Viewing Time

★ This presentation will take approximately one hour to complete.

Target Audience

★ This program is designed for primary care physicians.
★ Other health care professionals working with patients and their families may also find this program of interest.

Faculty Disclosure

★ It is the policy of Children’s Hospitals and Clinics of Minnesota to ensure balance, independence, objectivity, and scientific rigor in all its educational programs. Our faculty have been asked to disclose to our program audience any real or apparent conflicts of interest related to the content of their presentations.
★ They have also been requested to let you know when any products mentioned in their presentations are not labeled for the use under discussion or are still under investigation.

Speaker Faculty Disclosure

★ John J. McNamara, M.D. has disclosed that he was a consultant for Gilead, maker of Aztreonam.
★ During this educational activity Dr. McNamara will not be discussing the off-label use of any commercial or investigational product not approved for any purpose by the FDA.

Update on Cystic Fibrosis

Pediatric Grand Rounds: Nov. 1, 2012

★ John J. McNamara, MD
Medical Director, Cystic Fibrosis and Home Health Care
Children’s Hospitals and Clinics of Minnesota
Update on Cystic Fibrosis

A lecture about cystic fibrosis including information about the genetic defect, newborn screening, diagnosis, complications, the pipeline of new, promising therapies and the important role of the Cystic Fibrosis Foundation.

Program Objectives

Upon completion of this program, participants should be able to:

- Understand Cystic Fibrosis newborn screening.
- Understand the basic defect in Cystic Fibrosis.
- Be prepared to discuss the “Cystic Fibrosis pipeline” and potential new therapies in Cystic Fibrosis.
- Recognize how the Cystic Fibrosis community uses patient data for quality improvement activity.

Disclaimer

Children’s Hospitals and Clinics of Minnesota accepts no responsibility for the materials presented through these Grand Rounds seminars. Each professional presenter assumes all responsibility for maintaining confidentiality or obtaining authorization, in accordance with all applicable laws.

Accreditation

Children’s Hospitals and Clinics of Minnesota is accredited by the Minnesota Medical Association to provide continuing medical education for physicians. Children’s Hospitals and Clinics of Minnesota designates this educational activity for a maximum of 1 AMA Category 1 Credit™ toward the AMA Physician’s Recognition Award.

Each Physician should only claim credit for the actual time he/she spent in the activity.

Retention of CME Records

It is the policy of Children’s Medical Education program that we cannot offer to retain CME records for physicians attending or viewing the online CME activity.

The Minnesota Medical Association designates that physicians are responsible for maintaining their own CME records.

Receiving CME Credit

To receive CME credit, you must view the entire program. When the program is completed, click the Post Test button on the interface to access the Post Test.

You must successfully pass the Post Test to receive CME credit.
Update on Cystic Fibrosis

November 1, 2012

John McNamara, MD
Children's Respiratory & Critical Care Specialists, P.A.

Speaker Faculty Disclosure

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Update on Cystic Fibrosis

Goals

• Understand C.F. Newborn Screening
• Understand the basic defect in C.F.
• Be prepared to discuss the “C.F. pipeline” and potential new therapies in C.F.
• Recognize how the C.F. community uses patient data for quality improvement activity.

What is Cystic Fibrosis?

• C.F. is the most common life limiting genetic disease in the Caucasian population.
• Autosomal recessive genetics
• Carrier frequency and genotypes vary by race
• Median survival now 37 years.
• C.F. affects about one in 2200 live births (in 2007 MN incidence in newborn screening is 1/5600)
• The basic genetic defect affects a regulator protein for Chloride channels in the cell membrane, this affects salt balance on the cell surface which affects the behavior of secretions.

Median CF Life Expectancy

1940 - 2010

Organ Dysfunction in CF

Sinuses
• Sinusitis
• nasal polyps

Lung
• Endobronchitis
• Bronchiectasis

Pancreas
• Exocrine Insufficiency
• CF Related Diabetes

Intestine
• Meconium Ileus
• Constipation/DIOS

Liver
• Focal Sclerosis

Vas Deferens
• Failure to develop

Sweat Gland
• Salt-losing dehydration

Intestine
• Meconium Ileus
• Constipation/DIOS
Complications

- Meconium ileus
- Rectal prolapse
- Hypochloremia
- Vitamin deficiency
- Hepatobiliary disease
- Osteoporosis
- CFRD
- Depression
- Clubbing
- DIOS
- AMPA
- & cepica
- Hemoptysis
- Pneumothorax
- CBVAD

CF Diagnosis

- CF is a clinical diagnosis
- Early diagnosis is important
- The diagnosis is not always straightforward
- Sweat Chloride remains the gold standard but does not always give a clear answer
- Genotyping does not always provide clarity, more than 1500 mutations in CFTR (Cystic Fibrosis Transmembrane Regulator Protein) have been identified, not all of which result in CF
- Expand borderline range to 30-60 for infants <6mos.
- Concept of CFTR related disorders
- Genotype does not predict prognosis
- CRMS
- Guidelines Farrel et al. Aug. J. Peds 2008;153:S4-S1

Overview of Newborn Screening

- High throughput (~70,000/year)
- Birth hospitals send specimen cards to MDH
- Screening complete ~3 days

Laboratory Screening Algorithm

- Two-tiered approach \( \rightarrow \) IRT/DNA algorithm
- First-tier \( \rightarrow \) immunoreactive trypsinogen
- Second-tier \( \rightarrow \) mutation analysis
- Originally, 23 mutations were assayed
- August 1, 2006 39 mutations assayed

Overview of Newborn Screening

- Expecting 15-25 positive CF cases/year
- Expecting 200-240 abnormal CF newborn screening results/year

Laboratory Screening Algorithm

- run IRT
- IRT values > 770 and IRT > 96 percentile (based on daily curve that excludes IRT values greater than 170)
- mutation analysis
- 0 mutations
- 1 or 2 mutations
- repeat IRT is elevated
- repeat IRT is normal
- IRT < 96 percentile (based on daily curve that excludes IRT values greater than 170)
- NEGATIVE
- POSITIVE
- NEGATIVE
Overview of Newborn Screening

Positive Result Notification Model
- MDH contacts primary care provider
- MDH provides results, disorder fact sheets, contact info for appropriate specialists
- Primary care provider connects family with specialist
- Specialist and/or primary care provider report diagnostic info to MDH

2007 Newborn Screening
- Newborn Screening started March 2006
- 2007 data
  - 73,013 samples
  - 229 positive screens
  - 13 confirmed positives
  - 5.7% of positive screens confirmed to have C.F.
  - Incidence 1:5600

Complications from Failure to Diagnose CF During Infancy
- Hypochloremia: Alkalosis
- Hyponatremia: Dehydration, Failure to thrive
- Hypoproteinaemia: Kwashiorkor, False negative diagnosis
- Vitamin E Deficiency: Hemolytic anemia
- Vitamin K Deficiency: Bleeding diathesis
- Zinc Deficiency: Acrodermatitis

Cystic Fibrosis lung disease involves peripheral airways and begins early in life

Disease involves the peripheral airways

Inflammation in Infants with CF
Early Diagnosis Improves Growth

Pulmonary Function by Diagnostic Category

Pancreatic Function in Infants with CF

Genotype ≠ Phenotype

Basic Defect

- DNA
- RNA
- Protein synthesis
- Protein folding
- Transport to the cell membrane
- Activation of Chloride channel
- Chloride migrates out of the cell
- Sodium and water follow

Basic Defect

- Abnormal pericilliary fluid layer
- Inflammation
- Infection
- Bronchiectasis
- Respiratory failure
- Death
Mucus Clearance Is Key For Normal Lung Defense

DNA
- Over 1500 genotypes identified
- Variable dysfunction of protein
- Has not made diagnosis any easier
- Gene Therapy has been challenging
  - Triggers immune response
  - Targeting into genome can be problematic
  - Adenovirus vs. liposomes
  - Compacted DNA in nanoparticles (PLASmin) to enter pores in nuclear membrane (Phase 1 trials), avoid viral vector.

mRNA
- mRNA
  - PT124
    - May overcome stop codons in CFTR mRNA promoting read through
    - Relatively rare problem but almost 30% of CF genes in Israel
- Ataluren (formerly known as PTC124)
  - It is a novel, small molecular compound that promotes the read-through of premature truncation codons in the CFTR mRNA. These codons are due to “nonsense mutations.”
  - Phase 3 Study
    - Lower rate of pulmonary exacerbations
    - Lower decline of lung function

CFTR Protein
- CF gene encodes for the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein
- CFTR functions as an ion channel and controls the movement of salt and water into and out of cells
- Mutations in the CF gene impair this movement, critically altering host defense in the lung

CFTR Mutation Classes
- Protein Folding
  - Common problem (Delta F508 accounts for 68% of all CF genes and is one genotype associated with inability to fold CFTR protein appropriately)
  - CFTR protein does not get through the endoplasmic reticulum to the cell membrane
- Common “Corrector” molecule VX809 (molecular chaperone)
  - VX-809 is a new compound designed to move defective CFTR protein to the proper place in the airway cell membrane and improve its function as a chloride channel.
  - Final data from the Phase 2 trial completed in 2012 showed significant improvements in lung function for those with two copies of the Delta F508 mutation. Improvement was also seen for those who had one copy of Delta F508, though smaller than those with two copies.
  - Vertex plans to initiate a Phase 3 study in 2013.
**CFTR Modulation**

**CFTR Function**

- **Kalydeco (previously VX-770) – “potentiator”**
  - G551D or R117H
  - 20 patients for two weeks
  - Brought sweat test results down to borderline range; to normal in some individuals!
  - Significant improvement in FEV1 in only two weeks
  - Phase 3 Study
    - Improved lung function
    - Reduced pulmonary exacerbations
    - Increase in weight
    - Increase in quality of life

- **VX-661 – “corrector” AND “potentiator”**
  - Move defective CFTR protein to the proper place in the airway cell membrane
  - Improve CFTR protein function as a chloride channel
  - VX-661 can be potentiated by adding Kalydeco.
  - Currently enrolling Phase 2

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**Secondary Endpoints in Ivacaftor Phase 3 Studies**

*Absolute change from baseline through/at Week 48*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Study 102 Treatment effect</th>
<th>p</th>
<th>Study 103 Treatment effect</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>% predicted FEV1</td>
<td>10.5</td>
<td>&lt;0.0001</td>
<td>9.99</td>
<td>0.0006</td>
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<tr>
<td>Sweat chloride (mmol/L)</td>
<td>-48.1</td>
<td>&lt;0.0001</td>
<td>-53.5</td>
<td>&lt;0.0001</td>
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<tr>
<td>Weight (kg)</td>
<td>2.7</td>
<td>&lt;0.0001</td>
<td>2.77</td>
<td>0.0003</td>
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<tr>
<td>CFQ-R Respiratory domain</td>
<td>8.6</td>
<td>&lt;0.0001</td>
<td>5.1</td>
<td>0.1354</td>
</tr>
<tr>
<td>Time to First Pulmonary Exacerbation (Hazard Ratio)</td>
<td>0.46</td>
<td>0.0012</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
**Abnormal Secretions**

- **Pulmozyme**
  - human recombinant DNase
  - Thins and loosens mucus in the airways

- **Hypertonic Saline**
  - 7%/4ml bid by nebulizer
  - Increases hydration of airway surface liquid, thereby improving mucociliary clearance

- **Bronchitol**
  - Inhaled dry powder form of mannitol.
  - Rehydrates CF secretions, thereby improving airway clearance
  - Improved lung function in trials in Australia and Europe.
  - Approved for treatment in Australia

**Inflammation**

- **Alpha 1 Anti-trypsin**
  - Aerosolized protease inhibitor derived from human plasma

- **Ibuprofen**
  - PUR 118
  - Inhaled dry powder formulation of a cationic airway liquid modulator.
  - Increases mucociliary clearance

- **N-Acetylcysteine (Oral)**
  - Antioxidant that replenishes glutathione levels

- **KB001**
  - Humanized monoclonal Fab fragment that targets a Pseudomonas aeruginosa virulence factor (Type III secretion system)

- **GSK SB 656933**
  - Once daily anti-inflammatory agent for maintenance treatment.

**Inflammation**

- **Sildenafil**
  - Phosphodiesterase inhibitor

- **Hyponatremia**
  - Replenishes glutathione in neutrophils
  - Decreases inflammatory cells in lung
  - Increases FEV1

- **DHA**
  - UMass infant study

- **Inhaled Glutathione**

- **Hydroxychloroquine**

**Infection**

- **Tobi**
  - Azithromycin interferes with quorum sensing

- **Inhaled Aztreonam**

- **TIP (TOBI Inhaled Powder)**
  - TIP is an inhaled antibiotic, the powder form of tobramycin that may allow a faster, more convenient, dosing regimen

- **Levofloxacin (Inhaled)**
  - Previously known as MP-376
  - Inhaled formulation of antibiotic, levofloxacin
  - Management of chronic pulmonary infections due to Pseudomonas aeruginosa and other bacteria.
  - Reduction of sputum
  - Improve lung function

- **Arikace**
  - Aerosolized liposomal formulation of the antibiotic amikacin
  - Improve lung function
  - Reduce Pseudomonas aeruginosa density

- **Ciprofloxacin DPI**
  - Previously known as BAY Q3939
  - Inhaled dry powder version of the antibiotic ciprofloxacin
Bronchiectasis

- Lung Transplant
  - Inhaled cyclosporine
  - Improved mortality
  - Decreased chronic rejection

Clinical Outcomes are Improving

Cystic Fibrosis Foundation

- Huge fundraising: > $10,000/patient
- Cystic Fibrosis Care Center Network
- Fellowship and basic science support
- Philanthropic Venture Capitalism
- Drug Development Pipeline
- Lobbying for orphan drugs
- National Data Base for Quality Improvement
- Therapeutic Development Centers

Summary of Key Points

- Genetic discoveries have led to an improved understanding of the pathophysiology of CF
- Pulmonary exacerbations are the primary “red flag” for worsening lung disease and poor prognosis
- Therapies that reduce pulmonary exacerbations are associated with improved survival
- Complications are reduced with newborn screening, but continue to exist and increase with age
- Lung transplant is an end-stage, temporizing therapy
2011 Improvement Projects

Improve Hgb A1C in CF-related diabetes (CFRD)
- Improve outpatient screening (119/119 pts screened)
- Improve inpatient screening (CPOE order set in place by 7/1/11)
- Improve referrals to endocrinology (16/16 pts with CFRD seen)
- Median Hgb A1C 8.5 (2009) to 5.8 (2011 ytd 15/16 pts)
- Mary Sachs, Laura Gandrud, Mary Smieja, Sandy Landvik, Jan Majkozak Learning & Leadership Collaborative (LLC) project through the CF Foundation

Improve mean FEV1
- 4 Visits per year (80% have had 2 visits by 7/1/12)
- 4 proven therapies to improve lung function
- Evaluate adherence more broadly (Computer system tracks refills, we can now track vest use)
- Better management of CFRD
- Family advisory council input

Quality Improvement Project

Adherence to Four Interventions Proven in Large Prospective Trials - Pulmozyme, Hypertonic saline and Tobi and Azithromycin in Pseudomonas Positive Patients
- Statistically significant improvement in prescribing Pulmozyme, hypertonic saline and Tobi (p < 0.011)
- Hypertonic saline and Tobi positively improved mean FEV1 (p=0.018 and p=0.011)
- Moderate correlation between improved adherence and improved mean FEV1 (R=0.533)

![Graph showing adherence rate and FEV1% improvement over time](image-url)
Family Advisory Council Input/QI 2012

- Streamline lab process
- Separate labs from team consultation
- Concentrate on high risk events:
  - Newly diagnosed
  - Toddler feeding
  - Anticipate adolescent adherence issues
  - CF team communication tool
  - More efficient use of time
  - Allow for team consultation on more days than Wednesday

QUESTIONS?

John McNamara, MD
Children's Respiratory & Critical Care Specialists, P.A.
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QUESTION

You showed us a slide of FEV1 at several years of age in kids who had been screened for CF and kids who were diagnosed in the "wild" and it was lower. Also there were kids with meconium ileus, and they were even lower than kids diagnosed in the wild. But you'd think they would have been diagnosed right after birth. Why are they different?

QUESTION

For antibiotics, do you ever run into a fungus problem of significance?

Cystic Fibrosis Research

Current Research

- 17 open protocols (4 additional pending IRB review: STAR-100, CFFC, Vertex 112 & Novartis TIP)
  - 4 Prospective Treatment (3 additional pending review)
  - 8 Prospective Observational
  - 4 Retrospective Reviews
  - 1 registry
**Recent Publications**

- Increased Adherence to CFF Practice Guidelines for Pulmonary Medications Correlates with FEV1. *Pediatric Pulmonology*. In press.

**Program Development**

- Increasing Investigator Initiated Research
  - 8 open protocols (2 funded grants received in the past year)
  - 1 abstract accepted for thematic poster presentation at the 2012 European Respiratory Society Conference in Vienna
- Cystic Fibrosis Therapeutic Development Network Grant (TDN)
  - Received Continuation Award (Full grant re-submission required this September for future funding)
  - University of Minnesota cross campus research collaboration
Achievements

- Improved screening rates, identification of patients with CFRD, diabetes clinic follow-up rates and hemoglobin A1c values.
- Development of a standardized protocol for screening OGTT, which includes screening all inpatients, outpatients using standardized order sets and all patients receiving G-tube feeds.
- Establishment of a CFRD dashboard and improved education for diabetes self-management.

Recommended Reading

- Flume et al.: Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations 2009; 180: 802-8.

Our goal is to be the best clinical care center for Cystic Fibrosis that we can possibly be.