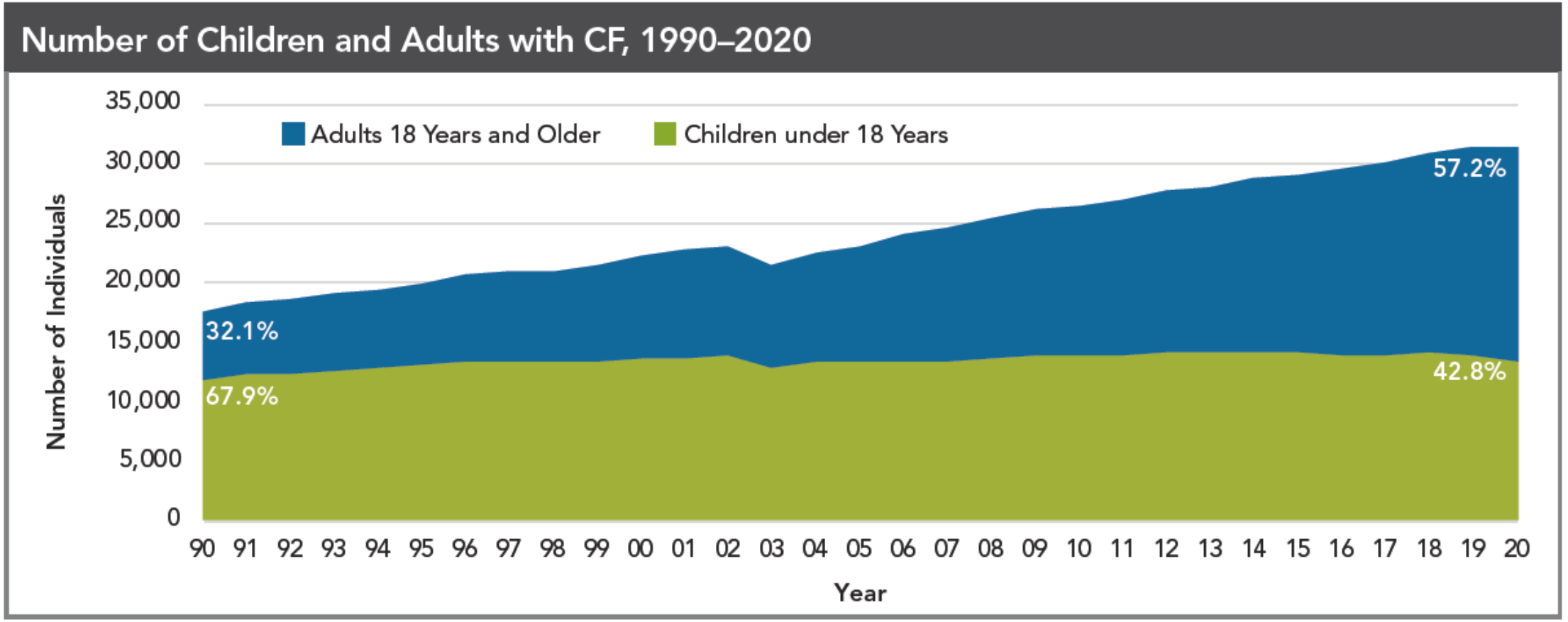
- Ivacaftor was approved in 2012. Ivacaftor is a CFTR potentiator that has proven clinical benefit in CF patients with G551D mutation, later showed some benefit in other mutations, even ΔF508
- Later, combination drugs containing a “chaperon” molecule that helps in CFTR trafficking defects, termed CFTR corrector, plus the CFTR potentiator Ivacaftor were approved for ΔF508 patients, and showed excellent clinical results in improving lung function and nutrition:
  - Lumacaftor / Ivacaftor
  - Tezacaftor / Ivacaftor
  - Elexacaftor / tezacaftor / ivacaftor **best one**
- Very expensive

Prognosis

- Worldwide, the median survival age is ~38 years **35-40**, but varies from country to country; it is highest in Canada (53 years) and the United States (49 years)
- The median survival age is higher in males than in females.
- With current treatment strategies, >80% of patients should reach adulthood
- Currently there are more CF adults than CF children

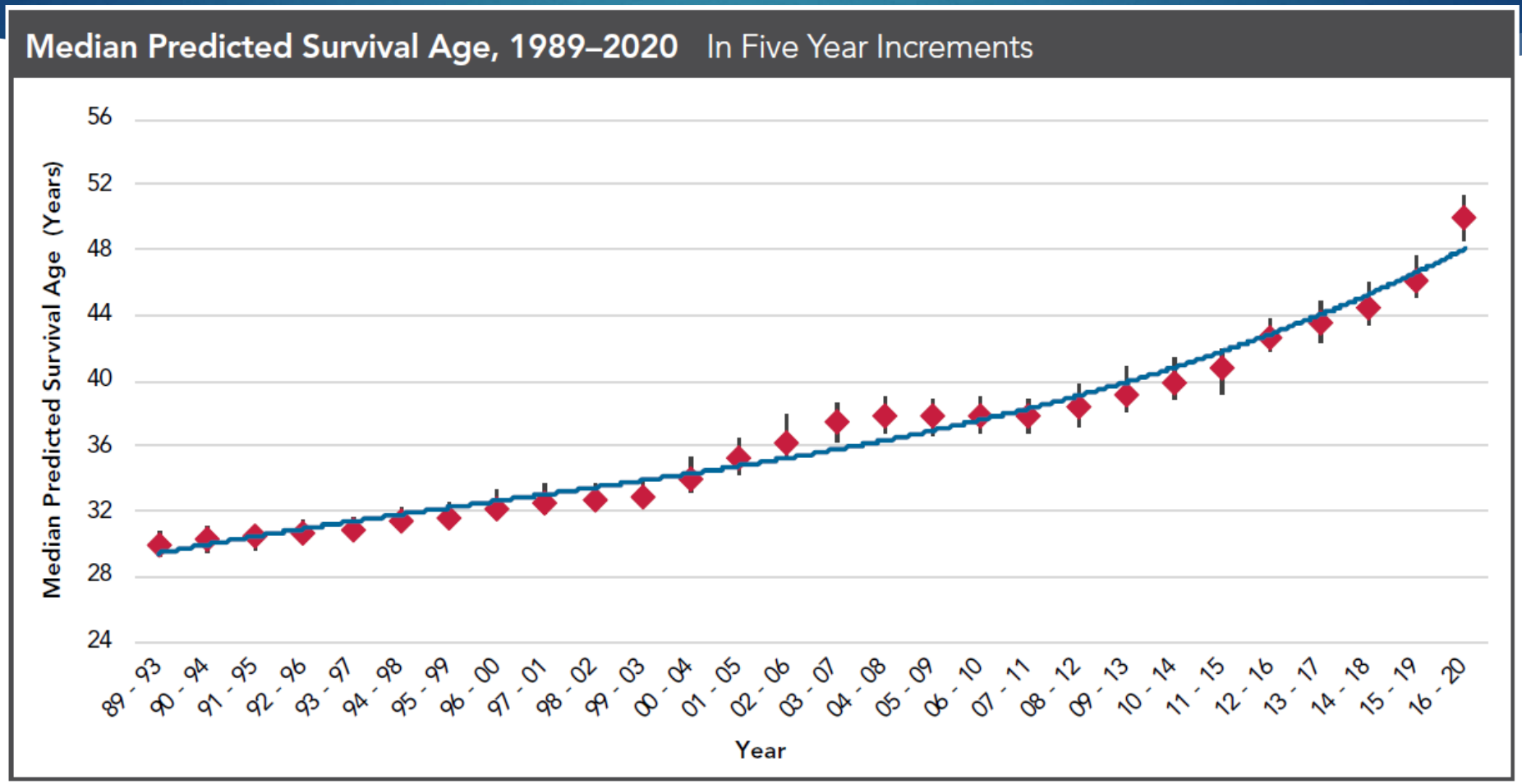
A pediatric disease?

this mean the survival rate improves and the pateints reach the adulthood.



CFF 2020 patient registry annual data report

Improving life expectancy - USA



CFF 2020 patient registry annual data report

conclusion

- CF is a multisystem disease caused by mutations in CFTR gene, main morbidity is chronic pulmonary infection and progressive pulmonary obstruction, bronchiectasis
- Common presentation is chronic cough, recurrent pulmonary infection, chronic diarrhea and malabsorption, sinusitis
- Less common is hepatobiliary disease, DM, electrolyte imbalance, infertility
- Diagnosis by newborn screening, sweat Cl-, genetic test
- Treatment focuses on airway clearance, early aggressive pulmonary infection treatment, good nutrition
- New therapy with CFTR modulators exists and is quite promising