Cystic Fibrosis

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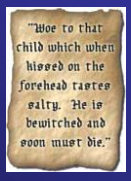
History of Cystic Fibrosis

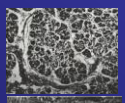
'Salty Kiss''



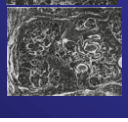
1938 Anderson:

cystic fibrosis of the pancreas: many small cysts in the pancreas of small children dying of severe malnutrition

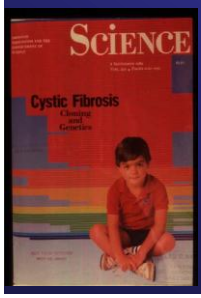
NI



CF



History of Cystic Fibrosis



1944 children dying of malnutrition, thick and sticky mucus in the lungs

1946 autosomal recessive inheritance

1953 increased salt in sweat

1980 defect in chloride transport

1985 CF gene on chromosome 7

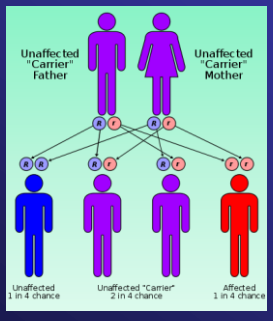
1989 sequence of CFTR-gene

20… new therapies

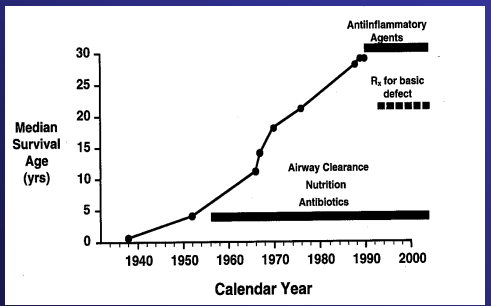
Cystic Fibrosis

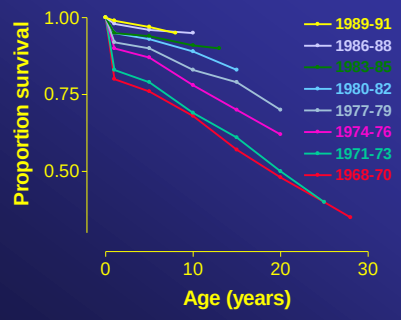
Most frequent
autosomal recessive inherited,
'life-shortening'
genetic
multisystem disease
of the indo-european population

Most frequent autosomal recessive inherited, 'life-shortening', genetic multisystem disease of the indo-european population



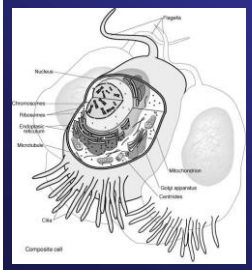
Most frequent autosomal recessive inherited, 'life-shortening', genetic multisystem disease of the indo-european population

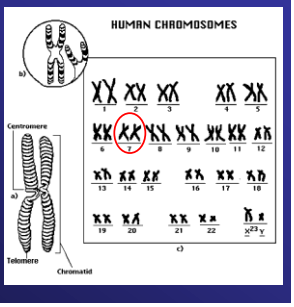




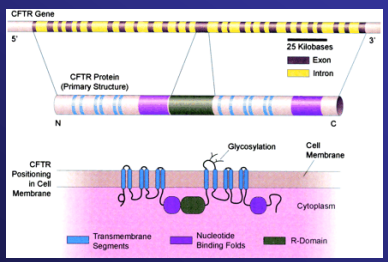
Dodge et al., Arch. Dis. Child. 1997

Most frequent autosomal recessive inherited, 'life-shortening', genetic multisystem disease of the indo-european population





CFTR gene
(CF transmembrane regulator protein)

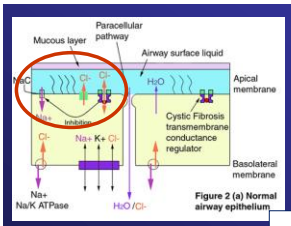


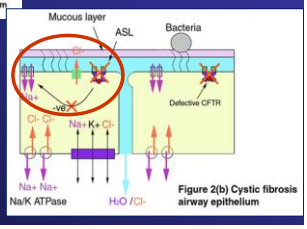
Gibson, RL, Burns, JL, and Ramsey, BW. Pathophysiology and Management of Pulmonary Infections in Cystic Fibrosis. AJRCCM 168 (918-951); 2003.

CFTR gene: 250.000 letters
> 1500 mutations

60 % ΔF508 - ΔF508 *homozygous*
20 % ΔF508 – other *heterozygous*
6 % other – other
<10% not known

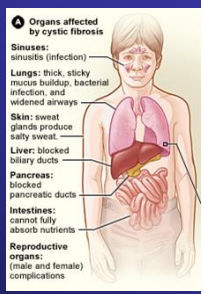
Bulgaria : 3 most common mutations: G542X - ΔF508 – N1303K





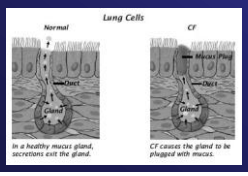
Most frequent autosomal recessive inherited, genetic, 'life-shortening', multisystem disease of the indo-european population

- ❖ Lungs and sinuses
- ❖ Gastro-intestinal tract:
  intestines, liver and pancreas
- ❖ Reproductive system
- ❖ Bones and joints - clubbing
- ❖ Sweat glands



Cystic Fibrosis

Normal function of the secretory glands is disturbed:



Defect of the CFTR gene

↓

Disturbed salt transportation

↓

Thick and sticky mucus

↓

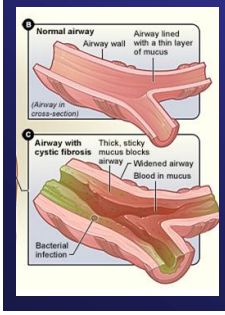
Thick mucus blocks the tubes or ducts

Cystic Fibrosis
multisystem disease

- Lungs and sinuses
- Gastro-intestinal tract:
  intestines, liver and pancreas
- Reproductive system
- Bones and joints - clubbing
- Sweat glands

CF lung

responsible for 95% of the morbidity and mortality



thick mucus obstructs the airways

↓

infection and inflammation

↓

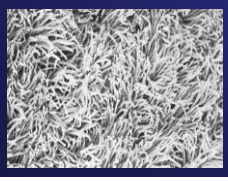
cough and sputum production

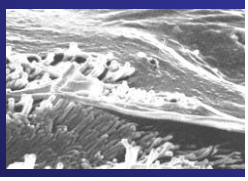
→ progression of lung disease

The normal lung

Normal mucociliary clearing

- Critical height of the epithelial lining fluid: chloride and sodium channel, hydratation
- Cilia move freely
- Watery mucus picks: particles, bacteria, ..

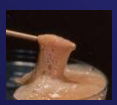




CF lung: thick mucus

Deficient mucociliary clearing:

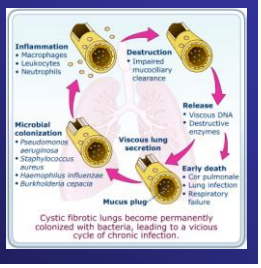
- No CFTR function, increased sodium absorption
- Dehydration of the mucus membrane, thick and sticky mucus.
- Cilia cannot move freely
- Stasis of secretions, high risk of infection



CF lung: infection

Bacteria:

- normal lower airways = sterile
- CF lower airways =
  - acute infections or exacerbations
  - chronic infection



CF lung: infection

Bacteria in CF:

- Haemophilus influenzae
- Staphylococcus Aureus

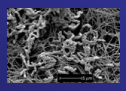
- Pseudomonas aeruginosa

- mucoid Pseudomonas aeruginosa

CF lung: infection

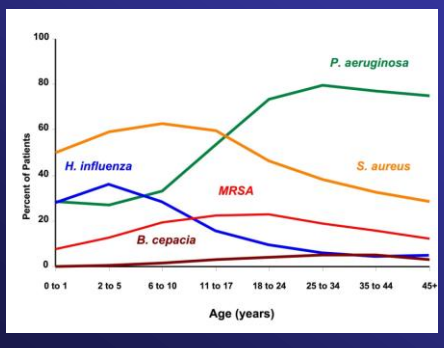
Bacteria in CF:

- Stenotrophomonas maltophilia

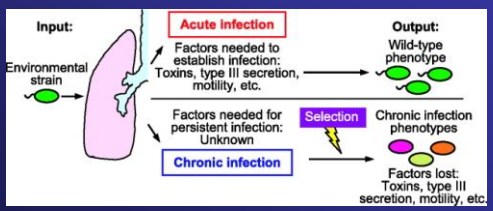


- Alcaligenes xylosoxidans
- Burkolderia cepacia complex: genomovar I to VI

CF lung: infection



CF lung: infection



The factors needed for acute infections are generally well understood, whereas those needed for chronic infection are not.

Nguyen D , Singh P K PNAS 2006;103:8305-8306

PNAS

CF lung: infection

Viruses

Cause of many respiratory infections (common cold)
sometimes lower airway infection (RSV)
= trigger for bacterial infection

CF lung: infection

Fungi

- Infection:

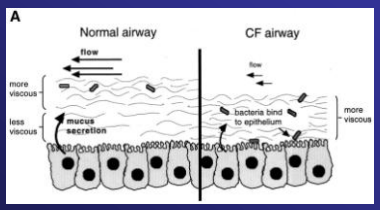
  aspergillus – candida – scedosporium

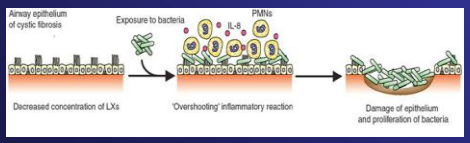
- Allergic reaction :

  Aspergillus fumigatus : ABPA

  (allergic bronchopulmonary aspergillosis)

CF lung: inflammation





CF lung: infection - inflammation

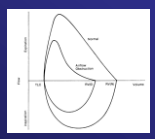
Damage of the airways:

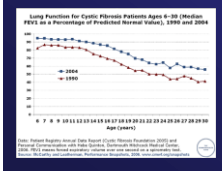
- Bacteria
- Inflammation

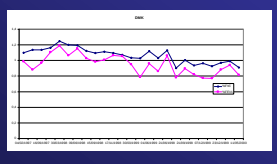
⇒ bronchiectasis
⇒ infected cysts
⇒ fibrosis

CF lung: technical evaluation

Lung function







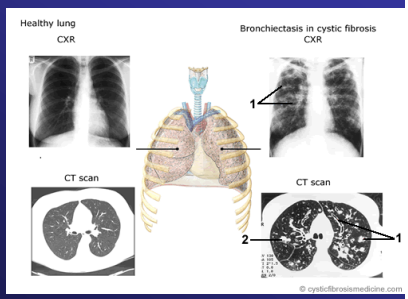
CF lung: technical evaluation

Thorax X-ray:

* acute problems
* periodic (6m)

CT-scan:

* detail
* bronchiectasis

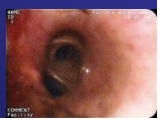


CF lung: technical evaluation

Sputum sample – throat swab

Bronchoscopy if needed:

* ongoing infection
* abnormal X ray (infiltrate, atelectasis
* coughing up blood

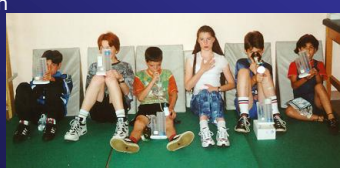


CF lung treatment
clearing mucus

Daily respiratory physiotherapy is crucial

Intention :

- ❖ improve mucus transport and mucus evacuation
- ❖ improve ventilation
- ❖ improve condition



CF lung treatment
clearing mucus

Nebulisation: mucus-thinning

Mesna or acetyscysteine , 1-2x/day

Hypertonic saline, 1-2x/day

Dornase alfa (Pulmozyme®), 1x/day - ≥5 years

CF lung treatment
antibiotics

* liberal use of antibiotics improves survival
* start with increasing symptoms :

cough – more sputum

* surveillance and early detection, frequent cultures

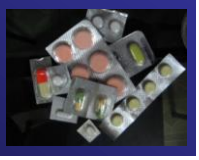
CF lung treatment
antibiotics

- CF patients require higher doses of antibiotics
- Acute exacerbation: prolonged, 14 days
- Chronic infection: continous (nebulised) antiobiotics
- Oral – nebulised - intravenously

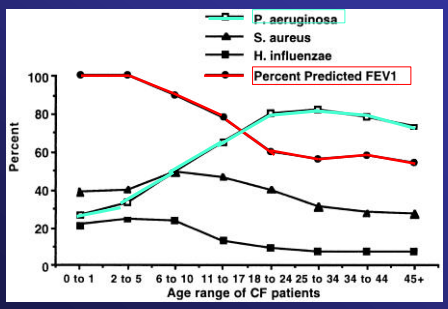
CF lung treatment
antibiotics

Oral antibiotics

Amoxicillin
Amoxicillin/clavulanic acid
(Flu)cloxacillin (chronic treatment?)
Ciprofloxacin
Co-trimoxazole



CF lung treatment:
Pseudomonas aeruginosa



Pier G B PNAS 2000;97:8822-8828

PNAS

CF lung treatment:
Pseudomonas aeruginosa: first or acute infection

need for aggressive antibiotic intervention of the Pseudomonas infection in attempt to eradicate the initial infection:

(1) Oral ciprofloxacin + inhaled colistin or tobramycin

(2) IV antibiotics for 14 - 21 days (exacerbation)

CF lung treatment:

Pseudomonas aeruginosa: chronic infection

chronic nebulisation :

Tobramycin (Tobi®, 300 mg), 2x/day,
28 days off / 28 days on
Colomycin or colistimethate, 2x2 milj U/day

Dry powder inhalation: colomycin, …

CF lung treatment

anti-inflammatory drugs

*** oral steroids**

improvement of FEV1 and reduction of exacerbation rate
but many side-effects: delay of growth, cataract, osteoporosis,

indication:
Allergic BronchoPulmonary Aspergillosis

*** inhaled steroids**

no controlled data

indication: asthma

CF lung treatment

anti-inflammatory drugs

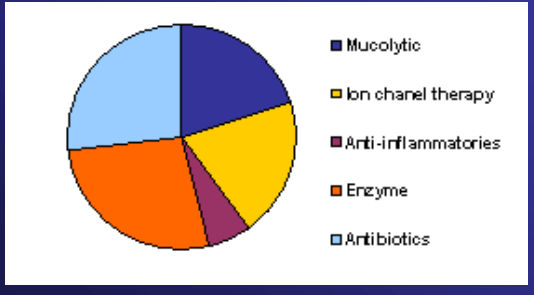
other anti-inflammatory treatment

* NSAI: ibuprofen

* Azithromycin <40 kg, 250 mg 3x/week
>40 kg, 500 mg 3x/week

Effects:
- ↑ FEV1 (3-7%) & FVC
- ↓ IV antibiotic use
- ↑ Quality of Life

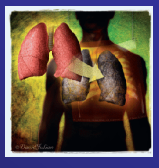
CF lung treatment



And .... No Smoking !!

CF lung treatment

Lung transplantation



Future therapies

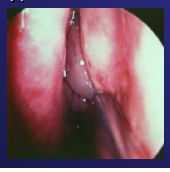
CF lung complications

- Hemoptysis
- Allergic Bronchopulmonary aspergillosis (ABPA)
- Pneumothorax
- Atelectasis
- Respiratory insufficiency:
  hypoxemia and cor pulmonale

CF upper airways

- Chronic sinusitis

- Nasal polyps 20-40% of CF patients



CF upper airways: treatment

- Nasal Wash

- Nasal corticosteroids

Daily Respiratory Care

Respiratory Physiotherapy
2 x / day

Nebulisation

Clearing mucus: 2 x / day

Antibiotics: 2 x / day

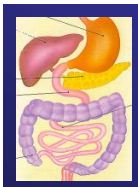
Cleaning of the nose
2 x / day

Antibiotics : liberal use

Cystic Fibrosis
multisystem disease

- Lungs and sinuses
- Gastro-intestinal tract:

  pancreas, intestines and liver
- Reproductive system
- Bones and joints - clubbing
- Sweat glands



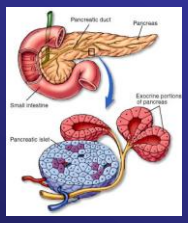
Pancreas

85% pancreatic insufficiency (DF508)

10 à 15% pancreatic sufficient

* exocrine function
  digestive enzymes

* endocrine function
  insuline



Exocrine pancreatic insufficiency

Pathogenesis

Obstruction of the pancreatic ducts

↙ digestive enzymes → maldigestion → dystrophy

autodigestion → microcysts → ↙ digestive enzymes

Exocrine pancreatic insufficiency

symptoms

- Fat maldigestion (lack of lipase)
  stools: frequent – plenty – oil drops
- Protein maldigestion (lack of protease: putrefaction)
  stools and winds: smell
- Carbohydrate maldigestion (lack of amylase)
  abdominal pain and bowel sounds

Exocrine pancreatic insufficiency

symptoms

malnutrition

- infants : very hungry
- weight stagnation or weight loss
- delayed puberty and growth spurt
- delayed menarche
- vitamin A, D, E, K deficiency

Exocrine pancreatic insufficiency

diagnosis

- Clinical symptoms
- Stool collection during 3 days (nl: 3–5 gr fat/d)
  + diet history
  = diagnostic - follow-up
- Faecal elastase on stool sample
  = diagnostic

Exocrine pancreatic insufficiency

treatment

Pancreatic enzymes (Creon®):

= lipase, protease en amylase
= small enteric coated microspheres

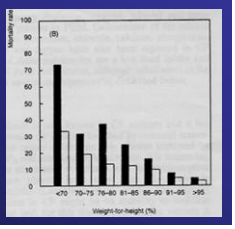
- with each meal (*troughout the meal*)
- no side effects
- dose depending on individual absorption
- ideal pH=7:
  sometimes need for proton pump inhibitors

Exocrine pancreatic insufficiency

treatment

Hypercaloric diet : + 30% !!

- High calory intake = high fat intake (35 – 40% RDA)
- 3 main meals – 3 snacks
- If insufficient weight gain:
  energy drinks
  gavage feeding (gastrostomy)



Exocrine pancreatic insufficiency

treatment

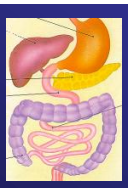
Fat soluble vitamines!!

- Vitamin A (retinol acetate) : 2500 IU – 10000 IU
- Vitamin D (dihydroxycholecalciferol): 400 IU – 1000 IU
- Vitamin E (alfa tocoferol): 100 IU – 200 IU
- Vitamin K (menadione bisulfiet): 1 mg

→ ***do not forget pancreatic enzymes!!***

Extra salt!!

Infants < 1 year
Fever
Hot summers



Intestinal obstruction

Neonatal meconiumileus (MIE)

= obstruction by dehydrated meconium at birth

vomiting bile – no stool (<24h) – distended abdomen

90% of children with MIE is diagnosed with CF

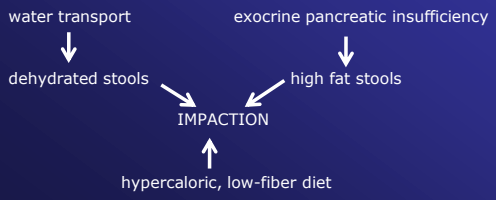
Possible complications:

hypoplasia of the large intestine
malrotation and / or perforation of the intestines

Intestinal obstruction

Distal intestinal obstruction syndrome (DIOS)

= obstruction of the intestine, at junction of the small and large intestine



Intestinal obstruction

Distal intestinal obstruction syndrome (DIOS)

Symptoms:

- colics
- lower stool frequency
- overflow diarrhea
- right lower abdominal mass

Real obstruction:

- painfull abdominal distention
- Vomiting
- no stool

Intestinal obstruction

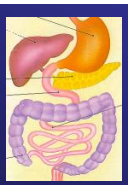
treatment

acute phase:

(repeated) enemas and laxatives
sometimes surgery
fluid replacement

chronic treatment:

increase dosage of enzymes
add fibers
more fluid



Cystic fibrosis liver disease

Remains somewhat of a mistery : unknown as to why some people with CF develop liver disease and some don't

Primary chloride channel defect results in *dehydrated, inspissated secretions* that plug and *obstruct* intrahepatic bile ducts initiating a *progressive periportal fibrosis*

Cystic fibrosis liver disease

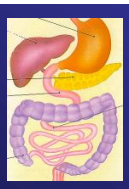
presentation

- Jaundice in babies and neonatal cholestasis
- Initially causes no symptoms
- Abnormal liver function tests
- Hepatomegaly
- Portal hypertension
- Oesophageal varices
- Biliary tract involvement – gall stones

Cystic fibrosis liver disease

treatment

- mostly suppportive
- medication: ursodeoxycholic acid, 20 mg/kg/day
- treatment of portal hypertension - oesophageal varices
- liver transplantation



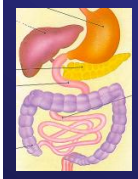
Gastro-oesophageal reflux

If respiratory symptoms don't respond to maximal therapy

exclude gastro-oesophageal reflux

Cystic fibrosis related diabetes mellitus

(CFRDM)



Scarring of the pancreas

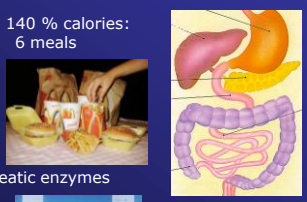
↓

Damage of insuline producing cells

Oral glucose tolerance test:
treatment : insulin injections

Daily Gastro-intestinal Care

120 à 140 % calories:
6 meals



Pancreatic enzymes

Ursodeoxycholic acid

Vit A, D, E, K

Salt

Insulin

Antireflux therapy

Laxatives

3 monthly consultation :

- Physician: clinical examination
  weight / length
- Dietician
- Physiotherapist
- Psychologist
- Social worker

- Culture: sputum-throat swab (3m)
- X-ray (6m) or CT (2y) of the lungs
- Lungfunction (3m)
- Blood examination (6m)
- Ultrasound of the liver (1y)

Hospital admission

Home IV therapy

CF-centered care

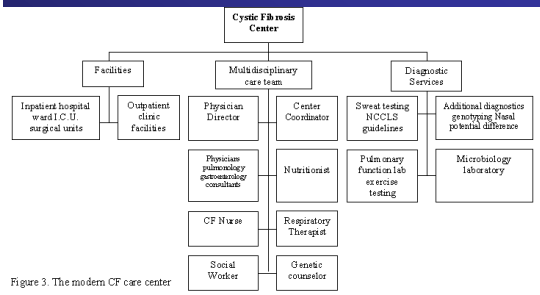


Figure 3. The modern CF care center