CONFLICT OF INTEREST DISCLOSURE

- Vertex Pharmaceuticals Inc., Advisory Board 2018 and Consultant 2019
  - Improve understanding of challenges that CF Centers would face with a potential approval of a new medicine in CF
  - Discuss safety and efficacy messages associated with products

- I have no other financial relationships, commercial interests/funding or other relevant conflicts of interest to disclose pertaining to today's presentation

OBJECTIVES

- Review current guidelines for diagnosing cystic fibrosis (CF) and related disorders:
  - CF-related metabolic syndrome (CRMS)
  - CFTR-related disorders
- Discuss the management of infants with CF
- Explore new and emerging therapies that target the cystic fibrosis transmembrane conductance regulator (CFTR)
BRIEF HISTORICAL OVERVIEW

- Description of CFTR gene and its initial mutations
- Introduction of ivacaftor, the first specific CFTR modifier drug
- Era of quality improvement
  - Comparative data on center performance related to key indicators
  - Newborn screenings
  - More detailed understanding of CFTR function and mutation classes
  - Multi-center studies
  - CF Foundation is formed by a group of interested parents

CYSTIC FIBROSIS EPIDEMIOLOGY

- Most common life-shortening inherited disease in Caucasians
- Cystic fibrosis is reported in all races and ethnicities
- Affects approximately 30,000 individuals in the U.S.
- 1 in 2500 live births in the U.S.
- Affects approximately 70,000 individuals worldwide
- Autosomal recessive genetic disease

CYSTIC FIBROSIS PATHOGENESIS

- Mutations are located on chromosome 7
- Chromosome 7 encodes a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR), an apical epithelial chloride channel
- To date >2000 CFTR mutations have been identified
- These mutations are categorized into 6 distinct mutation classes reflecting abnormalities of protein synthesis, structure and function
IMPROVED SURVIVAL

As announced at the North American Cystic Fibrosis Conference in 2017, the median predicted survival age is now 47 years.

Improvement in survival has resulted from:

- Specialized care centers
- Early diagnosis
- Timely screening
- Therapies to optimize pulmonary function and nutrition
- Clinical care guidelines to standardize symptom-based treatments

THERAPEUTIC SHIFT

- Symptom-based treatments ➔ therapies to target basic defect in CFTR-mediated chloride transport
- New therapies have been approved by the U.S. Food and Drug Administration (FDA) for individuals with specific CFTR gene mutations:
  - Ivacaftor (2012)
  - Lumacaftor/ivacaftor (2015)
  - Tezacaftor/ivacaftor (2018)
- These modulator therapies have the potential to alter the CF-disease trajectory

CF PRESENTATION

- Multisystem disease with profound effects on respiratory and digestive systems
  - Abnormally viscous airway mucus
  - Chronic sinopulmonary inflammation and infections
  - Pancreatic insufficiency (most individuals)
  - Intestinal obstruction
  - Cholestasis
  - Abnormal nutrient absorption

- 15% of infants with CF present with meconium ileus at birth
WHY DO A NEWBORN SCREENING (NBS) FOR CYSTIC FIBROSIS?

Benefits:
• Early diagnosis
• Slowing of lung disease progression
• Prevention of malnutrition
• Provision of psychosocial and extended medical support for affected individuals and families

Possible Risks:
• Increased medical interventions that may increase risk for complications
• Earlier exposure to pathogenic bacteria
• Antimicrobial resistance from early treatment of bacterial infection
• Financial considerations given high costs of therapies

WHAT’S THE DOWNSIDE TO THE NBS?

NBS LOGISTICS

- Measures amount of immunoreactive trypsinogen (IRT) from a few drops of blood from a heel prick on a Guthrie card.
- Mailed to a special state laboratory to test for certain conditions including CF
- Laboratories either perform:
  1. IRT/IRT
  2. IRT/DNA, if IRT is elevated
- Positive screen:
  1. Persistent elevation of IRT at 1-2 weeks of age
  2. Identification of at least 1 CFTR mutation
State NBS program is responsible for notification to primary care physician (PCP) of a positive CF screen result.

In RI, our CF Care Center at Hasbro Children’s Hospital is also notified (varies by state).

Family notification and counseling typically begins with PCP prior to obtaining confirmatory gold standard for diagnosis, the sweat chloride test.

CF DIAGNOSIS

CRMS DIAGNOSIS
INFANT CLINICAL CARE GUIDELINES FOR CF

Initial Diagnosis
- Treatment for infants diagnosed with CF by NBS should be done at an accredited CF care center
- The goal of initial visit within 24-72 hours of diagnosis

Nutritional Recommendations
- Pulmonary Recommendations
- Diagnostic Testing
- Chronic Pulmonary Therapies

NUTRITION RECOMMENDATIONS:
FEEDING AND PANCREATIC FUNCTION

- Breastmilk feedings should be encouraged. For infants who are fed formula, standard infant formula rather than hydrolyzed protein formulas should be used
- Calorie-dense feedings should be used if weight loss or inadequate weight gain is identified
- Pancreatic functional status should be measured by fecal elastase or coefficient of fat absorption (CFA)

NUTRITION RECOMMENDATIONS:
PANCREATIC ENZYMES

- Pancreatic enzyme replacement therapy (PERT) should be initiated (2,000-5,000 lipase units/feeding with a maximum daily dose of 10,000 lipase units/kg)
- PERT should be started in all infants with:
  - 2 CFTR mutations associated with pancreatic insufficiency (PI)
  - Fecal elastase <200 μg/g or CFA <85% (in infants <6 months of age) or objective evidence of PI
  - Unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results
- PERT should NOT be started in infants with 1-2 CFTR mutations associated with pancreatic sufficiency, unless objective testing indicates fat malabsorption; or infant has unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results
NUTRITION RECOMMENDATIONS: VITAMINS AND MICRONUTRIENTS

- A trial of zinc supplementation (1 mg/kg/day of elemental zinc in divided doses for 6 months) may be given to some infants who are not adequately growing despite adequate caloric intake and PERT
- Prescribe multivitamin supplements with recommended levels of vitamins A, D, E, and K for patients with CF shortly after diagnosis
  - Blood levels of fat-soluble vitamins should be measured approximately 2 months after supplement initiation and annually thereafter, with more frequent measurements if values are abnormal
- Supplement with 1/8 teaspoon table salt/day starting at diagnosis, increasing to 1/4 teaspoon of table salt/day by 6 months of age

GASTROINTESTINAL DISEASE

- Pancreatic insufficiency in 85% of CF population
- Fat and protein malabsorption
- Poor weight gain
  - Lung disease cavity
  - Appetite
  - Access to food
  - Other environmental and behavioral issues
- Nutritional status can be influenced by modifier genes

PULMONARY RECOMMENDATIONS

- Smoke-free environment should be provided and all caregivers be informed that cigarette exposure harms children with CF
- Airway clearance therapy should be initiated in first few months of life with albuterol before percussion and postural drainage
- Newly diagnosed patients should be separated from other patients cared for in CF clinics until adequate infection control education has been provided to, and is understood by, caregivers
- Oropharyngeal cultures should be performed at least quarterly
- Bronchoscopy and bronchoalveolar lavage should be considered in infants with signs/symptoms of lung disease, particularly with failed response to appropriate intervention
MUCOCILIARY TRANSPORT

Panel A: Normal mucociliary transport

Panel B: CF mucociliary transport

Panel C: CF mucociliary transport in the presence of an osmotic agent

DIAGNOSTIC TESTING AND CHRONIC PULMONARY THERAPIES

- Baseline chest radiograph should be obtained within first 3-6 months and again within first 2 years of life.
- Chest CT scans should be considered in infants with signs/symptoms of lung disease who fail to respond to appropriate interventions.
- Dornase alfa, recombinant human Dnase, and/or 3-7% hypertonic saline may be used in symptomatic infants <2 years of age.
- The CF Foundation does not recommend use of inhaled corticosteroids to improve lung function or reduce exacerbations in infants <2 years of age.

CHRONIC AIRWAY INFECTION MANAGEMENT

- Airway microbiology is a unique fingerprint.
- Several factors contribute to airway infection:
  - CFTR genotype
  - Climate
  - Temperature
- Routine surveillance: Respiratory cultures identify predominant organisms.
- Diversity of organisms narrows with antibiotic use and disease progression.
PROPOSING CRMS

- CF Foundation guidelines published in 2008 showed that this group of infants identified through NBS programs posed a diagnostic and management dilemma:
  - Elevated IRT
  - Sweat chloride value NOT in defining range of CF
  - Fewer than 2 CF disease-causing mutations in CFTR gene
- Often asymptomatic
- Consensus from a committee of experts in 2009:
  1. Provide families with a name that does NOT imply a diagnosis of CF
  2. Include mutations of unclear or unproven clinical relevance
  3. Associated CPT billing code

MANAGEMENT OF CRMS

- Infants with persistently elevated sweat chloride (indeterminate range) should undergo extended CFTR mutation analysis
- Third sweat chloride test should be performed at approximately 6 months of age
- Infants should be monitored by PCP and CF clinician due to increased risk for development of CF-like symptoms
  - Evolving signs/symptoms, new information about disease-causing CFTR mutations or changes in sweat chloride concentrations may ultimately lead to a diagnosis of CF
  - CF clinician assessment no later than 2 mo of age (at least twice in 1st yr of life, annual thereafter)
  - Obtain objective measure of pancreatic function and oropharyngeal culture
  - Chest radiograph if respiratory symptoms are present
  - Routine use of more extensive testing is not recommended

CF TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR)

- Development of CFTR modulators represents a new era in CF therapeutics
- These small molecule therapies target the basic defect in CF
- CFTR modulators are now clinically available for >60% of US CF population
**CFTR MUTATION CLASSES**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>No functional CFTR protein</td>
</tr>
<tr>
<td>II</td>
<td>CFTR trafficking defect</td>
</tr>
<tr>
<td>III</td>
<td>Defective channel regulation</td>
</tr>
<tr>
<td>IV</td>
<td>Decreased channel conductance</td>
</tr>
<tr>
<td>V</td>
<td>Reduced synthesis of CFTR</td>
</tr>
<tr>
<td>VI</td>
<td>Decreased CFTR stability</td>
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</tbody>
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**MINIMAL CFTR ACTIVITY**

**RESIDUAL CFTR ACTIVITY**

Class IV: Decreased channel conductance
Class V: Reduced synthesis of CFTR
Class VI: Decreased CFTR stability
CFTR ACTIVITY

TOTAL CFTR ACTIVITY

IVACAFTOR

- FDA-approved in 2012 (age < 12)
- New approved for individuals with CF age of months who have 1 of these 38 specified mutations
- Potentiator: increases activity of CFTR protein at the cell surface
- Shown to improve lung function (FEV1), decrease number of pulmonary exacerbations and stabilize/improve weight
- Younger children had substantial improvements in fecal elastase level suggesting that early use may help preserve pancreatic function
LUMACAFTOR/IVACAFTOR

- FDA-approved 2015 (age ≥ 12)
- Now approved for individuals age ≥ 2 who have F508del/F508del
- Phase 3 clinical study for children ages 1-2 years is underway
- Corrector/Potentiator for Class II mutations with a trafficking defect
- Total eligible in U.S. who could benefit → approximately 12,300
  - Improves lung function
  - Significantly reduces rate of pulmonary exacerbations → less hospitalizations

TEZACAFTOR/IVACAFTOR

- FDA-approved (2018) for:
  1. Age ≥ 12 with F508del/F508del
  2. Age ≥ 12 with CF who have a single copy of 1 of these 26 specified mutations
- Corrector/Potentiator for Class II trafficking mutations and some of the Class VI-IV splicing and residual function mutations
  - Expanding those with CF who could benefit from CFTR modulators
  - Impact based on in vitro data and/or clinical evidence given few patients with these mutations
- Just approved for age ≥ 6 years (June 2019)
- Approval paves the way for new, more effective triple combination therapies: VX-445

TRIPLE COMBINATION VX-445

- VX-445 with tezacaftor/ivacaftor
  - F508del/F508del (above tezacaftor/ivacaftor run-in)
    - Significant improvement in lung function (+11.1% in FEV1)
    - Improvement in sweat chloride (-39.6 mmol/L)
  - F508del and 1 minimal function mutation
    - Significant improvement in lung function (+13.8% in FEV1)
    - Improvement in sweat chloride (-39.7 mmol/L)
- Phase 3 clinical trials completed, submitted for FDA approval in May 2019
WHAT ABOUT NON-SENSE AND RARE MUTATIONS?

- Nonsense and rare mutations that do not produce CFTR effect an estimated 5-7% of individuals with CF
- These individuals will be unable to benefit solely from CFTR modulators
- In 2016, the CF Foundation launched the Nonsense and Rare Mutations Research and Therapeutics Initiative to help advance research by academic institutions and pharmaceutical companies focused exclusively on creation of therapies to “restore” CFTR production for these individuals.

CF CLINICAL PHENOTYPE

ADDITIONAL RESOURCES

- The Cystic Fibrosis Foundation: their mission is to cure CF and to provide all people with the disease the opportunity to lead full, productive lives. Check out their resources at https://www.cff.org.
- Clinical and Functional Translation of CFTR: The CFTR2 website (https://www.cftr2.org/) provides information about what is currently known about specific genetic variants related to CF.
- Clinical Trials: As a clinical trial volunteer, patients pave the way for new treatments. Search for trials that may be right for your patient/family at https://www.cff.org/Trials/finder.
QUESTION 1

What are the cornerstones for diagnosing cystic fibrosis (CF), CF-related metabolic syndrome (CRMS) and CFTR-related disorders?

A. Chest radiograph and newborn screening
B. Chest radiograph and sweat chloride testing
C. Newborn screening and sweat chloride testing
D. There are no cornerstones for diagnosing these disorders

ANSWER 1

What are the cornerstones for diagnosing cystic fibrosis (CF), CF-related metabolic syndrome (CRMS) and CFTR-related disorders?

A. Chest radiograph and newborn screening
B. Chest radiograph and sweat chloride testing
C. Newborn screening and sweat chloride testing
D. There are no cornerstones for diagnosing these disorders

QUESTION 2

True or False: Infants diagnosed with CF or with a positive newborn screen with only 1 known CF-causing mutation should be referred to a CF Center.
ANSWER 2

True: Infants diagnosed with CF or with a positive newborn screen with only 1 known CF-causing mutation should be referred to a CF Center.

QUESTION 3

Early CF diagnosis and treatment improves:
A. Growth and nutrition
B. Helps maintain lung function
C. Reduces hospitalizations
D. All of the above

ANSWER 3

Early CF diagnosis and treatment improves:
A. Growth and nutrition
B. Helps maintain lung function
C. Reduces hospitalizations
D. All of the above
QUESTION 4

True or False: Treatment of individuals with CF has been transformed by new and emerging therapies that target nonsense and rare mutations.

ANSWER 4

False: Treatment of individuals with CF has been transformed by new and emerging therapies that target nonsense and rare mutations.

• Treatment of individuals with CF has been transformed by new and emerging therapies that target CFTR.
• In 2016, the CF Foundation launched the Nonsense and Rare Mutations Research and Therapeutics Initiative to help advance research by academic institutions and pharmaceutical companies focused exclusively on creation of therapies to “restore” CFTR production for these individuals.
• There are no existing therapies for nonsense and rare mutations to date.

SUMMARY AND KEY POINTS

◆ Newborn screenings and sweat chloride testing are cornerstones for diagnosing cystic fibrosis (CF), CF-related metabolic syndrome (CRMS) and CFTR-related disorders
◆ Infants diagnosed with CF or with +NBS should be referred to a CF Center
◆ Early CF diagnosis and treatment improves growth/nutrition, helps maintain lung function and reduces hospitalizations
◆ Treatment of individuals with CF has been transformed by new and emerging therapies that target CFTR
CLOSING INSPIRATION

• Local CF care teams and CF Foundation: Your contributions to our CF Center and the CF community are sincerely appreciated and gratefully acknowledged.

• To all the patients, families and others impacted by CF for your strength, endless support, kindness and understanding spirits: You inspire us every day. Thank you!

ACKNOWLEDGEMENTS

THANK YOU FOR YOUR TIME AND ATTENTION. QUESTIONS?

A complete list of references can be supplied upon request.
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