CYSTIC FIBROSIS

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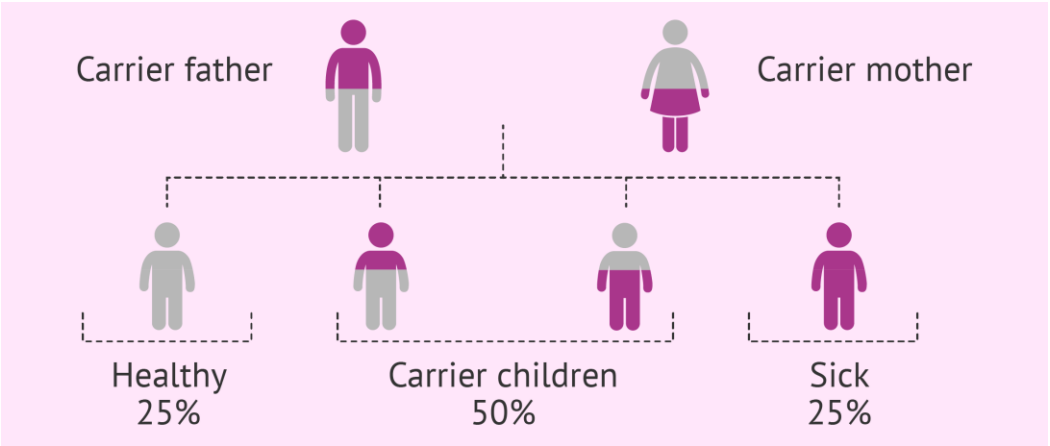
DEFINITION

- Most frequent congenital metabolic disease
- Autosomal recessive inheritance – only a person with 2 clinically significant mutations becomes ill
- Progressive lung disease, pancreatic insuficiency, high concentration of electrolytes in sweat, azoospermia, affects liver, intestines
- Described in 1938, gene discovered in 1989, name refers to pancreatic fibrotic and cystic conversion



EPIDEMIOLOGY

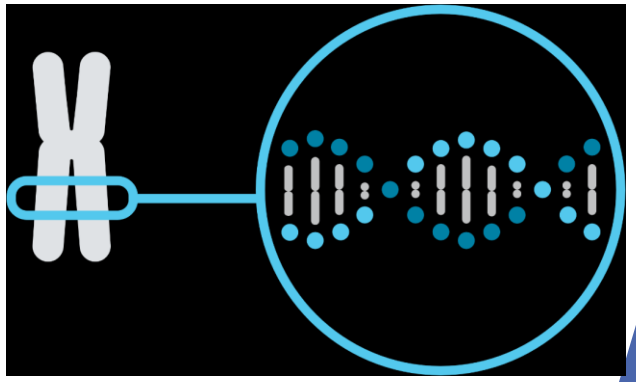
- 1:2500 – 4500 Caucasian newborns
- 35 newborns with CF per year in Czech Republic
- Every 25th person CFTR mutation carrier

Český registr cystické fibrózy

European Cystic Fibrosis Society ecfs Patient Registry

GENETICS

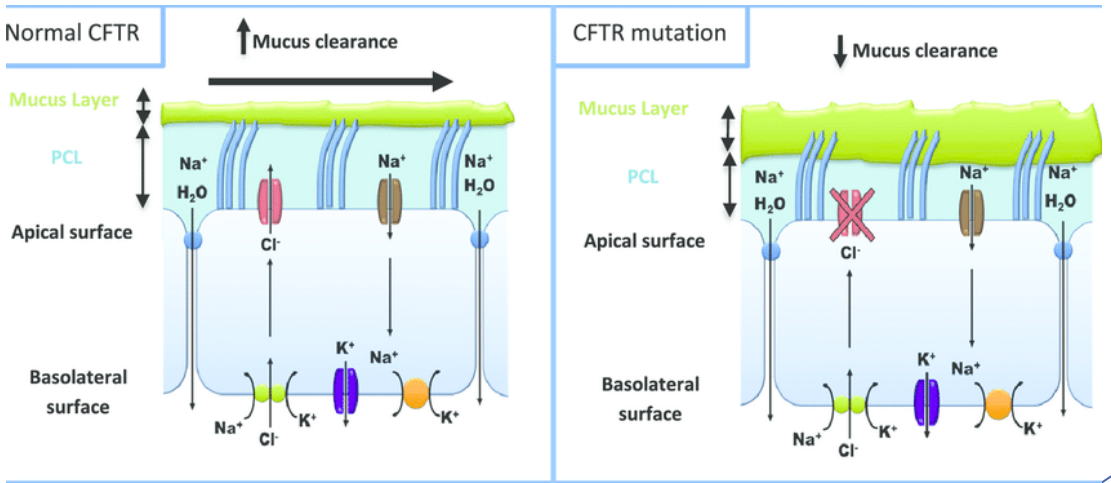
- CFTR gene codes CFTR protein (ion transmembrane conductance regulator)
- > 2000 mutations known – most of them are rare or don‘t cause manifest disease
- 30 mutations cause manifest CF
- Most frequent mutation *F508del*



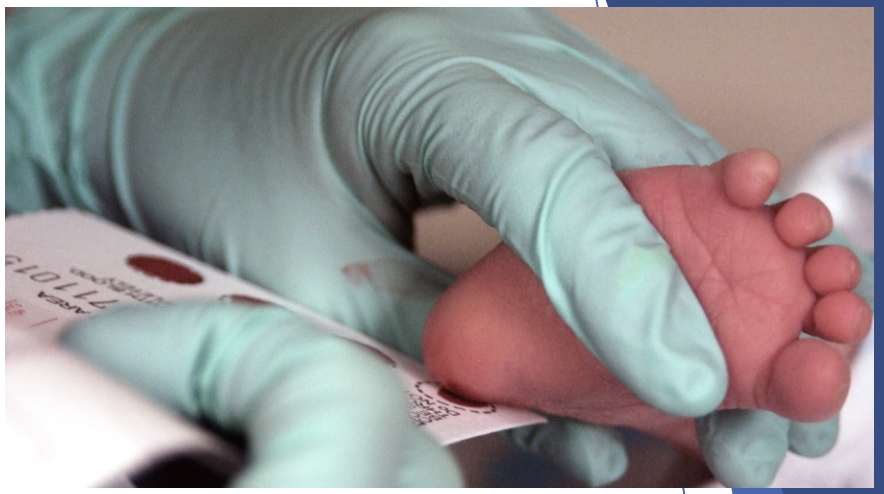
- <u>Relationship of the genotype and the phenotype:</u>
- Severe mutations – classic signs of CF
- Mild mutations – atypical forms – sufficient pancreatic function, borderline limits of the sweat test, late onset and mild respiratory manifestation, normal liver function

PATHOPHYSIOLOGY

- Gene product – chloride chanel on the epithelial cell‘s membrane
- <u>Impermeability to chloride ions:</u>
- 1. thickening of the mucus secretions – mucociliary clearance disorder – mucus retention – bacterial colonisation (biofilm) – neutrophil infection – bronchiectasis, obstructive ventilation disorder, respiratory insuficiency, blockage the ducts carrying digestive enzymes - demage of the pancreas and liver, reduced fertility
- 2. chlorides and sodium cannot be resorbed in the sweat glands



DIAGNOSTICS

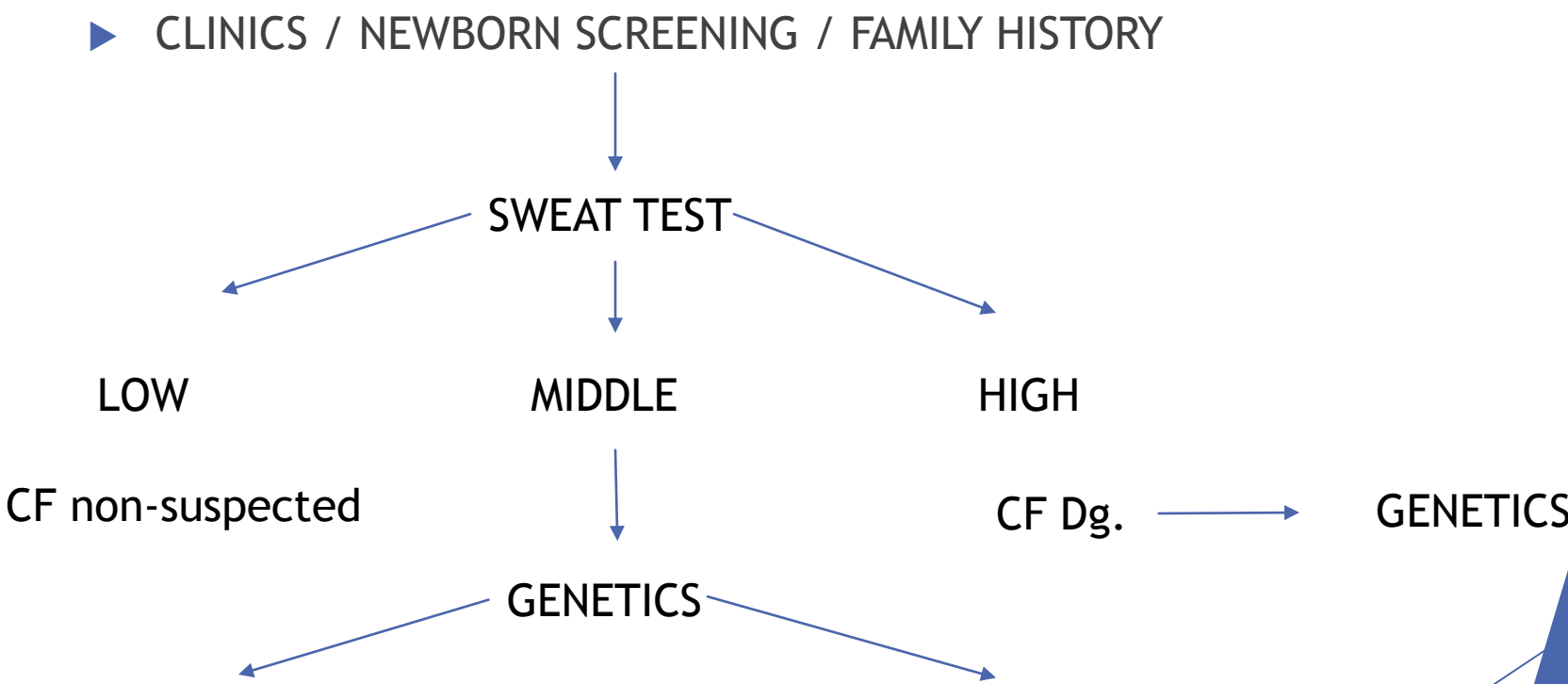


- Typical clinical signs and/or
- Family history and/or
- Newborn screening – blood tests for rare diseases and genetics, kiss your baby test

+

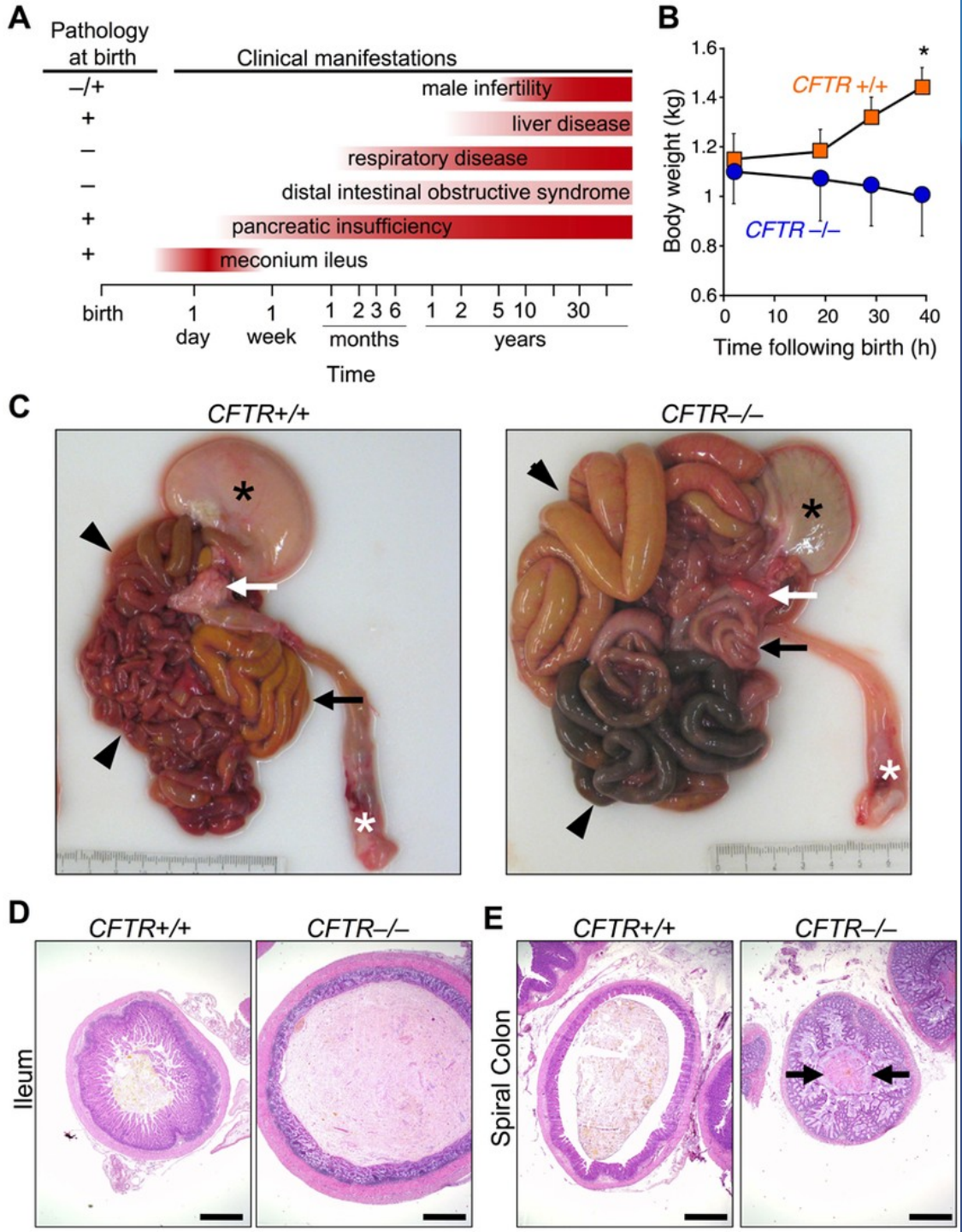
- Positive sweat test and/or
- 2 classical CFTR gene mutations

ALGORITHM


CLINICS / NEWBORN SCREENING / FAMILY HISTORY
SWEAT TEST
LOW
MIDDLE
HIGH
CF non-suspected
CF Dg.
GENETICS
GENETICS
2 MUTATIONS
1 – 0 MUTATIONS
Atypical CF / CFTR - RD
CFTR-RD / healthy carier / false positive SwCl

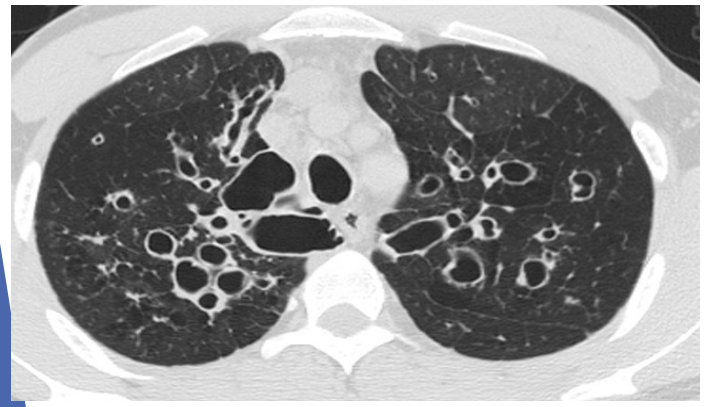
CLINICAL SYMPTOMS

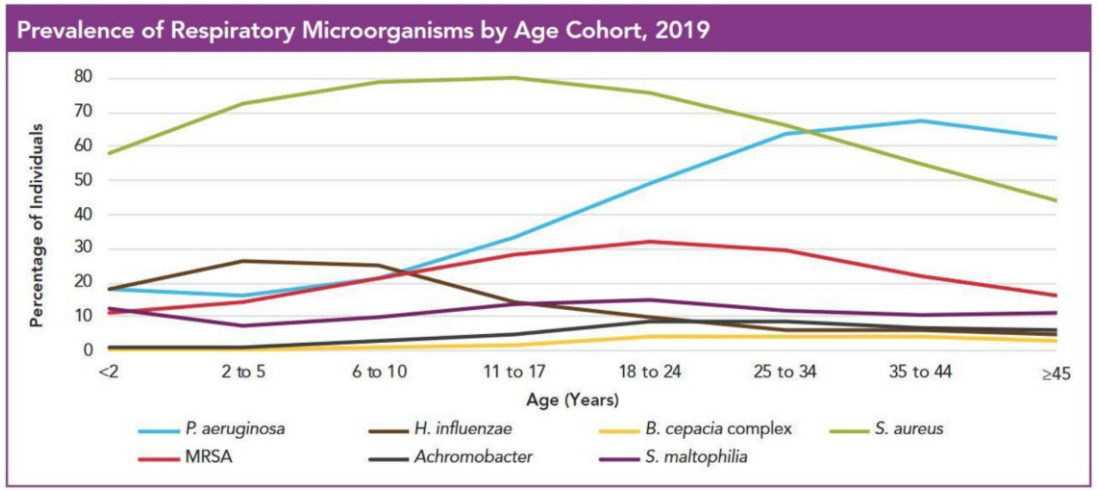
- Newborns – meconium ileus, lower birth weight, long newborn jaundice
- Older babies and kids – respiratory + gastrointestinal manifestation, salt loss syndrome (acute hyponatremic dehydratation with shock, chronic metabolic alkalosis), poor growth and weight gain
- Adolescents + adults – infertility / azoospermia, bronchiectasis, Pseudomonas aeruginosa cultivation, pancreatic insufficiency, mental health problems, osteoporosis

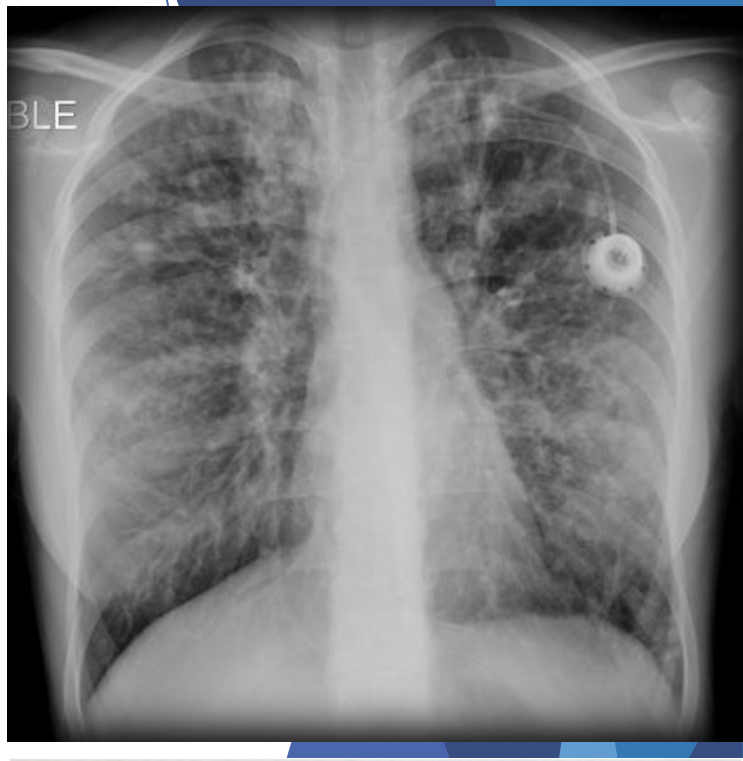


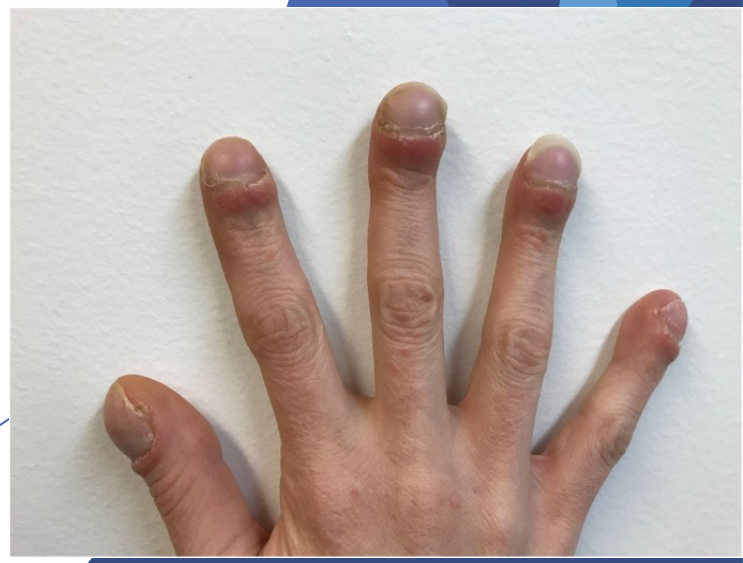
RESPIRATORY SYMTOMS

- Persistant pathogen colonisation – *Staphylococcus aureus*, *Haemophillus influenzae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *MOTT*
- Chronic respiratory infection – cough, sputum production, X-ray changes, obstructive ventilatory disorder, clubbing fingers
- Chronic sinusitis – nasal polyps, pansinusitis





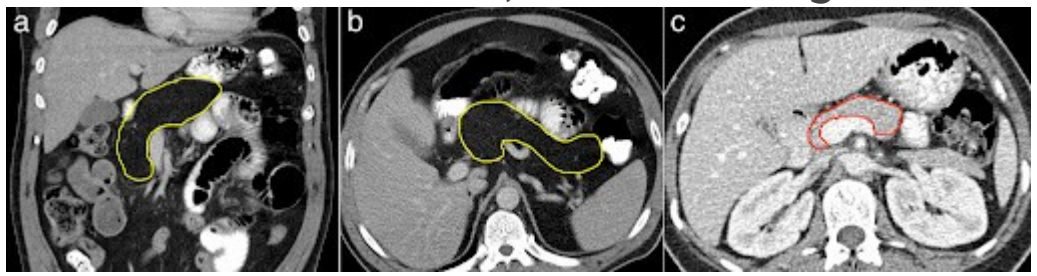


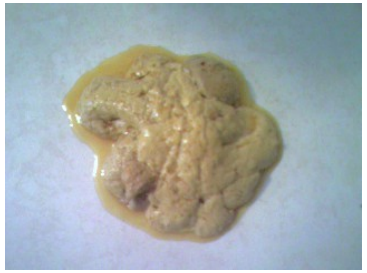


- <u>Complications:</u>
- Bronchiectasis, allergic bronchopulmonary aspergillosis, atypical mycobacteriosis, atelectasis, pneumothorax, hemoptysis, pulmonary hypertension, cor pulmonale, hypoxemia, respiratory failure

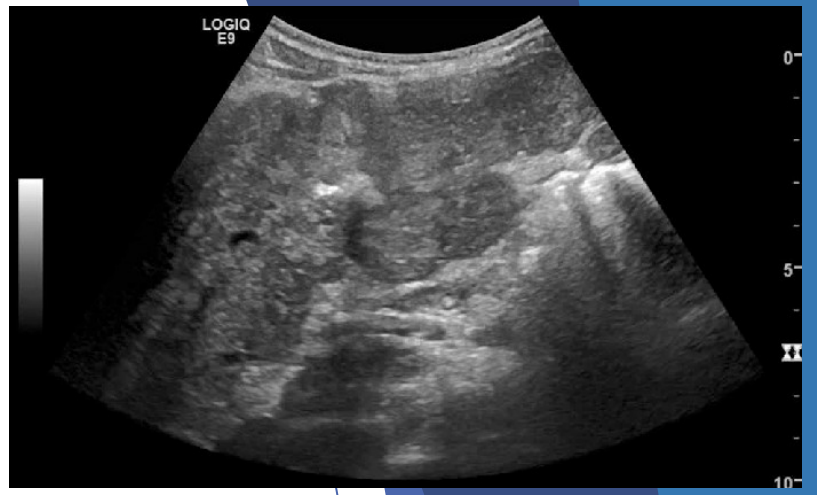
GASTROINTESTINAL SIGNS

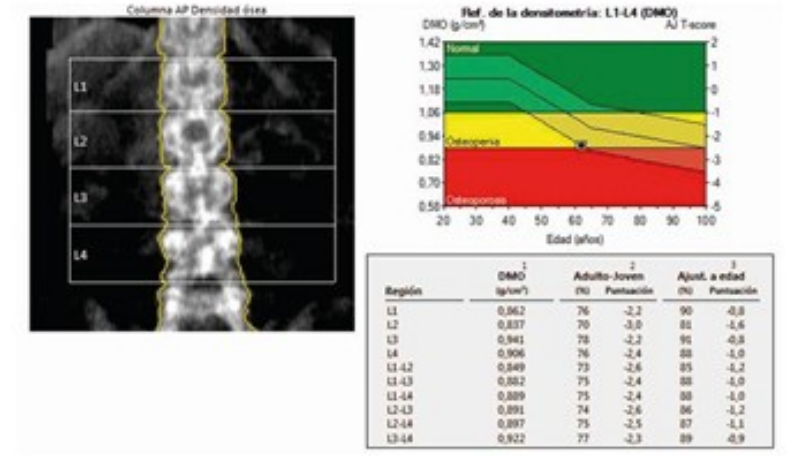
- Intestinal disease – distal intestinal obstruction syndrome, rectal prolapse
- Pancreatic disease – exocrine insufficiency, steatorhea, relaps of pancreatitis
- Chronic hepatobiliary disease – cirrhosis
- Malabsorbtion, malnutrition, hypoprotein odema
- Avitaminosis – ADEK, blood clotting disorder

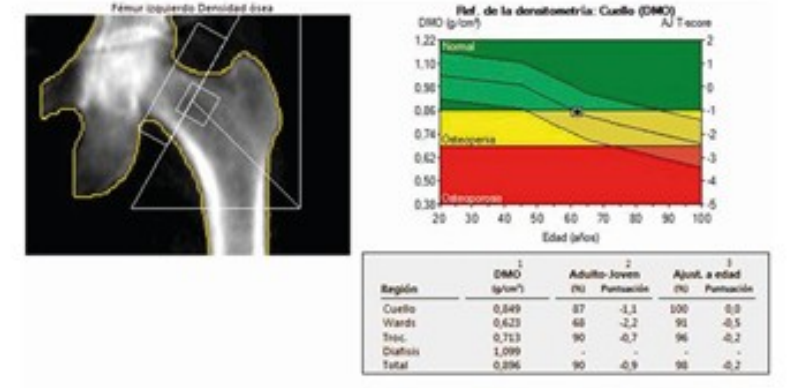




- <u>Complications:</u>
- Gastroesophageal reflux, oesophagitis, gastroduodenal ulcerations, fibrotic colonopathy, portal hypertension, distal bile duct stenosis, cholelithiasis, gallstones, CFRDM, metabolic bone disease





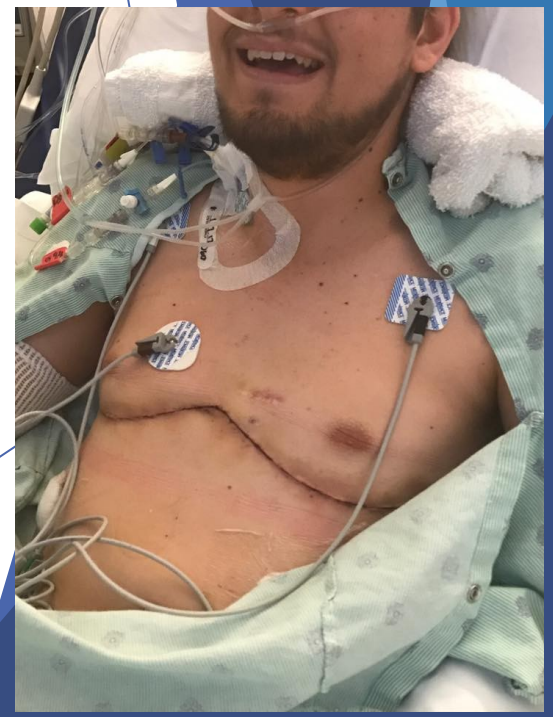


TREATMENT

- At specialist multidisciplinary centers
- 1. Proactive treatment of airway infection
- 2. Good nutrition - supplementation
- 3. Pulmonary rehabilitation
- 4. Causal therapy
- 5. Psychological support, complications solution
- 6. Epidemiological and hygine restrictions

TREATMENT – RESPIRATORY DISEASES

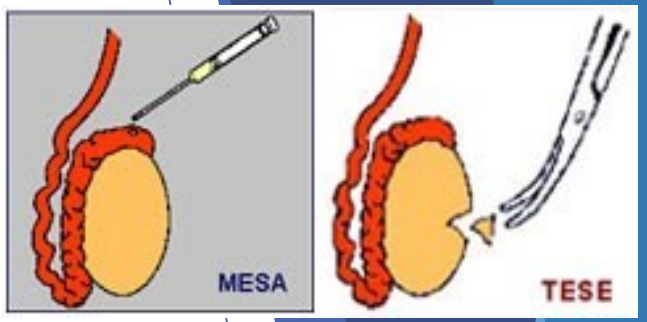
- Airway clearance – mucolytics – dornase alfa, hypertonic saline
- Pulmonary infection – ATB according to sensitivity, never empirical, high dosage, long duration (2-3 weeks), cure every exacerbation, ATB combination
- *Ps. aeruginosa* - ciprofloxacin + tobramycin / colistin inhalation, amikacin /gentamycin + ceftazidim / meropenem
- *B. cepacia* – meropenem + amikacin + cotrimoxazole + chloramfenicole
- Home oxygen therapy
- Surgical removal of the infected part of the lung
- Lung transplatation – WL: FEV1< 30% or rapid FEV1 decrease, frequent exacerbations, recurrent PNO, recurrent hemoptysis uncontroled by bronchial artery embolization. Performance indication : oxygen dependent respiratory failure, hypercapnia, pulmonary hypertension



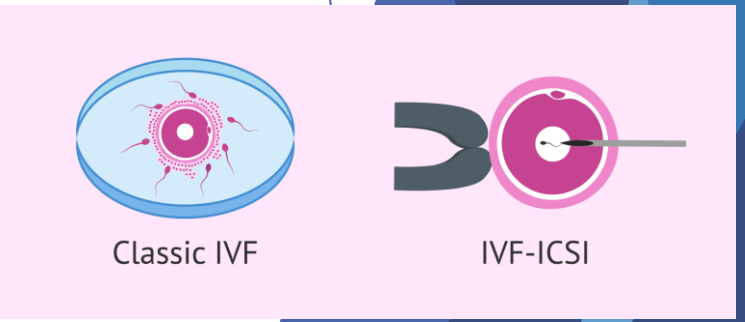
TREATMENT – GASTROINTESTINAL DISEASE

- Exocrine pancreatic insufficiency – lipase substitution
- CF related DM – insulin injections / pump, diet never reccomended
- Hepatic cirrhosis - ursodeoxycholic acid, taurin
- Metabolic bone disease – prevention = exercise, vitamine D, calcium, bisfosfonate
- Malnutrition – increased caloric intake (150-200% of the standard), sipping, nasogastric probe, gastrostomy (PEG), parenteral nutrition
- Vitamine and mineral substitution – Ca, Mg, Zn, Se, Fe, fat soluble vitamines
- Pancreatic or liver transplantation

REPRODUCTION



- In 98% infertility (CBAVD) - genetics examination of the partner
- Micro epididymal sperm aspiration (MESA) /Testicular sperm extraction (TESE) – spontaneus IVF / intracytoplasmic sperm injection (ISCI) – embryo transfer



- Absolute gravidity contraindications: pulmonary hypertension, cor pulmonale, hypercapnia, resting hypoxemia
- Relative contraindications: FEV1 < 50%, rapid pulmonary function decrease, *Burkholderia* colonisation, recurent pulmonary infections with IV ATB treatment, malnutrion, CFRDM
- Third party reproduction

HYGIENE, EPIDEMIOLOGICAL AND OTHER RESTRICTIONS

- Prevention of salt loss by the sweat, avoid physical exercise, sauna and hot dry conditions and dust environment, regular change of clothes because salty sweat irritates skin
- Prevention of respiratory infection by avoiding crowded places, contact with humid subjects, stagnant water, nor its aerosol (toilet flushing only with closed toilet board), wash hands regularly, have their own bathroom – must be daily cleaned by chlorine preparations, cannot grow plants and water them, cannot wash dishes, avoid to molds on the wall and moldy things
- Strictly isolate patients to prevent the transmission of infections to each other

CAUSAL TREATMENT

- Orphan drugs – rare diaseses (prevalence < 5/10 000 newborns)
- <u>Disease modifying drug:</u>
- Defective CFTR protein aktivator – increase capacity of ion channels for transport chloride ions – ivacaftor (*Kalydeko*)
- Defective CFTR protein corrector – binds and stabilizes the channel in the membrane of the epithelial cell – lumacaftor (LUMA/IVA – *Orkambi*), tezakaftor (TEZA/IVA – *Symkevi*), elexacaftor (ELEXA/IVA/TEZA – *Kaftrio*)

PROGNOSIS

- Median age of survival 44 years
- Quality of life expectations in causal treatment
- Cardiorespiratory complications and acute infections cause death in 80%
- 9 years median survival posttransplant

THANK YOU

FAKULTNÍ NEMOCNICE BRNO

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