

General

- Most common lethal genetic disease among Caucasians, aut rec, 1/1500 (incidence), 1/20 (carrier rate)
- 90% diagnosed in childhood after recurrent respiratory illnesses, failure to thrive, and steatorrhea (18% within the first 24 hours of life because of meconium ileus)
- 10% diagnosed after 10yo w/ infertility, diabetes mellitus
- Improvements in treatment now brings median survival age to 32 for males and 29 for females

Molecular Biology

- AR mutation of the **CF Transmembrane conductance Regulator (CFTR)** a protein (Chr 7q31) which regulates a Cl^- channel which in turn regulates other ion channels thus affecting all exocrine processes
- The thing to remember is that the CFTR protein regulates sometimes opposite functions in different epithelium

*Physiology***Sweat Glands:**

↓ Cl^- resorption → ↓ Na^+ resorption → hypertonic sweat

Airway, Distal GI:

↓ Cl^- secretion → ↑ Na^+ resorption → ↑ H_2O resorption → obstruction by inspissated mucus

Liver, Gallbladder, Salivary Glands, Pancreas, Proximal GI, Mesonephric Tubules:

↓ Cl^- resorption → ↓ HCO_3^- and Na^+ secretion → ↓ H_2O secretion → obstruction by inspissated mucus

N.B. recent studies suggest that there also exist abnormalities in fatty acid metabolism resulting in increases in arachidonic acid and thus the formation of inflammatory prostaglandins and leukotrienes (omega-3-FA treatment?)

Diagnosis

- **Cl- Sweat Test:**
 - pilocarpine (muscarinic agonist) stimulates sweat glands
 - Normal Pts: $[\text{Cl}^-] < 40 \text{ mEq/L}$ vs CF Pts: $[\text{Cl}^-] > 60 \text{ mEq/L}$ (child) adult $> 70 \text{ mEq/L}$ (adult)
 - High sensitivity but highly dependent on operator
 - Mod specificity (false +: nephrogenic DI, myxedema, mucopolysaccharidosis, adrenal insufficiency, hypoTH, ectodermal dysplasia, anorexia nervosa)
- **Molecular Analysis**
 - over 1200 mutations exist
 - 70% of patients have the primary mutation (loss of a phenylalanine residue at 508 (ΔF_{508}))
 - 90% of patients have 1/25 mutations that are picked up by most screens
 - because 10% of CF pts have 1 of 1175 mutations, therefore analysis is not entirely sensitive
 - molecular analysis is performed under the following situations:
 - (1) inadequate amounts of sweat for analysis
 - (2) sweat test results are borderline or equivocal
 - (3) sweat test does not correlate with clinical symptoms
 - (4) you are suspecting CF b/c of FHx or in utero because of dilated loops of bowel suggesting meconium ileus
- **IRT Newborn Screening**
 - CF infants have increased Immuno Reactive Trypsin (IRT)
 - not sensitive after 8wks
 - early diagnosis is important because studies have shown that nutritional intervention improves neurologic outcome
 - screening varies from state to state (Texas does not screen)

New Tx

- Steroids (given during exacerbation b/c it is found that inflammation plays a very big role not just infection)
- Correctors (meds that increase trafficking of CFTR to membranes)
- Potentiators (meds that increase function of CFTR already on membranes)

*Pathology*Pulmonary

- Pathology
 - Paradigm
 - Obstructive Pattern 2/2 Inspissation → Multiple Infections → Restrictive Pattern 2/2 Repetitive Inflammation
 - URT: sinusitis leading to nasal obstruction, rhinorrhea, and very commonly nasal polyps
 - LRT: first symptom is a cough (obstructive pattern) that with time becomes persistent, paroxysmal, and productive (viscous-green sputum) but after a while bronchiectasis, clubbing, hemoptysis, cor pulmonale, resp failure develop (restrictive pattern)
- Infections

- Common Early Infections
 - ***Staphylococcus aureus* (usually MRSA)**
 - ***Hemophilus influenza***
- Common Later Infections:
 - ***Burkholderia cepacia***
 - very dangerous b/c highly resistant, fast decline, contagious
 - stay away from soil!!!!
 - ***Pseudomonas aeruginosa***
 - Why is *P. aeruginosa* so common in CF patients?
 - normal CFTR serves as a presenter of the LPS of *P. aeruginosa* for the immune system
 - inspissated mucus has a low oxygen content, this hypoxia in turn induces phenotypic changes particularly the production of alginate and loss of motility giving the bacteria a "mucoid appearance" allowing it live in mucus for years causing reinfection and gaining resistance and also protects bacteria from antibiotics
 - Once CF patients have been infected with either BC or PA the organisms usually persist despite most aggressive treatments.
 - Others: *Proteus* spp., *E. coli*, *Klebsiella* spp., *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Mycobacterium* spp. (usually in adults and usually non-TB species), *Aspergillus fumigatus* (50% of pts with 10% exhibiting Allergic Bronchopulmonary Aspergillosis treat with itraconazole)
- PFTs (obstructive and restrictive pattern)
 - ↑ RV:TLC and ↓ FEV at 35-75% is the most sensitive measure of obstruction
 - reversible (increase in secretions) and irreversible (destruction of wall) changes in FEV1 and FVC
 - FEV1 inversely proportional with survival therefore when FEV1 drops below 30% transplant is indicated
- CXR
 - 1st hyperinflation with flattened diaphragm and loss of retrosternal space reflecting small airway destruction (creates a barrel-shaped chest on PEx)
 - 2nd interstitial markings (usually the right upper lobe displays the earliest and most severe findings)
 - 3rd bronchiectasis (manifesting as peribronchial cuffing and "tram track" appearance of bronchi) and cysts (sometimes resulting in pneumothorax)
 - 4th kyphosis
- Treatment
 - Home Breathing/Aerobic Exercises
 - Chest Percussion Treatment (CPT) handheld vibrators or vibrating vests which physically promote mucus clearance
 - Flutter Valve (FV) which resonate down airways promoting mucus clearance
 - Postural Drainage (PD)
 - Hypertonic Saline Aerosols augment mucus clearance
 - Antibiotics
 - *Pseudomonas*
 - Treatment: aminoglycoside (primarily TOBI = inhalational tobramycin) + antipseudomonal penicillins (Ticarcillin/Pipercillin) or 3rd cephalosporins (ceftazidime/cefepime) or carbapenems
 - Pseudomonal infections require TWO drugs with different mechanisms of action
 - NB because patients take aminoglycosides over long periods of time there is actually a significant risk of nephrotoxicity and ototoxicity
 - current antibiotics are being developed which interfere with biofilm production
 - Prophylaxis: oral Cipro for 10days every 3months or inhalational TOBI for 2days with 28days off
 - Other Bugs
 - Columbia University Lab has extensive information on antibiotic synergy for multidrug-resistant organisms isolated from CF patients (<http://cpmcnet.columbia.edu/dept/synergy>)
 - antibiotic treatment is difficult because poor penetration, resistance, defects mucosal defenses
 - do routine sputum culture and resistance profiles yearly to identify chronic bugs, this can be used for immediate treatment of acute exacerbations without waiting for culture results
 - new antibiotics called desmins appear to be very effective in CF patients
 - Recombinant Human DNase (Dornase Alpha Nebulizer) degrades concentrated DNA in CF sputum thereby decreasing sputum viscosity
 - Curcumin (constituent of the spice turmeric) appears to improve chloride channel function by increasing levels in the ER
 - Inhaled beta-Adrenergic Agonists and Anticholinergics are only good for a short-term increase in airflow, long-term benefit has not been shown
 - Hypertonic Saline Inhalation (pulls water out of membrane onto surface)
 - There is evidence that super high doses of Ibuprofen is helpful
 - Oral/INH Glucocorticoids appear to be not that effective
 - Transplant
 - A good of thumb is that if FEV1 drops below 30 % than transplant is indicated
 - 2-year survival exceeds 60% with death usually resulting from graft rejection often involving obliterative bronchiolitis

- the big problem is that the sinuses and proximal airways of transplant patients still remain a reservoir for bacteria nevertheless only *B. cepacia* species are considered contraindications for transplantation (multidrug resistant *P. aeruginosa* is not considered a contraindication)
- United Network for Organ Sharing (UNOS) changed the method of how they allocate cadaveric lungs; rather than based on time on waiting list (as done in past) allocation is based on predictors of mortality (age, FEV1, gender, weight, other complications of CF, other infections)
- Gene Therapy
 - using vectors to introduce normal CFTR genes into cells
 - studies suggest that genetic correction of as few as 10% of cells can bring the electrophysiologic properties of cells back to normal
 - the biggest feat is finding out an effective way of introducing the plasmid into the cell

Genitourinary System (95% Male and 20% Female)

- **Delayed puberty** due to poor nutrition to support endocrine function (this is primary problem in females)
- **Infertility** due to anatomical anomalies (this is the primary problem in males)
 - Male: congenital bilateral agenesis or obstruction of vas deferens
 - Females: obstruction of fallopian tube and thick cervical secretions

Musculoskeletal System

- **Low Bone Mineralization**
- **Hypertrophic Osteoarthropathy** abnormal proliferation of skin/bone at distal extremities
- **Arthropathy** pain and swelling with occasional nodules and papules

Other

- **Hyponatremia**
- **Hypochloremic Metabolic Alkalosis**



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