Update on Cystic Fibrosis

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Seattle Children's Hospital
Disclosure Statement

• I do not have any conflict of interest, nor will I be discussing any off-label product use.

• This class has no commercial support or sponsorship, nor is it co-sponsored.
Objectives

- Review basic multi-organ pathophysiology in Cystic Fibrosis (CF)
- Summarize newborn screening algorithm for CF
- Describe common treatment modalities for CF lung disease and pancreatic insufficiency including new highly effective modulator therapy
- Identify resources for support of care for patients with CF in the community, including guidelines of care
Cystic Fibrosis: History

• Condition appears to be first described as early as 3,000 BCE
• 1857 Almanac of Children’s Songs and Games from Switzerland:

“Woe to the child who tastes salty from a kiss on the brow, for he is cursed and soon must die”

May CD. Cystic Fibrosis of the Pancreas in Infants and Children 1954. Courtesy of Jon Cogen MD
Cystic Fibrosis: History

1950’s: Cystic Fibrosis Foundation (CFF) founded (1955)

1960’s: CFF establishes accredited care center network (1961)
Median age of survival is 10 (1962)
CFF launches CF patient data registry (1966)

1980’s: Median predicted age of survival is 18 in 1980, improves to 29 by 1989
CF gene discovered (1989)


2000’s: Median predicted age of survival is 32 (2000)
Hypertonic Saline (2004), inhaled aztreonam (2010), development of CFTR modulators (ongoing)
Cystic Fibrosis: Today

- Predicted median survival 47.4 years old if born in 2018
CF: Multi-Organ Disease

- Life-shortening, multi-system disease caused by a defect in the gene that codes for the CFTR protein on chromosome 7
  - CFTR = Cystic Fibrosis Transmembrane Conductance Regulator
  - CFTR responsible for Cl- and HCO3- transport across cell membranes in exocrine ductal epithelial tissue in the respiratory, GI, and reproductive tracts
  - Defective CFTR causes dehydration and increased viscosity of secretions produced by these organs
Cystic Fibrosis: Genetics

- Autosomal recessive inheritance
- Predominance in Caucasians but occurs in all racial/ethnic groups
- >1800 variants/mutations identified (not all disease causing)
- F508del most common at ~85%
- ~1 in 35 Americans are asymptomatic carriers

10 million carriers in the US
- 1 in 29 Caucasian-Americans
- 1 in 40 Hispanic-Americans
- 1 in 65 African-Americans
- 1 in 90 Asian-Americans
CFTR Variants

Normal

Class I
CFTR protein is created, moves to the cell surface, and allows transfer of chloride and water.

Class II
No functional CFTR is created.

Class III
CFTR protein is created, moves to the cell surface, but the channel gate does not open properly.

Class IV
CFTR protein is created and moves to the cell surface, but the function of the channel is faulty.

Class V
Normal CFTR protein is created and moves to the cell surface, but in insufficient quantities.

MUTATION EXAMPLES

No mutation
GS42X
W1282X
RS33X
aka "null mutations," which include nonsense mutations, small insertions, and deletions.

% of people with CF who have at least one mutation in first class
22%

WHAT'S HAPPENING IN THE CELL

Mutations in the DNA result in faulty production of CFTR protein.

POTENTIAL THERAPIES

Find new compounds that allow production of full-length CFTR, or remove the mutations.

Find new compounds that help the protein fold correctly.

Find new compounds that increase the function of normal CFTR.
Cystic Fibrosis: Epidemiology

- ~30,000 patients in the US, 70,000 worldwide
- ~1:4000 newborns in the US diagnosed with CF
- ~200 patients followed at SCH CF Center

Summary of the Cystic Fibrosis Foundation Patient Registry, 2003–2018

<table>
<thead>
<tr>
<th>Demographics</th>
<th>2003</th>
<th>2008</th>
<th>2013</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with CF (n)</td>
<td>21,421</td>
<td>25,286</td>
<td>28,030</td>
<td>30,139</td>
<td>30,775</td>
</tr>
<tr>
<td>Newly diagnosed individuals (n)²</td>
<td>1,027</td>
<td>1,140</td>
<td>1,048</td>
<td>990</td>
<td>852</td>
</tr>
<tr>
<td>Detected by newborn screening (%)</td>
<td>11.9</td>
<td>43.0</td>
<td>60.0</td>
<td>56.7</td>
<td>61.5</td>
</tr>
<tr>
<td>Individuals with first CF event in less than 60 days after birth (%)²</td>
<td>32.9</td>
<td>55.7</td>
<td>69.6</td>
<td>66.1</td>
<td>70.8</td>
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<tr>
<td>Mean age at diagnosis for all people with CF (years)</td>
<td>3.2</td>
<td>3.6</td>
<td>3.8</td>
<td>4.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Median age at diagnosis for all people with CF (months)</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Mean age (years)</td>
<td>17.2</td>
<td>18.9</td>
<td>20.2</td>
<td>21.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>15.1</td>
<td>16.9</td>
<td>17.9</td>
<td>19.3</td>
<td>19.8</td>
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<tr>
<td>Adults &gt;18 years (%)</td>
<td>39.7</td>
<td>46.3</td>
<td>49.8</td>
<td>53.6</td>
<td>54.6</td>
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<tr>
<td>Race (not mutually exclusive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White (%)</td>
<td>95.4</td>
<td>94.7</td>
<td>94.0</td>
<td>93.6</td>
<td>93.5</td>
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<tr>
<td>African American (%)</td>
<td>3.8</td>
<td>4.3</td>
<td>4.6</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Other race (%)</td>
<td>1.8</td>
<td>2.4</td>
<td>3.1</td>
<td>3.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Hispanic (any race) (%)</td>
<td>5.8</td>
<td>6.6</td>
<td>8.1</td>
<td>9.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Malas (%)</td>
<td>51.9</td>
<td>51.7</td>
<td>51.5</td>
<td>51.6</td>
<td>51.8</td>
</tr>
</tbody>
</table>

CF Patient Registry, 2018
Diagnosing CF: Early is better

- Early diagnosis leads to early interventions and improved outcomes
- 67% of all individuals in 2018 CF Patient Registry were diagnosed in the first year of life

CF Newborn Screening (NBS)

- Started in WA State in 2006
- Performed by all states by 2010
- Basis of all CF NBS is detection on elevated immunoreactive trypsinogen (IRT) in dried blood spots (marker of pancreatic injury)
- Most states use IRT-DNA algorithm
  - If IRT elevated on 1st blood spot → genetic testing for CFTR variants (DNA)
  - High sensitivity (~97-98%) but detected carriers at ~ 10:1 compared to CF cases
- WA State originally chose IRT-IRT- sweat test algorithm
  - Elevated IRTs collected on two blood spots collected 1-2 weeks apart were a positive screen → sweat chloride test
  - 95-96% sensitivity while minimizing carrier detection
  - Follow up often delayed due to age, birth weight, or clinical status (must be >2kg and at least 36 weeks corrected gestational age for sweat test)
**CF Newborn Screening**

- **WA State changed to IRT-IRT-DNA algorithm October 2019**
  - Originally developed in CO, used in TX and other states
- Persistently elevated IRT run 40 variant DNA panel from blood spot
  - Will run on 1st blood spot if 2nd not received by 16 days of life
- 96-98% sensitivity without huge increase in carrier detection
- Variants found by NBS must be confirmed by CLIA certified lab

*Used with permission from Margaret Rosenfeld, MD*
CF Lung Disease

- Progressive obstructive lung disease hallmark of cystic fibrosis
- FEV1 used to trend lung disease (start spirometry at 4yo)
- Cough most common manifestation of early disease
- Other signs include hypoxemia, exercise intolerance, weight loss, and decreased pulmonary function testing
- Rare, life-threatening pulmonary complications include pulmonary hemorrhage or pneumothorax
- Goal of therapy is prevention of lung injury and preservation of lung function
CF Lung Disease


Courtesy of Chelsea Davis MD
CF Lung Disease

Normal CFTR Function

Cell with CF

Videos courtesy of CFF/NACFC 2008
CF Microbiology

- Endobronchial infection begins early in life, usually with *S. aureus* and *H. influenza*
- *Pseudomonas aeruginosa* (Pa) is an important pathogen in CF lung disease
  - Prevalence in airway cultures ↑ with age
  - Chronic Pa infection is associated with early morbidity and mortality
  - Early Pa infection more amenable to eradication

### Prevalence of Respiratory Microorganisms by Age Cohort, 2018

<table>
<thead>
<tr>
<th>Percentage of Individuals</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>&lt;2</td>
<td>2 to 5</td>
<td>6 to 10</td>
<td>11 to 17</td>
<td>18 to 24</td>
<td>25 to 34</td>
<td>35 to 44</td>
<td>≥45</td>
<td></td>
</tr>
</tbody>
</table>

- 2+ *Pseudomonas aeruginosa*, Nonmucoid
- 2+ *Pseudomonas aeruginosa* #2, Nonmucoid
- 2+ *Stenotrophomonas maltophilia*
  This is a Small Colony Variant.
  Small Colony Variant *S. maltophilia* Suggests Trimethoprim/ Sulfadiazine Resistance by Thymidine Auxotrophy.
  In Vitro Susceptibility Is Not Valid For This Organism.
- 1+ *Candida albicans/dubliniensis*
- 1+ *Candida species, not albicans*

### Drug Susceptibility Table

<table>
<thead>
<tr>
<th>Drug</th>
<th><em>P. aeruginosa</em></th>
<th><em>P. aeruginosa</em> #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Suscept</td>
<td>Suscept</td>
</tr>
</tbody>
</table>

CF Patient Registry, 2018
Managing CF Lung Disease

• Monitor Clinical Symptoms and PFTs Quarterly

• Optimize Nutritional Status
  - Pancreatic enzymes
  - High caloric intake

• Minimize Exposure to Airway Irritants
  - Respiratory viral illnesses (influenza vaccine/ synagis – done at PCP)
  - Environmental factors
Managing CF Lung Disease

Medications:

- **Bronchodilators/ Anti-inflammatory**
  - Albuterol
  - Steroids (inhaled/oral)
  - High Dose Ibuprofen

- **Mucolytics/Hydration**
  - Dornase alfa QD
  - 7% Hypertonic Saline BID

- **Antibiotics**
  - **Maintenance**
    - Inhaled tobramycin solution BID 28 days on/off
    - Inhaled aztreonam TID 28 days on/off
    - Azithromycin M,W,F
  - **Intermittent- treat acute exacerbations**
    - Oral, Inhaled, or IV
Managing CF Lung Disease

Optimize Airway Clearance Therapies (ACT) 2-4 times/day

- Use hydrators/ mucolytics
- Airway Clearance Technique of choice
- Exercise

Chest Physical Therapy/ Clapping/Active Cycle of Breathing

Oscillating Positive Expiratory Pressure (PEP) Devices

High Frequency Chest Wall Oscillating Devices

Photos courtesy of CFF.org
Pulmonary Exacerbation

- Change in respiratory signs and symptoms from patient’s baseline necessitating ↑ treatment
- Increased exacerbations are associated with worse lung function

### Mild:
- May be treated over the phone by the CF team
- Increased mucus production and cough
- Fever
- Mild increased RR, WOB
- Decreased exercise tolerance
- Generalized fatigue
- Loss of appetite/ weight loss
- Treatment: oral/inhaled antibiotics and increased ACT

### Severe:
- Mild symptoms AND:
  - Decreased FEV1>10 %
  - Rales and rhonchi
  - Leukocytosis
  - Decrease in oxygen saturation
  - New infiltrate on CXR
  - Hemoptysis
  - Treatment: IV antibiotics and increased ACT, optimize nutrition
CF Infection Prevention

• All patients with CF are in contact isolation when on SCH Campus

• Patients are to wear masks anywhere in the hospital except in clinic/inpatient rooms

• SCH CF Infection Control policy has guidelines for both inpatient and in clinic areas


• CFF Infection Prevention Guidelines have recommendations for outside of healthcare facilities, including schools

CF Nutrition

FEV\textsubscript{1} Percent Predicted vs. BMI Percentile for Children 6 to 19 Years in 2018

Goal: 50th percentile

CF Patient Registry, 2018
CF Nutrition/ GI Issues

- Nutrition = better lung function
- Goal: BMI percentile ≥50th percentile.
- ~85-90% of patients with CF are pancreatic insufficient
  - Impairs digestion of fats and protein
  - Malabsorption of fat soluble vitamins
  - Malnutrition and growth failure
  - Crampy abdominal pain, excessive flatus, frequent bulky stools, rectal prolapse

Increased caloric need
- Increased metabolism
- Chronic infection/ increased caloric expenditure

Decreased caloric intake
- Malabsorption
- Loss of appetite
- Coughing to emesis
Nutrition Management

- Increase Caloric Intake (1.5 x RDA for ideal body weight = estimated caloric needs)
- Increase Protein, fat, and sodium intake
- Pancreatic Enzyme Replacement (lipase, amylase, protease)
- Vitamin Supplements (A, D, E, K)
- Salt supplementation for infants
- Commercial Oral Supplements
- Tube Feedings
  - Gastrostomy tube
  - Continuous drip feeds at night or daytime boluses
- Total Parenteral Nutrition (TPN)
  - Rarely used
GI Pathophysiology

- **Meconium Ileus/ DIOS**
  - Occurs in 15-20% of cases
  - Obstruction/partial obstruction of meconium/mucus/partially digested food
  - Essentially diagnostic of CF in newborn
  - Not fully understood in older children

- **CF Related Diabetes**
  - Occurs in 10-20% overall (35% in patients >25 years)
  - Insulin deficiency VS insulin resistance
  - Screen annually for CFRD with OGTT for outpatients, inpatient pre/post prandial glucose for 48 hours

- **CF Liver Disease**
  - Most CF patients will develop evidence of mild focal biliary fibrosis
  - 3-5% will develop severe biliary cirrhosis with portal hypertension
  - Quarterly examination of abdomen for organomegaly and annual LFTs
  - Ursodeoxycholic acid (ursodiol) improves LFTs but does not stop disease progression
New CF Medications

• CFTR Modulators
CFTR Modulators

• Medications that work to restore CFTR function

• There are two main types of CFTR modulators currently available:
  • Potentiators-work at the cell surface to help chloride flow through the CFTR protein channel by opening the “gate” of the CFTR channel
  • Correctors- help the CFTR protein to fold correctly so that it is able to move -- or traffic -- to the cell surface.
CFTR Modulators

Potentiator:

• Ivacaftor (Kalydeco) 2012
  • Originally approved for patients with at least 1 copy of Class III gating mutation- G551D (4%), now expanded to 38 mutations
  • Currently approved for patients >6 months of age.
  • 1 tablet/ granule packet twice a day with fat containing foods
  • FEV1 improved by 10.6%
  • 55% reduction in pulmonary exacerbations
  • 2.7kg weight gain
  • Limited side effects: headache, rash, dizziness
  • Monitor LFTs, cataracts

Highly effective modulator therapy, but limited patient eligibility!
CFTR Modulators

Corrector + Potentiator Combinations

- **Lumacaftor + Ivacaftor (Orkambi) 2015**
  - Approved for patients with two copies of F508del ≥2 years
  - 2 tablets/1 granule packet twice daily with fat containing foods
    - FEV1 improved by 2.6-3%
    - Decreased rate of pulmonary exacerbations by 30-40%
  - Lots of drug-drug interactions
  - Chest tightness, dyspnea, nausea, elevated LFTs
  - Monitor LFTs, bili, cataracts

- **Tezacaftor + Ivacaftor (Symdeko) 2017**
  - Approved for patients ≥6 year of age homozygous F508del, or one of 26 responsive mutations
  - 1 tablet twice daily with fat containing food
    - FEV1 improved by 4%
    - Rate of pulmonary exacerbation decreased 35%
  - Less drug-drug interactions
  - Dizziness, headache, nausea
  - Monitor LFTs, bili, cataracts

More patients eligible, but not highly effective!
CFTR Modulators

- Elexacaftor + Tezacaftor + Ivacaftor (Trikafta) 2019
  - Approved for patients with at least one F508del mutation ≥12 years old
  - ~90% of patients with CF qualify for this medication
  - 2 tablets in AM and 1 in PM daily taken with fat containing food
  - Dramatic improvements in FEV1, sweat chloride, and quality of life
  - Reduction in pulmonary exacerbations by 63%

CFTR Modulators

- Elexacaftor + Tezacaftor + Ivacaftor (Trikafta) 2019
  - Less drug-drug interactions
  - Headache, stomach pain or diarrhea, flu-like symptoms
  - Monitor LFTs, bili, cataracts

Highly effective modulator therapy for ~90% of patients!
Resources: http://www.cff.org
Welcome to the CFTR2 website

Our Purpose:
CFTR2 is a website that provides information for patients, researchers, and the general public about specific variants in what is commonly referred to as the cystic fibrosis (CF) gene. For each variant or variant combination included in the database, the website will provide information about:
1. Whether the variant or variant combination is CF-causing, and
2. Information about sweat chloride, lung function, pancreatic status, and Pseudomonas infection rate in patients in the CFTR2 database with this variant or variant combination.

Information on the CFTR2 website is being updated as further analysis is completed. The most up-to-date clinical information and results of functional testing are available on individual variant pages. For a complete list of CFTR2 variants and their characterizations, please visit CFTR2 Variant List History.

What this site is intended to do:
- This website provides information for members of the general public, including cystic fibrosis patients and their family members, about what is currently known about specific cystic fibrosis variants.
- Patients encourage research into better care for patients.
- This website is intended to help diagnose anyone with CF.

What this site is NOT intended to do:
- This website is not intended to help diagnose anyone with CF.
- The information about groups of patients

Click here to switch to general view

FOR PATIENTS AND FAMILY MEMBERS: This detailed medical and genetics information is complicated and potentially confusing. We encourage you to discuss this information with your doctor, a genetic counselor, or a CF specialist. The information shown is for educational purposes only and is not intended for diagnostic use. You should not make any medical or reproductive decisions or change your health behaviour based on this information without talking to your doctor. To find a genetic counselor near you, click here. To find a CF care center near you, click here.

Results for F508del and G551D
Variant F508del can be referred to as F508del, p.Phe508del, c.1521_1523delCTT, or c.1521_1523del or 1523delCTT,
- The drug combination of ivacaftor and lumacaftor (Orkambi) has been approved in some countries for certain individuals with this variant. Please contact your physician to discuss whether the combination of ivacaftor and lumacaftor is appropriate for you.
Variant G551D can be referred to as G551D, p.Gly551Asp, c.1652G>A, or ,
- The drug ivacaftor (Kalydeco) has been approved in some countries for individuals with this variant. Please contact your physician to discuss whether ivacaftor (Kalydeco) is appropriate for you.

Summary Information  Clinical Information  Functional Testing  Population Analysis  Additional Information

The combination of F508del and G551D is seen in 2,064 patients in our worldwide database. This genotype is expected to result in CF. Patients with this genotype are expected to be pancreatic insufficient.
Resources: SCH

- Pulmonary Tool Kit on CHILD

Cystic Fibrosis
- Cystic Fibrosis and School Issues: Information for teachers and other school staff - PE646
- Cystic Fibrosis Exercise Program - PE1474
- Cystic Fibrosis Parent Handbook - PE387 (link to Patient and Family Education Database, where order for booklet can be placed)
- Cystic Fibrosis Pulmonary Exacerbation Magnet - PE1705 (link to Patient and Family Education Database, where order for magnet can be placed)
- Developmental Guide for Your Child with Cystic Fibrosis: Birth to 2 years - PE2111
- Developmental Guide for Your Child with Cystic Fibrosis: 2 to 4 years - PE2112
- Developmental Guide for Your Child with Cystic Fibrosis: 4 to 6 years - PE2113
- Developmental Guide for Your Child with Cystic Fibrosis: 7 to 9 years - PE2114
- Developmental Guide for Your Child with Cystic Fibrosis: 10 to 12 years - PE2122
- My Cystic Fibrosis Care Checklist: 13 to 14 years - PE2123
- My Cystic Fibrosis Care Checklist: 15 to 17 years - PE2124
- Developmental Guide for Your Child with Cystic Fibrosis: Ages 18 to 21 - PE2125
- Exercise and Muscle Group Definitions for the “Exercise Your Future: Staying Fit With Cystic Fibrosis” Video - PE1459
- Exercise Your Future: Staying Fit with CF-Toddler - PE1106 (Spanish)
- Exercise Your Future: Staying Fit with CF-School-age - PE1161
- Exercise Your Future: Staying Fit with CF-Adolescent - PE1162
- Going to the Hospital for a CF Lung Exacerbation - PE912
- Ibuprofen Levels and OGTT Tests Scheduled in the Same Day - PE1856
- Insideoutcare
- Lab Tests for High-Dose Ibuprofen Therapy - PE1865
- Nebulizers: Every medication should have its own nebulizer - PE805 (Spanish)

- SCH CF Team

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Any Questions?


