Cystic Fibrosis—What’s New for the Anesthesiologist?

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Objectives
- Describe the changing epidemiology for patients with cystic fibrosis.
- Review the pathophysiologic changes associated with cystic fibrosis.
- Discuss the vital components of the preoperative evaluation for patients with cystic fibrosis.

Diagnosis by Clinical Triad
- Elevated Sweat Chloride
- Pancreatic Insufficiency
- Chronic Pulmonary Disease
  Diagnosis by Mutation Analysis
  - F508del
  - Class 1-3 pancreatic insufficiency
  - Class 4-5 pancreatic sufficiency

Diagnosis by Sweat Test
- Sweat Test
  - Pilocarpine iontophoresis
  - >60 meq/L chloride
  - Inaccurate in first month of life
- Other causes of elevated sweat chloride
  - Untreated hypothyroidism
  - Glycogen storage disease
  - Addison’s disease
  - Ectodermal dysplasia

Atypical CF Diagnosis
- Often occurs in adolescence
- PMH in retrospect of CF-like symptoms
- Lung, sinus, liver, male infertility
  Diagnosis by Mutation Analysis
  - One identifiable mutation plus intron modifier
  - Frequently Class 4-5 pancreatic sufficiency
CF is one of the most common lethal autosomal recessive inherited disorders. Chronic obstructive pulmonary disease, Pancreatic exocrine insufficiency, Elevated sweat electrolytes.

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

- **Primary Function**
  - Chloride Channel

- **Secondary Function**
  - Regulates ENaC, the sodium channel

### Genetics
- 1:2-4000 Caucasians, carrier rate 1:28
- 1:9200 Hispanics
- 1:15,000 African Americans, carrier rate 1:60
- 1:31,000 Asians
- Gene is on chromosome 7, CFTR, most common mutation is ΔF508
- cAMP-regulated chloride channel, a nucleotide transporter, ion channel regulator

### Clinical Manifestations of CF
- **Respiratory**
  - Chronic cough and bronchitis
  - Bronchiectasis
  - Recurrent pneumonia (staph aureus, *Pseudomonas aeruginosa*)
  - Chronic sinusitis, nasal polyps
  - Hemoptysis, pneumothorax
  - Chronic airways obstruction, irreversible
Controlling Pseudomonas Aeruginosa Infection: Lessons learned from the Cystic Fibrosis Patient

Disorders affecting the airways with similar characteristics to CF or infections with Pseudomonas Aeruginosa

- Pan-bronchiolitis
- Chronic bronchitis
- Idiopathic bronchiectasis
- IgA, IgG, IgG subclass deficiencies
- COPD
- Patients with tracheostomy tubes

Progressive Lung Disease in Patients With Cystic Fibrosis

- Chronic cough
- Sputum production
- Wheezing
- Obstructive lung disease
- Persistent radiographic abnormalities
  - Hyperinflation
  - Atelectasis
  - Bronchiectasis
- Chronic infection with bacterial (and other) opportunistic pathogens

Respiratory Infections in Cystic Fibrosis Patients

<table>
<thead>
<tr>
<th>Infection With Pseudomonas aeruginosa and Progression of CF Lung Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td>Time</td>
</tr>
</tbody>
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Anti-infective Therapy for P. aeruginosa

<table>
<thead>
<tr>
<th>Oral</th>
<th>Aerosolized</th>
<th>Parenteral</th>
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<tr>
<td>Ciprofloxacin</td>
<td>Tobramycin</td>
<td>β-lactam Related</td>
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<td>Levofloxacin</td>
<td>Colistin</td>
<td>Ticarcillin-Clavulanate</td>
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<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>Aztreonam lysine**</td>
<td>Ceftazidime</td>
</tr>
<tr>
<td>Azithromycin*</td>
<td>Other parenteral antibiotics</td>
<td>Piperacillin/Tazobactam</td>
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<tr>
<td></td>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem</td>
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<tr>
<td></td>
<td></td>
<td>Aztreonam arginine</td>
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<tr>
<td></td>
<td></td>
<td>Cefepime</td>
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Prevalence of MRSA in Cystic Fibrosis

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<thead>
<tr>
<th>Year</th>
<th>Prevalence</th>
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<tr>
<td>1996</td>
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<tr>
<td>1999</td>
<td>11.8</td>
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<tr>
<td>2003</td>
<td>14.6</td>
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<tr>
<td>2004</td>
<td>17.2</td>
</tr>
<tr>
<td>2005</td>
<td>18.9</td>
</tr>
<tr>
<td>2006</td>
<td>21.2</td>
</tr>
<tr>
<td>2007</td>
<td>22.6</td>
</tr>
<tr>
<td>2008</td>
<td>23.7</td>
</tr>
<tr>
<td>2009</td>
<td>25.7</td>
</tr>
<tr>
<td>2010</td>
<td>25.9</td>
</tr>
</tbody>
</table>

Airway Clearance Techniques

Active Techniques
- Forced expiratory technique (“huff maneuver”)
- Autogenic drainage
- Positive expiratory pressure mask
- Oral airway oscillators

Passive Techniques
- High-frequency chest wall oscillator (“vest”)
- Intrapulmonary percussor ventilator

Progression of CF lung infections
- Bacterial endobronchial colonization
- Intense inflammatory reaction
- Obstructive lung disease with superimposed pulmonary exacerbations
  - Increased cough, sputum, dyspnea, declining PFTs
  - Weight loss, fatigue, rarely fever
- Intermittent courses of antibiotics
  - Oral, inhaled, intravenous
  - Airway clearance, bronchodilators, anti-inflammatories

CF Gastrointestinal Disease
- Meconium ileus, meconium peritonitis
- Small bowel atresia
- DIOS, intussusception
- Pancreatic insufficiency, malabsorption
- Hepatic cirrhosis, portal hypertension,
- Neonatal direct hyperbilirubinemia,
- Gall bladder obstruction
- Rectal prolapse
- Edema, hypoalbuminemia, hypovitaminosis A,K,E

Pancreatic Disease
- Reduced volumes and bicarbonate content of pancreatic fluid
- If residual pancreatic function, prone to recurrent pancreatitis
- CF-related diabetes
  - 3% of children, 7% of age 11-17
  - 14% of adults
  - Blockage of islets leads to reduction of both insulin and glucagon, so ketoadidosis is rare
  - Stresses like pregnancy, corticosteroids, pulmonary exacerbation, can trigger hyperglycemia requiring therapy

Hepatobiliary Disease
- Eosinophilic concretions in bile ducts
- High incidence of gall bladder disease, gall stones, microgallbladder
- Cirrhosis
  - 3%
  - Portal hypertension, splenomegaly, esophageal varices
**Effects of General Anesthesia on Pulmonary Function and Clinical Status in Children with CF**

- Common surgical procedures in CF
  - Bronchoscopy with lavage (surveillance and clinical indications), nasal polypectomy, venous access procedures
  - Additional indications: thoracoscopy, FESS, lung/liver TX, intraoperative GPT*
- Assessment of lung function key to predicting morbidity
  - Mid 1980’s, 4.5% perioperative mortality
  - Older studies used anesthetics that affected postoperative lung function
  - Australian study 2013—use of LMA, use of anesthetics with bronchodilator properties (sevofluorane, propofolon spirometry 24 hrs post procedure)*

**Pandit et al, Pediatric Anesthesia 24 (2014) 164-169

**Preoperative Evaluation of the Patient with Cystic Fibrosis**

- Parental assessment of presence of acute illness, malaise, dyspnea, weight loss, fever, increased sputum, night cough, diabetes
- Physical Exam: presence of wheezing
- Oropharyngeal or sputum microbiology
- obstructive sleep apnea, GER
- Oxygen saturation at rest
- Capnography
- Review recent chest radiograph if available
- Review medications: corticosteroids, antibiotics

**Diagnosis by CFTR Genotyping**

- Greater than 1800 different mutations in CFTR
  - Common mutations in USA: F508del, G542X
  - Mutations in China: I556V, M469V, E527N, F508del
- Conventional commercial genotyping
  - Genzyme: 86 mutations
  - Ambry: all coding mutations
  - Many cases are either one or two unknowns at this time

**Table of mutations in each class**

<table>
<thead>
<tr>
<th>Class of mutation</th>
<th>Molecular Mechanism*</th>
<th>Pancreatic status (if known)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No CFTR protein synthesis</td>
<td>PI</td>
<td>W1282X, G542X, R553X, G1221X, 1717–1G→A, 3904insT, 1046delTT</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal CFTR processing and trafficking</td>
<td>PI</td>
<td>R505X, M1343X, F508I</td>
</tr>
<tr>
<td>3</td>
<td>Defective CFTR regulation (normal trafficking)</td>
<td>PI</td>
<td>G551D, G551S, G547S, G547E, S535P</td>
</tr>
<tr>
<td>4</td>
<td>Decreased CFTR chloride conductance</td>
<td>PS</td>
<td>R117H, R505X, R553X, P547I</td>
</tr>
<tr>
<td>5</td>
<td>Reduced synthesis and trafficking of normal CFTR</td>
<td>PS</td>
<td>A455E, 3849–10kbC → T (5T)</td>
</tr>
<tr>
<td>5A</td>
<td>Reduced apical stability</td>
<td>PI</td>
<td>S1468X, S412X, 4230delTC, E476A</td>
</tr>
<tr>
<td>6B</td>
<td>Defective regulation of other ion channels</td>
<td>PI</td>
<td>G551D</td>
</tr>
</tbody>
</table>

**Treatments for CF**

<table>
<thead>
<tr>
<th>High Sweat Chloride</th>
<th>Dietary Salt*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick Airway Mucus</td>
<td>Chest Physiotherapy/DNase*</td>
</tr>
<tr>
<td>Chronic Lung Infections</td>
<td>Antibiotics*</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Anti-Inflammatories*</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>Lung Transplant*</td>
</tr>
<tr>
<td>Pancreatic Insufficiency</td>
<td>Pancreatic Enzymes*</td>
</tr>
<tr>
<td>Meconium ileus</td>
<td>PEG, stool softeners</td>
</tr>
<tr>
<td>Islet Cell Loss</td>
<td>Insulin*</td>
</tr>
<tr>
<td>Male Infertility, CBAVD</td>
<td>In Vitro</td>
</tr>
<tr>
<td>Biliary tract Insufficiency</td>
<td>Bile acid salts</td>
</tr>
</tbody>
</table>

**Median Predicted Survival Age 1985-2007**

1985-2007 (with 95 percent confidence bounds)

The whiskers represent the 95 percent confidence bounds for the survival estimates.
2012 Center Specific Summary

- 487 patients (pediatrics and adult)
- 12 transplanted
- FEV1 vs BMI in optimal quartile in 2012 ages 6-17

<table>
<thead>
<tr>
<th></th>
<th>Johns Hopkins University</th>
<th>Care Center Network Median</th>
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<tbody>
<tr>
<td>FEV1</td>
<td>BMI Percentile</td>
<td>FEV1</td>
</tr>
<tr>
<td>2002</td>
<td>92.5</td>
<td>37.1</td>
</tr>
<tr>
<td>2012</td>
<td>95.9</td>
<td>50.5</td>
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</table>

Advances since 2012: CFTR Modulator Therapies

- Ivacaftor, Kalydeco®, approved by FDA 2012 for G551D CFTR a gating mutation Class III.
- Lumacaftor, a corrector of F508del trafficking defect, alone, insignificant benefit, together with ivacaftor under Phase III clinical trials now.
- PTC-124, restores normal CFTR to stop codon mutants, very effective in the short term in Israel and Belgium, in Phase III multicenter clinical trial and open label extension phases.

Classes of CFTR Mutations

<table>
<thead>
<tr>
<th>Normal</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No synthesis</td>
<td>Block in processing</td>
<td>Block in regulation</td>
<td>Altered conductance</td>
<td>Reduced synthesis</td>
</tr>
<tr>
<td>G542X</td>
<td>F355I</td>
<td>G551D</td>
<td>R117H</td>
<td>D1152H</td>
<td>ST A455E</td>
</tr>
<tr>
<td>12%</td>
<td>87%</td>
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F508del
- 44% of CF patients are homozygous
- 45% of CF patients are heterozygous
- 11% of CF patients do not have ΔF508
- ΔF508 accounts for 70% of Northern European, 50% Southern European, 46% Hispanic, 30% Ashkenazi, 48% African American, < 5% Native American chromosomes

Molecular Consequences of CFTR Mutations

- Normal
- Block in processing
- Block in regulation
- Altered conductance
- Reduced synthesis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GS42X</th>
<th>Frameshift</th>
<th>A deletion</th>
<th>ΔF508</th>
</tr>
</thead>
<tbody>
<tr>
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<td>GS42X</td>
<td>F508del</td>
<td>GS551D</td>
<td>R117H</td>
<td>ΔF508</td>
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</table>

IVACAFTOR

Absolute Change From Baseline Through Week 48 in % Predicted FEV₁

<table>
<thead>
<tr>
<th>Day</th>
<th>Wk</th>
<th>Wk</th>
<th>Wk</th>
<th>Wk</th>
<th>Week 48</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>N=83</td>
<td>N=81</td>
<td>N=80</td>
<td>N=79</td>
<td>N=79</td>
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<tr>
<td>Ivacaftor</td>
<td>N=85</td>
<td>N=81</td>
<td>N=80</td>
<td>N=79</td>
<td>N=79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Ivacaftor</th>
</tr>
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<tbody>
<tr>
<td>Change in % Predicted FEV₁</td>
<td>10.5%</td>
<td>10.6%</td>
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<tr>
<td>P Value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Time to First Pulmonary Exacerbation* Through Week 48

- 55% reduction
- Hazard Ratio: 0.455
- P Value: 0.0012

Absolute Mean Change From Baseline in Weight

- +2.7 kg
- P Value: 0.0001
### Change From Baseline in Sweat Chloride Levels

- **Treatment effect through Week 24**
  - Change: $-47.9$ mmol/L
  - *P* < 0.0001
- **Treatment effect through Week 48**
  - Change: $-48.1$ mmol/L
  - *P* < 0.0001

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### Other CFTR Gating Mutations

2. ~1% of patients
3. **Vertex 770-111 Clinical Trial: Effect of Ivacaftor in Other Gating Mutations**
   - Very little benefit, very high cost

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### Classes of CFTR Mutations

<table>
<thead>
<tr>
<th>Class</th>
<th>No synthesis</th>
<th>Block in processing</th>
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### Vertex Clinical Trial 770-110

- **Role of Ivacaftor in R117H**
- Normal: G542X, G551D, R117H, D1152H, 3849+10kbC→T, 5T
- Ivacaftor: G551D, R117H, D1152H, 3849+10kbC→T, 5T

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### Classes of CFTR Mutations

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<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Frequency</th>
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<tr>
<td>G542X</td>
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### Conclusion

- **VX-809, VX-661 N30**
Some thoughts on Costs

- Ivacaftor is not a cure, required lifelong
- Orphan Drug designation incentivized development. CFF and fundraisers enabled it as well, yet price astronomical
- Ivacaftor being studied in other conditions, even cigarette smoking, incr. potential
- Combinations with Ivacaftor likely to be equally costly for the lifetime of a patient
- Not the most expensive orphan drug, but will need additional combinations which if priced equivalently cannot be sustained.

Acknowledgements

- Cystic Fibrosis Foundation
- National Institutes of Health
- Johns Hopkins CF Centers
- Patients and Families