Objectives

- Cystic Fibrosis (CF) is a fatal genetic disorder that affects many organ systems in the body.
- As the surviving population of people with CF increases so do the chances of encountering patients with CF in our anesthetic practice.

Objectives Continued

- An understanding of the pathophysiology of the disease as well as anesthetic implications and management is crucial to the safe administration of anesthesia in this population.

What is Cystic Fibrosis?

- Cystic fibrosis (CF) is an inherited autosomal recessive disease that causes thick, sticky mucus to build up in the lungs and digestive tract.
- It is one of the most common type of chronic lung diseases in children and young adults, and may result in early death.

Understanding CF

- To understand Cystic Fibrosis, it is important to know normal physiology.
- As will be discussed, Cystic Fibrosis is a disease that affects the body's homeostasis mechanisms at the cellular level, as well as physical and emotional.
The Second Messenger

- Hormones bind in the body to a cell membrane receptor
- This “binding” triggers a response which results in the activation of an enzyme system
- This enzyme system generates intracellular signals referred to as “second messengers”

The Most Famous 2nd Messenger

- Second messengers serve to greatly amplify the strength of the signal
- There are many different “second messenger” systems in the human body
- The most widely described second messenger system is the cyclic adenosine monophosphate (cAMP) system

Cyclic AMP

- Initiated when receptor occupation activates the plasma enzyme adenyl cyclase
- Adenyl cyclase will then catalyze the intracellular conversion of adenosine triphosphate (ATP) to cAMP
- cAMP becoming the second messenger, activates other intracellular enzymes, which in turn modify cell membrane permeability

So Why Is This Important?

So Why Is This Important?

- The Most Famous 2nd Messenger

CFTR

- Cystic Fibrosis Transmembrane Conductance Regulator or CFTR is a cyclic AMP dependent protein kinase regulated Cl- channel, located in the membranes of epithelial cells
- CF is characterized by abnormal ion transport across epithelial cells of the exocrine glands caused by mutations in the CFTR

Healthy CFTR

Healthy CFTR

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(Marcet, et al. 2004)
What is Cystic Fibrosis?

- Since CF results from an autosomal recessive gene mutation of the CFTR, both parents must have the trait in order for the child to have it.

- Incidence is 1:4

CF Timeline

- 1938 – The year that CF was recognized as existing.
  - Dorothy Hansine Anderson wrote about cystic fibrosis of the pancreas, and hypothesized that the lungs were involved as well. She wrote papers on the subject, and even speculated that the disease was recessive.

CF Timeline...

- 1943 – While cystic fibrosis was gaining recognition in 1938, it was not until 1943 that it was considered a legitimate disease.
1953 – Changes in sweat were noticed in CF patients by Paul di Sant’Agnese. From that point on until 1962, a sweat test was developed and perfected. The test measured the sweat electrolytes in a patient’s body to see if they were affected by CF or not.

1988 – The first mutation that causes CF was found at the Hospital for Sick Children located in Toronto.
Since that first mutation, there have been more than a thousand other mutations that have been found that are known causes of CF.

1989 – The same team that found the mutation in 1988 found the gene that was directly responsible for cystic fibrosis.

Present day– Genetic research is currently underway in attempt to prevent the transmission of CF.

Prevalence of CF
- Cystic fibrosis occurs in one out of every 15,000 African-American births.
- An estimated 1 in 29 or 3% of Caucasian Americans have the CF gene.

| Table 1. Incidence of cystic fibrosis in various American populations* |
|-----------------------------|------------------|
| Group                      | Incidence        |
| White                      | 1 in 3,300       |
| Hispanic                   | 1 in 8,500       |
| African American           | 1 in 15,900      |
| Asian American             | 1 in 32,100      |
| Native American            | 1 in 3,970 (Pueblo) |
|                            | 1 in 1,580 (Zuni) |

*Adapted from National Institutes of Health.
According to the most recent US Census Data there are 307,006,550 current legal US citizens. Of these, 79.8% are Caucasian or roughly 245,605,240. Of these, roughly 7,368,157 people have the CFTR gene. Andrew Simmons, a professional wrestler with CF.

The disease is the most common, deadly, inherited disorder affecting Caucasians in the United States. It's more common among those of Northern or Central European descent. (Wiehe & Arndt, 2010)

It is estimated that CF affects 30,000 adults and children in the United States, with approximately 1,000 new cases diagnosed each year. Frankie Abernathy from MTV’s Real World San Diego 2004, died at age 25 r/t CF complications.

Cystic fibrosis is a serious genetic disorder with reduced life expectancy. The life expectancy of cystic fibrosis patients has been increasing over the past 40 years. In the 1980s life expectancy of people with cystic fibrosis was 14 years. The median age of survival for cystic fibrosis is now over 37. (Wiehe & Arndt, 2010)

CF can be detected in children even before they are born. Newborn screening tests also make it possible to diagnose cystic fibrosis in babies shortly after they were born. The sweat test is also used, since people who have the disease tend to have a higher salt content in their sweat.

The Sweat Test is considered to be the gold standard for the diagnosis of CF. Sweat glands on the forearm are stimulated by using prilocarpine. Sweat is collected and analyzed for high Chloride concentrations (>60 mmol/L).
Diagnostic Statistics

- 80% of patients are diagnosed by the age of three
- 10% of patients are diagnosed at the age of 18
- 3% patients are diagnosed in adulthood

Systems Affected...

- Only 10% to 15% of babies have symptoms at birth
- People with cystic fibrosis have exocrine glands that produce an excess of mucus in their lungs, liver, intestines and pancreas.
- Because their mucus is so thick, it can be a thriving breeding ground for bacteria in their lungs, which can lead to infections as well as a weakened immune system.

CF Effects

- Since their pancreas is also affected, children with this condition experience poor growth rates, even malnutrition.
- Their pancreas is incapable of providing enough enzymes to help the body absorb nutrients, particularly the fat-soluble vitamins.
- This results nutrient deficiencies, and thus, poor growth

Symptoms in General

- There are more than 1,000 mutations of the CF gene, symptoms differ from person to person
- They include:
  - Belly pain from severe constipation
  - Coughing or increased mucus in the sinuses or lungs
  - Delayed growth
  - Fatigue
Childhood Symptoms
- Infants may have salty-tasting skin
- No bowel movements in first 24 to 48 hours of life
- Stools are pale or clay colored, foul smelling, or that float
- Recurrent respiratory infections such as pneumonia or sinusitis
- Weight loss, or failure to gain weight normally in childhood

ENT Considerations
- URI are often common
- Chronic Sinusitis and nasal polyps often require corticosteroid treatment
- Purulent nasal discharge is common, even when healthy

Pulmonary Symptoms
- Pulmonary system is most typically affected with this causing >90% of morbidity
- Viscous secretions and abnormal mucociliary clearance
- Airway obstruction and chronic pulmonary infections
- Chronic hypoxemia and cor pulmonale

CF Effects on the Respiratory System
Mucus
- Large amounts of mucus buildup in the lungs if somebody is suffering from cystic fibrosis.
- Phlegm production will increase at alarming rates and this can cause inflammation of the lungs which could possibly lead to infection.
- The inflammation and infection may actually lead to negative changes within the lungs themselves, making it difficult for the patient to breathe at times.
- Patients often cough very frequently and may have difficulty with ADLs.

Polyps
- When a sufferer of CF is experiencing chronic sinus infections, it can cause the skin inside the nasal cavities to grow uncontrollably.
- These growths are called polyps, and they can actually block the nasal cavity, causing further obstruction and even more difficulty breathing.
CF Effects on the Respiratory System

Pneumonia –
- When bacteria filled mucus starts filling the lungs, pneumonia can develop.
- This development will cause a fever, difficulty breathing, and chest pain, adding to the previous systems.
- All of these symptoms together will generate severe discomfort and pain for sufferers of cystic fibrosis.

Bronchiectasis-
- Abnormally dilated and thick walled bronchi that are chronically inflamed and infected.
- Occurs after sustained inflammatory injury, causing structural damage with loss of elasticity, muscle integrity, and cartilage.

Hemoptysis-
- Happens during cystic fibrosis when the mucus has been causing inflammation for a long period to the point where it makes the patient start to cough up blood.

Pulmonary hypertension-
- When this occurs in cystic fibrosis patients, there is a chance that heart failure may occur in the future.

V/Q mismatch-
- Common due to chronic obstruction.
- Decreased arterial oxygen tension and normal or elevated carbon dioxide tension usually leads to respiratory acidosis

Hyperactive Airway-
- R/t thick secretions, chronic inflammation, and bronchitis

Respiratory failure –
- After infection, inflammation, bleeding, and hypertension, the lungs can have difficulty operating normally.
- Cystic fibrosis patients that experience respiratory failure will have to be assisted when breathing, usually with an oxygen tank and breathing mask.
An early diagnosis of CF and a comprehensive treatment plan can improve both survival and quality of life.

Lisa Bentley, tri-athlete with CF

Respiratory Treatment

- Treatment for lung problems includes:
  - Antibiotics to prevent and treat lung and sinus infections
  - Inhaled medicines to help open the airways
  - DNAse enzyme replacement therapy to thin mucus and make it easier to cough up
  - Lung transplant in some cases

Preop Anesthetic Management of Pulmonary Complications

- Check Baseline RA sat
- Check for Sputum culture and sensitivity
- Cancel elective cases in presence of URI
- Check baseline Abg, chest-xray, and pulmonary function tests (helps to determine progress of disease)
- Check preop med list-is patient on steroid?
**Preop Anesthetic Management of Pulmonary Complications**
- Respiratory depression should be minimized, consider low dose preop sedative to no preop sedative
  - Pre-treat with bronchodilators
  - Chest PT and Drainage

**Anesthetic Management of Pulmonary Complications**
- Pt's have increased airway hyperreactivity leading to increased chances of bronchospasm.
- Avoid histamine releasing drugs (MS04, STP)
- Pretreat prior to intubation with LTA
- Avoid use of Des
- Pretreat prior to extubation with Albuterol inhaler

**Intraop Management**
- Positive pressure ventilation may be detrimental as it can suppress cough and airway reflexes
- Maintain spontaneous breathing if possible
- Humidified O2 along with aggressive suctioning, esp. prior to extubation
- Avoid Nitrous d/t potential for rupture of bullae and pneumothorax (esp. in lung/thoracic surgery)

**Potential Pulmonary Complications**
- Hemotypsis (believed to be a result of bronchiectasis)
- Pneumothorax
- Bronchospasm
**Maintenance Therapy**
- Chest physical therapy
- Bronchodilators
  - Aerosolized
  - Oral

**Cardiovascular Considerations**
- Cardiac involvement is usually secondary to chronic pulmonary infections, hypoxemia, and destruction of lung parenchyma. (Wiehe & Arndt, 2010)
  - Pulmonary htn second to bronchiectasis can lead to cor pulmonale
  - Advanced diseases require preop EKG and possible cardiac clearance

**Cardiovascular Management**
- Atropine may be ineffective in patients with autonomic neuropathy
- Early treatment of Bradycardia with Epinephrine has been successful in preventing further complications
  
  (Wiehe & Arndt, 2010)

**GI Manifestations**
- GI manifestations include malabsorption, which leads to deficiency in fat-soluble vitamins (K,A,D,E)
  - Reduced levels of factor II, VII, IX, X.
  - Increased risk for DM.

**Pancreatic Considerations**
- Inability of the pancreas to secrete NaHCO3 and H2O lead to thick secretions which block the pancreatic ducts
- Because of this pancreatic enzymes are continually secreted and eventually destroy pancreatic tissue
- Diabetes can result from pancreas destruction

**Pancreatic Complications**
- Steatorrhea clinical sign of malabsorption secondary to pancreatic insufficiency.
- Advanced cases may require insertion of enteral feeding tubes
- Malnourished patients are more prone to heat loss resulting in increased oxygen consumption
- Significant GERD is often present
Non-CF Pancreas Cells
- PANCREAS CELLS OF CF PATIENT

Hepatic Considerations
- Subject to defective salt and water secretion
- Cholelithiasis contributes to liver damage
- Fatty liver is witnessed in up to 60% of all CF patients
- Synthesis of Vitamin K dependent factors are impeded

GI Treatment
- Treatment for intestinal and nutritional problems may include:
  - A special diet to help with nutrition
  - Pancreatic enzymes to replace those that are missing
  - Vitamin supplements, especially vitamins A, D, E, and K

Nutrition
- People with Cystic Fibrosis need to make sure they have an adequate intake of certain nutrients.
  These include:
  - Iron
    - Iron is essential for carrying oxygen to all the body’s cells. Found in some cereals, meats, dried fruits, and dark green vegetables.
**Nutrients**

- **Zinc**
  - Zinc is important for growth, healing, and staying healthy. Found in meats, liver, eggs, and seafood.

- **Calcium**
  - Calcium helps build strong bones. Milk, yogurt, cheese, and calcium-fortified juices are rich in calcium.

**Nutrients continued**

- **Salt**
  - Patients with CF lose a lot of salt in their sweat, especially during hot weather and when they exercise.
  - A good way to replace this salt is by adding salt to food and eating salty snacks.

**Nutritional Guidelines**

- Weight loss is common in CF patients
- Check body weight and admission and every 3-5 days daily to guide nutrition.

**Nutritional Guidelines**

- Diabetes:
  - If diabetes is present, it is managed with oral hypoglycemics or insulin and not by caloric restriction
  - Pancreatic enzyme replacement
  - Vitamin supplementation (K, A, D, E)
  - GERD and gastric hyperacidity*

**Genitourinary Considerations**

- Kidneys not primarily affected by CF
- Nephrotic syndrome and diabetic neuropathy have been reported in a small amount of patients with CF

**Neurological Considerations**

- In theory hypoxia, hypercarbia, and encephalopathy d/t liver involvement can alter neuro status.
- Not typically seen in CF patients

Albert Einstein, is now considered by many to have had a mild form of CF
**Musculoskeletal Considerations**

- Pts with CF may develop:
  - Osteopenia
  - Osteoporosis
  - Arthropathies

- Bone disease is often linked to malnutrition

**Musculoskeletal Considerations**

- Other associated conditions include
  - Rheumatoid Arthritis
  - Amyloidosis
  - Drug-induced arthritis

- Avoiding muscle relaxants, or using low doses of short acting relaxants is crucial.

**Reproductive Considerations**

- Late onset of puberty
- 95-99% rate of infertility in males
- 20% rate of infertility in females
- Current research suggests that approximately 4% of CF become pregnant each year

**The Pregnant Pti with CF**

- Pregnancy can worsen cystic fibrosis symptoms, and is regarded and always managed as high risk.

- It is therefore imperative that a careful eye is kept on the pregnant woman through the course of the pregnancy.

**The Pregnant Pti with CF**

- As long as mom’s FEV one is at least 70%, pregnancy should be well tolerated

- Coag studies must be performed prior to epidural placement/C-section

- Faster than usual oxygen desaturation during induction of anesthesia

**The Pregnant Pti with CF**

- Prostaglandin E - which is the most popular induction agent - is safe to use in cystic fibrosis sufferers.

- Oxytocin (Syntocinon) is also used, when necessary, to augment labor.
**Pseudomonas aeruginosa**

- Most people with cystic fibrosis are likely to develop *Pseudomonas aeruginosa* infections by the time they are teenagers.

- Between the ages of 6 and 10, about 40% of patients with cystic fibrosis have *Pseudomonas aeruginosa* infections.

- By the age of 17, nearly 60% of people with cystic fibrosis have *Pseudomonas aeruginosa* infections in their lungs.

- Up to 80% of adults with cystic fibrosis between the ages of 25 and 34 have *Pseudomonas aeruginosa* infections.

Infections may lead to inflammation that causes:

- Increased cough
- Shortness of breath
- Tightness in the chest

This inflammation can damage the airways.
Laboratory Evaluation

- Initial:
  - Hemogram, urinalysis and chemistry panel should include electrolytes, creatinine, screening for liver disease, diabetes (random blood sugar >110 g/dL), malabsorption (albumin, pro-time, vitamin A and vitamin E levels).
  - Amylase and lipase may be appropriate in the setting of abdominal discomfort.

- Serial:
  - Creatinine is monitored approximately every 3 days if receiving aminoglycosides.
  - CBC is repeated if the initial hemoglobin suggests anemia (Hbg <10 g/dL) or the admitting WBC showed neutropenia.

ABG’s

- Arterial blood gases:
  - Obtain ABGs when the O2 saturation on room air is < 93%, the serum HCO3 is elevated, the patient is severely ill, complains of morning headaches or if there is evidence of cor pulmonale.

Yearly Tests

- AFB culture should be requested at least once/year
- Sputum culture and sensitivities should be obtained on each admission unless obtained within the previous week.

Cultures

- Sinus cultures should be obtained if there is evidence of sinusitis by clinical examination or sinus CT scan
- Sputum for fungal stain and culture.
- Blood cultures are usually not indicated except for patients with high fevers, sepsis syndrome or suspected indwelling catheter infection.

Maintenance Therapy

- Antibiotics
  - Oral
  - Inhalational
  - Intravenous
- Anti-inflammatory agents
  - Corticosteroids
  - Ibuprofen
**Antibiotics in CF**

1. To treat sinopulmonary exacerbations of cystic fibrosis
2. To prevent exacerbations due to increased density of bacteria particularly *pseudomonas*
3. To sterilize the airway after an initial infection by *pseudomonas*.

**Final antibiotics decisions should derive from a culture obtained no more that 7 days before hospitalization.**

*Pseudomonas* is generally treated with two drugs of different classes.

**FYI**

- *S. aureus* and other bacteria more typical of community acquired respiratory pathogens are generally treated with single agents.

**Commonly Used Antibiotics in CF**

- Tobramycin 10 mg/kg IV q24h plus
  - Ceftazidime 50 mg/kg IV q8 h or
  - Cefepime 50 mg/kg IV q8 h or
  - Piperacillin/tazobactam 100 mg/kg/piperacillin IV q6 or i.e. 50 kg patient Zosyn 5.625g IV Q6h
  - Imipenem 20 mg/kg/dose IV q6 h

**Other Antibiotics Used**

- If anaphylaxis to β-lactams:
  - Aztreonam 50 mg/kg IV q6h

- Possible alternative to tobramycin:
  - Ciprofloxacin 400 mg IV q8h or 750 mg PO BID [not weight based]
65 Roses

- 65 Roses is what some children with cystic fibrosis call their disease because the words are much easier for them to pronounce.
- It is also another name for the Cystic Fibrosis Foundation.
- Please visit their website at http://www.cysticfibrosis.org

References