Cystic Fibrosis
Cystic Fibrosis:

“Cystic fibrosis is an inherited multisystem disorder of children & adults

Characterized chiefly by obstruction & infection of airway & by maldigestion & its consequences”
Genetics:

It is inherited as an autosomal recessive trait

Gene locus on long arm of chromosome 7

Cystic fibrosis gene codes for a protein of 1,480 amino acids called CF transmembrane regulator (CFTR)

CFTR is expressed on epithelial cells of airway, GIT, sweat glands & genitourinary system

Most prevalent mutation of CFTR is deletion of a single phenylalanine residue at amino acid 508 (508)
Autosomal recessive

Carrier father

Carrier mother

Unaffected son
Carrier daughter
Carrier son
Affected daughter

Unaffected
Affected
Carrier
Pathogenesis:

There are 4 important observations

1- Failure to clear mucous secretions
2- Paucity of water in mucus secretions
3- Elevated salt content of sweat & other serous secretions
4- Chronic infection limited to respiratory tract

Membrane of CF epithelial cells are unable to secrete chloride ions in response to cyclic AMP mediated signals & excessive amount of sodium are absorbed through these membranes
Pathogenesis (cont...) Epithelial Pathophysiology in Airway

There is inability to secret salt & water in presence of excessive reabsorption of salt & water

 Leads to insufficient water on airway surface

This causes desiccated secretions to become Viscous & elastic & are harder to clear

Secretions are Retained & obstruct airway
CFTR: A cAMP-Regulated Chloride Channel

NORMAL

Airway Lumen

Submucosa

Cystic Fibrosis

PROGNOSIS. Overall, prognosis for children with chronic pulmonary abscesses is excellent. The prognosis improves significantly with early and effective treatment.
Pathology:

Lungs:

Bronchiolitis is the earliest lesion
With time inflammation extends to larger airway causing bronchitis
With long standing disease there is bronchiolar obliteration, bronchiolectasis & bronchiectases
Bronchiectatic cysts & emphysematous bullae or subpleural blebs, pneumothorax may occur in advanced lung disease
Tortuous & enlarged bronchial arteries occur leading to hemoptysis
Medial hypertrophy of small pulmonary arteries occur in sec. pulm. HTN
Pathology (cont...)

Lining contains hyperplastic & hypertrophied secretory elements
Polypoid lesions, mucopyocele & erosion of bone may occur
Multiple polyps from base surrounding ostia of maxillary & ethmoidal sinuses

Pancreas:
Small & cystic
In 85-90% pts. Lesion progresses to complete or almost complete disruption of acini
Replacement of acini with fibrosis & fat. Foci of calcification may occur
Pathology (Cont…) 

Intestinal Tract: 

- Minimal changes 
- Esophageal, duodenal glands, crypts of appendix & rectum distended with mucus secretions

Biliary System:

- Focal biliary cirrhosis, causes occasional cases of prolonged neonatal jaundice becomes more prevalent extensive with age 
- Symptomatic multilobular biliary cirrhosis 
- Fatty infiltration of liver in 30% pts 
- Gallbladder may be hypoplastic with secretions & stones 
- Atresia of cystic duct & stenosis of distal common bile duct
Pathology (Cont...)  

Glands of Male & Female Genitourinary system  

Endocervicitis in teenagers & young women  

Body & tail of epididymis, vas deferens & seminal vesicles are abliterated in >95% males  

Generalized amyloidosis rare
Clinical Manifestations:

**Respiratory Tract:**

- **Symptoms**
  - COUGH, most constant symptom, dry & hacking first & later productive
  - Wheezing
  - Shortness of breath
  - Exercise intolerance
  - Failure to gain weight
  - Rhinorrhea
  - Nasal obstruction

- **Signs**
  - Digital clubbing
  - Cyanosis
  - Increased AP diameter of chest
  - Generalized hyper resonance
  - Scattered or localized coarse crackles
  - Expiratory wheeze
  - Acute sinusitis
  - Nasal polyps
Clinical Manifestations

Intestinal Tract:

**Meconium Ileus:**

- In 15-20% newborns with cystic fibrosis
- Abdominal distension, emesis & failure to pass meconium appear within first 24-48 hrs of life
- Meconium peritonitis occurs as a complication

**Meconium Plug Syndrome**

- Less specific than meconium ileus
- Distal intestinal obstruction syndrome or meconium ileus equivalent in ileal obstruction with fecal material occurs in older pts
Clinical Manifestations:

Intestinal Tract:

- **Symptoms**
  - Frequent, bulky, greasy stool
  - Excessive flatus
  - Epigastric pain
  - Acid or bile reflux
  - Failure to gain weight
  - Dementia
  - Peripheral neuropathy
  - Bleeding diathesis
  - Night blindness
  - Rickets

- **Signs**
  - Protuberant abdomen
  - Decreased muscle mass
  - Poor growth
  - Delayed maturation
  - Intussusception
  - Fecal impaction of cecum
  - Subacute appendicitis
  - Periappendiceal abscess
  - Anasarca (In malnourished)
Clinical Manifestations (Cont…)

Biliary Tract:

- Biliary cirrhosis symptomatic in 2-3% pts
- Icterus
- Ascites
- Hematemesis
- Hypersplenism
- Neonatal Hepatitis like picture
- Hepatomegaly
- Biliary colic
Clinical Manifestations (Cont…)

Pancreas

Exocrine pancreatic insufficiency

Hyperglycemia

Glycosuria

Polyuria

Weight loss

Recurrent acute pancreatitis

After 10 yrs of age when 8% acquire diabetes
Clinical Manifestations (Cont…)

Genitourinary system

An average of 2 yrs delay in sexual development

Males

>95% azoospermic
Sexual function unimpaired
Increased incidence of inguinal hernia, hydrocele & undescended testis

Females

Secondary amenorrhea
Cervicitis
Decrease fertility
Good pulmonary function → pregnancy well tolerated
Clinical Manifestations (Cont…)

Sweat Glands

During gastroenteritis & warm weather

Excessive loss of salt in sweat

Hypochloremic alklosis
Diagnosis:

Diagnostic Criteria for Cystic Fibrosis

- Presence of typical clinical features
  - OR
- History of CF in a sibling
  - OR
- Positive newborn screening test
  - PLUS
- Lab evidence for CFTR dysfunction
- Two elevated sweat CL conc, obtained on separate days
  - OR
- Identification of 2 CF mutations
  - OR
- An abnormal nasal potential difference measurement
Diagnosis

**Sweat Testing**

> 60mEq/L of chloride in sweat is diagnostic for CF when one or more other criteria are present

Threshold levels of 40mEq/L have been suggested

Values b/w 40-60mEq/L suggest CF at all ages

**Other Diagnostic Tests**

In pts with equivocal or frankly normal sweat chloride values, following tests are used to confirm diagnosis

- Increased potential difference across nasal epithelium
- Loss of this difference with topical amiloride application
- Absence of a voltage response to a β-adrenergic agonist
- Failure to sweat when a combination of isoproterenol and atropine is injected in skin
Diagnosis

Radiology

Pulmonary

- Hyperinflation of lung
- Bronchial thickening & plugging & ring shadows (sugg. Bronchiectasis)
- Nodular densities, patchy atelactasis, confluent infiltrates
- Prominent hilar lymph nodes
- Depression of diaphragm
- Anterior bowing of sternum
- Narrow cardiac shadow
- Cystic formation, extensive bronchiectasis, dilated pulmonary artery segments, segmental or lobar atelactasis

Paranasal Sinuses

- Pan opacification
- Failure of frontal sinus to develop

Fetal USG

- Ileal obstruction with meconium in 2\textsuperscript{nd} trimester
Diagnosis

Pulmonary Function

Not obtained till 5-6 yrs of age
Residual volume & functional residual capacity are increased (early finding)
Declining total lung capacity & vital capacity (late finding)

Microbiological Studies
Staph aureus, pseudomonas aeruginosa,
B. cepacia
Diagnosis:

Newborn Screening

Immunoreactive trysinogen in blood spots
Confirmatory sweat & DNA testing
95% sensitive

Other Investigations as Indicated

Cardiac: ECG, Echocardiography

GIT: S. proteins, LFTs, coagulation studies, x-ray abdomen, USG abdomen, hepatobiliary Tc-99 Scintigraphy, PTC, ERCP, pancreatic function tests

Other: urea & electrolytes
Treatment

1- Pulmonary therapy

2- Nutritional therapy

3- Treatment of Complications
Pulmonary Treatment:

Antibiotic therapy

Oral Antibiotic Therapy

Indications:
- Presence of respiratory tract symptoms
- Identification of pathogenic organisms in respiratory tract cultures

Organisms
- Staph aureus, H. influenzae,
- P. aeruginosa, Burkholderia cepacia

Duration of therapy
- 2 wks or more
Pulmonary Treatment (Cont…)

Antibiotic Therapy

**Aerosolized Antibiotic Therapy**

- Inhaled tobramycin, 300mg twice daily on alternate months for 6 months
- Ticarcillin, 0.5g, BD OR QID
- Colistin, 20-40mg, BD OR QID

**Intravenous Antibiotic Therapy**

- Indicated in pts. Who have progressive or unrelenting symptoms or signs despite intensive home measures
- Period of treatment is 14 days
- Pseudomonas requires 2 drug therapy
- B. cepacia refractory to antibiotic therapy
### Atimicrobial Agents for CF Lung Infection

<table>
<thead>
<tr>
<th>Route</th>
<th>Organisms</th>
<th>Agents</th>
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<tbody>
<tr>
<td>Oral</td>
<td>Staph. aureus</td>
<td>Dicloxacillin</td>
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<td>Cephalexin</td>
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<td>Clindamycin</td>
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<td>Amoxicillin-clavulanicante</td>
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<td></td>
<td>H. Influenzae</td>
<td>Amoxicillin</td>
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<td></td>
<td>P. Aeruginosa</td>
<td>Ciprofloxacin</td>
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<td></td>
<td>B. Cepacia</td>
<td>Trimethoprim-sulfamethoxazole</td>
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<tr>
<td></td>
<td>Empirical</td>
<td>Azithromycin</td>
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<td></td>
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<td>Erythromycin</td>
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### Pulmonary Treatment (Cont…)

**Atimocrobial Agents for CF Lung Infection**

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<tr>
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<tbody>
<tr>
<td>Intravenous</td>
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<td><em>P. aeruginosa</em></td>
<td>Vancomycin</td>
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<td>Tobramycin</td>
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<td>Amikacin</td>
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<td>Ticarcillin/ calvulanate</td>
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<td>Imipenem</td>
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<td></td>
<td><em>B. cepacia</em></td>
<td>Ceftazidime</td>
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<tr>
<td>Aerosal</td>
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<td>Chloramphenicol</td>
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<td></td>
<td></td>
<td>Tobramycin</td>
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Pulmonary Treatment (Cont…)

Nebulized Treatment

- Bronchodilators
- Distilled water
- Mucolytics
- Antibiotics
- Gromolyn
- Corticosteroids
- Hypertonic 6% saline
- Nebulized amiloride
- Uridine triphosphate
- Antiprotease proteins
- Recombinant alpha 1 antitrypsin
- Recombinant human secretory leukoprotease inhibitor
Pulmonary Treatment (Cont…)

**Bronchodilator Treatment**
- Inhaled B2 agonists
- Anticholinergics
- Oral theophylline

**Anti Inflammatory Treatment**
- Long term use of oral corticosteroids & ibuprofen

**Mucolytic Treatment: Dornase Alpha (Recombinant Human Deoxyribonuclease 1)**
- Cleaves extracellular DNA & decreases viscoelasticity of purulent secretions
- Used in chronic suppurative disease or obstructive disease
- Dose: 2.5 mg OD
Pulmonary Treatment (Cont…)

Chest Physical Therapy
10-20 min
One to 4 time a day
Routine aerobic exercises

Endoscopy & Lavage
Tracheobronchial suctioning or lavage

Expectorants
Lodides
Guaiphenesin
Postural drainage is a technique for loosening mucus in the airway so that it may be coughed out.

Tapping is performed in certain areas with the patient in different positions.
Nutritional Therapy

90% pts have complete loss of exocrine pancreatic function & inadequate digestion of fats & proteins.

Diet

CF pts require 120% of normal energy requirement.

Liberal diet containing:
- Fats
- Sugar
- Salt
- Milk products
- Protein foods

Advanced lung disease → NG tube or gastrostomy.
Nutritional Therapy (Cont...)

Pancreatic Enzyme Replacement

Fat absorption improvements from 60% without therapy to 85-90% with therapy
An upper limit of 10,000 units lipase/kg/day
PERT for infants ----- 500-1000 units lipase per gram of dietary fat
PERT for children ---- 500-4000 units lipase per gram of dietary fat
Thank You