# Genetics & Pathophysiology

- **Autosomal recessive disease**
- **Most common life-threatening genetic disease inflicting Caucasian Americans**
- **CFTR gene**
  - Cystic Fibrosis Transmembrane Conductance Regulator
  - Cl– channel regulator (regulated by cAMP): as Cl– is moved out of the cell, Na+ and H2O follow
    - Dysfunctional channel $\rightarrow$ ↓Cl– $\rightarrow$ ↓Na+ $\rightarrow$ ↓H2O $\rightarrow$ ↑viscosity of secretions $\rightarrow$ obstruction
    - Thick mucus $\rightarrow$ infection $\rightarrow$ inflammation
  - Located on many membranes: sweat glands, pancreas, lung kidney, digestive tract
  - >1500 mutations identified (most common: delta F508)

## Clinical Presentation

- **Pulmonary disease**
  - 90% of fatalities
  - Multiple pulmonary infections (*S. aureus, H. flu, P. aeruginosa*) because thick mucus secretions are a great environment for bacteria to grow in
  - Chronic productive cough
- **Pancreatic insufficiency**
  - 90% of patients
  - Steatorrhea + malnutrition
    - ↓Lipase $\rightarrow$ ↓absorption of fat & fat soluble vitamins (A, D, E, K) $\rightarrow$ steatorrhea + malnutrition
    - ↓Digestive enzymes $\rightarrow$ ↓absorption of food $\rightarrow$ malnutrition
  - Insulin deficiency
- Intestines: obstruction
- Liver: biliary cirrhosis, portal hypertension
- Sweat glands: hyponatremia if sweating a lot due to ↓reabsorption of Na+
- Reproductive: obstruction of epididymis & vas deferens (more infertility in males than females), delayed puberty
- Hematologic: chronic anemia
- Bone & joint: arthritis & osteopenia due to malnutrition and inability to reabsorb vitamin D

## Diagnosis

- Diagnosis usually by 1 y/o (70%)
- Prenatal screening: before 20th week; amniocentesis, chorionic villus sampling, pancreatitis associated protein
- Neonatal screening: ↑immunoreactive trypsinogen in blood
- *Sweat test: gold standard, positive if >60mEq/L*
  - Diagnosis with 2 tests on 2 different occasions + ≥1 of [COPD, pancreatic insufficiency, familial history]
  - False positives: adrenal insufficiency, hypothyroidism
- Nasal potential difference (NPD): because sweat test inaccurate for infants <2 months
  - False positives: inflamed nasal mucosa (e.g. sinusitis), pancreatitis
- CF mutation identification: difficult since >1500 mutations, only detects most common
  - Used if patient has indeterminate sweat test

## Treatment

- Nutritional therapy
- Airway clearance techniques
- Pulmonary exacerbation antibiotic therapy
- Chronic suppressive therapy to suppress bacteria colonization in lungs
- Anti-inflammatory agents for lung damage
- Mucolytic agents to remove thick secretions
- Lung transplant if necessary
- Gene therapy to fix genetic defect (undergoing research)
Pulmonary exacerbation

- Definition: ↓FEV₁, ↑cough, ↑dyspnea, ↑sputum, ↑hemoptysis, fever, ↓weight, malaise, CXR infiltrate
- Antibiotic treatment vs. (S. aureus, H. flu, P. aeruginosa)
  - Aminoglycoside + extended spectrum penicillin with β-lactamase inhibitor
  - Aminoglycoside + 3rd generation cephalosporin (ceftazidime)
  - Aminoglycoside + [monobactam (aztreonam) –or– carbapenem (imipenem/cilastatin, meropenem)]

Antibiotics

- Aerosolized antibiotics: TOBI via nebulization
  - Added to systemic antibiotics for pulmonary exacerbations and/or chronic suppressive therapy
- P’kinetic considerations: systemic dosing different due to p’kinetic variations
  - ↓pH + ↑Vd + ↑CL → need ↑dose and/or ↑frequency (q4-6 hours)
- Monitoring parameters: pulmonary function, cough/sputum production, appetite/weight, aminoglycoside conc.

Dornase alpha (Pulmozyme)

- Indicated for ≥ 5 y/o + FVC > 40% (i.e. need somewhat healthier lungs)
- Guidelines recommend for all patients > 6 y/o with moderate/severe lung function
- May be used in patients 3 months to 5 y/o to prevent lung damage
- Assessment after 4 weeks of therapy
  - Relative improvement (>8%): continue
  - Drop in lung function: stop
  - Suboptimal improvement (<8%): continue if symptomatic benefit for 3 months then reassess
  - Frequent exacerbations (≥4/year) + IV antibiotics: extend trial for 6 months even if no improvement in lung function but there is improvement in symptoms
- Dosing: 2.5mg qd or bid via nebulization (do not mix with other solutions)
- SE: hoarseness, pharyngitis, allergic reactions, rash (relatively mild SE)
- $$$ Expensive: $5-10,000/year

Hypertonic Saline 7%

- Dose: 4ml bid via nebulization
- Effects: ↑lung function + ↓pulmonary exacerbations
- SE: coughing, throat irritation, chest tightness (not easily tolerable by all patients, too hypertonic)

Ibuprofen (NSAIDs)

- Inflammation: neutrophils release elastase
  - → Elastase digests structural proteins → airway damage
  - → Elastase damages phagocytosis mechanisms → ↑risk of infection
  - → Elastase ↑mucus secretions
  - → Elastase promotes inflammatory cycle → ↑leukotrienes
- IBU effect: inhibits neutrophil migration & elastase release
- Dosing: 20-30mg/kg/dose bid (really high dose compared to for fever at 5-10mg/kg); max 1600mg
- Patient population: 5-13 y/o with FEV₁ > 60%

Other

- Azithromycin: long term, low dose
- Albuterol inhalation: good if patients reacting to other agents
- Gene therapy: correct mutation in CFTR gene
- Lung transplants: sick enough for justification, healthy enough to survive it
Gastrointestinal treatment

- Nutrition
  - Diets high in fat (35-45% of caloric intake)
  - ↑Caloric requirement: 120-150% RDA

- Pancreatic enzyme supplementation
  - Goals: ↑nutritional status, ↑weight, ↓steatorrhea, ↓abdominal cramping/bloating
  - Chronic malabsorption → chronic conditions
  - Pancreatic micropsheres: lipase, amylase, & protease (enteric coated)
  - Dosing: based on lipase component, weight based
    - < 4 y/o → 1000 U/kg/dose/meal
    - > 4 y/o → 500 U/kg/dose/meal
    - For snacks: use ½ of meal dose
    - Modify dose based on symptoms, individualized to control # of stools and cramping/bloating
  - SE: mouth ulcerations, perianal irritation, severe diaper rash, anaphylaxis, colonic strictures
  - Monitoring
    - ↓Steatorrhea: immediately
    - ↑Weight gain: about 3 days
    - ↑Lipase & amylase concentrations
    - Fecal fat quantification: not routinely done
    - Nutritional assessment: annually

- Vitamin supplementation (ADEK)
  - Older children/adults: up to 2x recommended
  - ADEK or AquADEK: contains all four vitamins (may have problems with bioavailability and cost $)
  - Alternative: standard multivitamins x2
    - ADE: liquid formulations available
    - K: tablet only
  - Individualized dosing based on age