

CYSTIC FIBROSIS – ADVANCED MEDICAL SLIDE NOTES (DETAILED VERSION)

INTRODUCTION

Cystic fibrosis (CF) is a life-limiting autosomal recessive disorder caused by mutations in the CFTR gene, leading to defective epithelial ion transport. The hallmark is dehydrated epithelial secretions, affecting lungs, pancreas, liver, intestine, and reproductive tract.

CORE PATHOLOGICAL PRINCIPLE

The central defect is:

- ↓ Chloride secretion (via CFTR)
- ↑ Sodium absorption (via ENaC upregulation)
- ↓ Water movement into lumen

Result:

Thick, sticky mucus

Impaired mucociliary clearance

Progressive obstruction + infection + inflammation

CFTR PROTEIN – NORMAL PHYSIOLOGY

CFTR is an ATP-regulated chloride channel located on apical epithelial surfaces:

Airways

Pancreatic ducts

Intestine

Sweat glands

Functions:

Chloride secretion

Bicarbonate transport

Regulation of sodium channels

Maintains hydration of mucus layer

SLIDE 4: CFTR MUTATION TYPES

Class I: No protein production

Class II ($\Delta F508$): Misfolding → degradation (most common)

Class III: Gating defect

Class IV: Reduced conductance

Class V: **Reduced synthesis**

Clinical severity correlates with class.

AIRWAY SURFACE LIQUID PATHOLOGY

Normal:

Thin airway surface liquid allows cilia movement

In CF:

Dehydrated mucus layer

Ciliary dysfunction

Mucus stasis → infection trap

This is the starting point of lung destruction.

VISCIOUS CYCLE OF LUNG DAMAGE

1. Mucus plugging

2. Bacterial colonization
3. Neutrophilic inflammation
4. Protease release (elastase)
5. Airway wall destruction
6. Bronchiectasis → Cycle repeats

BRONCHIECTASIS DEVELOPMENT

Structural destruction includes:

Permanent airway dilation

Loss of elastic recoil

Thick purulent secretions

Chronic productive cough

MICROBIOLOGY EVOLUTION IN CF LUNGS

Early:

Staph aureus

Haemophilus influenza

Later:

Pseudomonas aeruginosa (biofilm formation)

Burkholderia cepacia (poor prognosis)

Biofilm protects bacteria from antibiotics.

PSEUDOMONAS ADAPTATION

Pseudomonas in CF:

Converts to mucoid phenotype

Produces alginate

Forms antibiotic-resistant biofilms

INFLAMMATORY MECHANISM

Neutrophil dominance

Release of elastase, oxidants

DNA from dead neutrophils increases mucus viscosities

This worsens obstruction.

PANCREATIC PATHOPHYSIOLOGY

CFTR dysfunction → thick secretions block pancreatic ducts:

Enzyme retention → autodigestion

Progressive fibrosis

Exocrine pancreatic failure

MALABSORPTION MECHANISM

Due to enzyme deficiency:

Fat malabsorption → steatorrhea

Protein malnutrition → muscle wasting

Carbohydrate malabsorption (less severe)

FAT-SOLUBLE VITAMIN DEFICIENCY

Vitamin A → night blindness

Vitamin D → osteopenia

Vitamin E → neuropathy

Vitamin K → bleeding tendency

MECONIUM ILEUS (NEONATES)

Thick meconium obstructs ileum

First clinical sign in 10–20% newborns

Requires contrast enema or surgery

LIVER DISEASE PATHOGENESIS

Thick bile → biliary obstruction

Cholestasis

Portal fibrosis → cirrhosis

SWEAT GLAND ABNORMALITY

CFTR normally reabsorbs chloride in sweat ducts:

CF → failure of chloride reabsorption

→ high sweat chloride concentration

Diagnostic basis of sweat test.

REPRODUCTIVE PATHOLOGY

Male:

Congenital bilateral absence of vas deferens (CBAVD) Female:

Thick cervical mucus → subfertility

RESPIRATORY SYMPTOMS EXPLAINED

Chronic cough → mucus retention

Wheeze → airway obstruction

Dyspnea → reduced gas exchange

Clubbing → chronic hypoxia

DIAGNOSTIC SWEAT TEST PRINCIPLE

Pilocarpine iontophoresis stimulates sweat:

Chloride > 60 mmol/L = diagnostic

GENETIC TESTING VALUE

Confirms CFTR mutation

Guides targeted therapy (CFTR modulators)

Family screening

SPIROMETRY PATTERN

Obstructive lung disease:

↓ FEV1

↓ FEV1/FVC ratio

IMAGING FEATURES

Chest X-ray:

Hyperinflation

Tram-track opacities

CT scan:

Bronchiectasis (gold standard imaging)

AIRWAY CLEARANCE THERAPY RATIONALE

Goal:

Reduce mucus viscosity

Improve clearance Methods:

Chest physiotherapy

PEP devices

Oscillatory vests

DORNASE ALFA MECHANISM

Recombinant DNase:

Breaks down extracellular DNA

Reduces mucus viscosity

HYPERTONIC SALINE

Draws water into airway lumen

Hydrates mucus

Improves mucociliary clearance

ANTIBIOTIC STRATEGY

Acute exacerbations: IV antibiotics

Chronic: inhaled tobramycin

Aim: suppress *Pseudomonas* biofilm

CFTR MODULATORS (ADVANCED THERAPY)

Ivacaftor: potentiator (gating mutations)

Lumacaftor: corrector ($\Delta F508$)

Improves ion transport

PANCREATIC ENZYME REPLACEMENT

Lipase, protease, amylase supplementation

Taken with meals

Improves absorption + weight gain

NUTRITIONAL THERAPY

High-calorie diet (120–150% normal needs)

High protein intake

Salt supplementation (loss via sweat)

CF-RELATED DIABETES

Mechanism:

Pancreatic fibrosis → islet destruction

Mixed insulin deficiency + resistance

PULMONARY COMPLICATIONS

Bronchiectasis

Pneumothorax (ruptured bullae)

Respiratory failure

HEMOPTYSIS MECHANISM

Fragile bronchial vessels

Chronic inflammation

Bronchial artery hypertrophy

LUNG TRANSPLANT INDICATIONS

FEV1 <30%

Recurrent severe infections

End-stage respiratory failure

: PROGNOSIS FACTORS

Improved by:

Early diagnosis

CFTR modulators

Aggressive infection control

Median survival now >40–50 years (developed settings)

SUMMARY CONCEPT

CF is fundamentally:

A disorder of epithelial ion transport

Leading to dehydrated secretions

Resulting in chronic infection, inflammation, and progressive organ failure