Author: Richard H. Simon, M.D., 2008-2010

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Cystic Fibrosis

- Richard H. Simon
  Pulmonary and Critical Care Medicine
  Department of Internal Medicine
Objectives

- Understand:
  - The genetic nature of cystic fibrosis (CF)
  - The pathophysiology of CF lung disease

- Know how to diagnose CF

- Learn the basic approach to treating CF lung disease
Cystic Fibrosis

- Inherited disease
  - Autosomal recessive
- Gene cloned in 1989: “CFTR”
  - Cystic Fibrosis Transmembrane conductance Regulator
- 1601 mutations in CFTR known to cause CF
- An extensive amount of information is known about CFTR
Schematic Representation of CFTR
Pathophysiology of CF

CFTR Dysfunction

Disease manifestations
- Lungs
- Sinuses
- Pancreas
- Liver
- Bones
- Vas deferens
Airway Cross Sectional View

- Mucus layer
- Pericellular layer with cilia
- Epithelial cell layer

Knowles & Boucher 2002;109:571
Required Geometry for Effective Mucociliary Clearance

Mucus Layer

Periciliary Layer

Cell Surface

Knowles & Boucher 2002;109:571
Pathophysiology of CF Lung Disease
Consequences of CFTR Deficiency on Airway Clearance

Knowles & Boucher 2002;109:571
Pathophysiology of CF Lung Disease

CF Gene Mutation

Ion Transport Abnormalities

Altered Airway Environment

Inflammation

Infection

Tissue Damage

R. Simon
Pathophysiology of CF Lung Disease

CF Gene Mutation
- Recurrent Bronchitis
  - Bronchiectasis
    - Chronic Respiratory Failure
      - Death
Prevalence of Infections in CF Patients

- **P. aeruginosa**
- **S. aureus**
- **H. influenzae**
- **MRSA**
- **S. maltophilia**
- **B. cepacia**

Cystic Fibrosis Foundation Patient Registry Data. 2005
Natural History of CF Lung Infections

- *Ps. aeruginosa* or *B. cepacia* complex species persist in the lung
- True infection, not “colonization”
- Difficulty in eradicating infection:
  - Intrinsic antibiotic resistance
  - Acquired antibiotic resistance
  - Poor antibiotic penetration into secretions
  - Alginate produced by mucoid *Ps.* (biofilms)
  - CF-related defects in mucosal (but not systemic) defenses
Diagnostic criteria for cystic fibrosis
Part 1: Clinical Manifestation of Disease

At least one of the following:

1) One or more clinical manifestations of CF
   - Meconium ileus
   - Chronic bronchitis / bronchiectasis
   - Chronic infection of the paranasal sinuses
   - Pancreatic insufficiency
   - Salt loss syndromes
   - Male infertility due to congenital bilateral absence of the vas deferens

2) Positive newborn screening test

3) History of CF in a sibling
Diagnostic Criteria for Cystic Fibrosis
Part 2: Laboratory evidence of CFTR abnormality

- At least one of the following:
  1) Elevated sweat chloride test
  2) Identification of a mutation in each CFTR gene known to cause CF
  3) In vivo demonstration of characteristic abnormalities in ion transport across nasal epithelium (not widely available)
Sweat Test for Diagnosis of CF

Shwachman H, Mahmoodian A. Mod Prob Pediatr 1967;10:158
Use of Genotyping to Diagnose CF

Population Frequency of Specific CFTR Mutations Causing CF

- 1601 CFTR mutations known to cause CF
- Only 25 mutations have a frequency ≥ 0.1%

<table>
<thead>
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<th>Mutation</th>
<th>Frequency, %</th>
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<tr>
<td>ΔF508</td>
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<tr>
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<td>W1282X</td>
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<tr>
<td>R347P</td>
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</table>
Genotyping for CF Diagnosis

- Current commercial screening tests
  - Look for presence of between 25 - 100 mutations
  - These will detect a CF allele only \(~90\%\) of time

- For a group of patients with known CF, genotyping would be diagnostic in only \(~81\%\) of patients

- Screening for most common mutations is not as sensitive as sweat testing (98\%) to diagnose classic CF
Genetic Diagnosis of CF

- Tests becoming commercially available for detecting mutations more broadly
  - PCR used to amplify all exons and surrounding splice sites
  - Heteroduplex formation screening and/or sequencing
  - Analysis for large deletions and duplications
  - Cost ~ $2,500
Acute Exacerbations of CF Lung Disease

- Symptoms
  - Increased cough with sputum production
  - Hemoptysis
  - Increased shortness of breath
  - Fever (not required)
  - Reduction in FEV1
  - Worsening infiltrates on chest x-ray (not required)
Acute Exacerbations of CF Lung Disease

- Antibiotic treatment
  - Oral antibiotics
    - If symptoms are mild, and
    - Bacteria are susceptible
  - Intravenous antibiotics otherwise
Management of Chronic Lung Disease in Cystic Fibrosis
Aerosolized Antibiotics

- High dose tobramycin proven for chronic infection
  - TOBI® 300 mg in 5 ml bid every other month

Mucolytic Therapy for CF

- DNase (Pulmozyme®)
  - Chronic use improves FEV1 and causes fewer exacerbations

Fuchs HJ, et al. NEJM 1994;331:637-642
Bronchodilators in CF

- No studies in acute exacerbations but routinely given
- Chronic use -- FEV1 improves acutely in some patients
  - β-adrenergic agonists (e.g. albuterol, salmeterol)
  - Anticholinergic agents (ipratropium bromide, tiotropium)
Anti-Inflammatory Treatment in CF

- **Glucocorticoids**
  - **Oral (prednisone)**
    - Preserves lung function, but too many adverse effects
  - **Inhaled**
    - Used for subgroup of with bronchial hyperreactivity (asthma) symptoms

- **Ibuprofen**
  - Beneficial for young patients
  - No evidence for improvement in adults
Macrolide Therapy for CF

- **Azithromycin in CF**
  - Improved FEV1
  - Fewer exacerbations of CF lung disease
  - Uncertain mechanism of action
    - Anti-inflammatory?
    - Bacterial toxin or biofilm production?

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Nebulized Hypertonic Saline (7%)

- **Effect on FEV1**
  - Randomized, double-blind, placebo controlled trial
  - N = 164
  - Inhalation of 4 ml of 7% vs. 0.9% saline bid for 48 weeks

Effect of 7% Saline on Frequency of Pulmonary Exacerbations

Physiotherapy for CF

- No studies in acute exacerbations
  - But “standard of care” treatment
- Beneficial for chronic management
Physiotherapy Options for CF

- Flutter
- Acapella
- PEP
- Vest
Supplemental Oxygen

- Use same guidelines as COPD
Home Versus Hospital Therapy for Acute Exacerbation

- Home regimen must duplicate full hospital program
  - IV drugs
  - Physiotherapy
  - Nutrition
  - Et cetera

- Results from small studies showed mixed results
Assisted Ventilation in CF

- Past studies show very poor outcomes
- Non-invasive ventilation being used as a bridge to lung transplantation
Lung Transplantation CF

- Bilateral lung transplantation
- Outcome similar to non-CF transplantation
- Problems
  - Long waiting lists
  - Many exclusions
- Living donor transplants
Number of CF Patients With Lung Transplants 1988 - 2005

Source: Undetermined
Median Predicted Survival for Cystic Fibrosis

Calendar Year

Age, yr

Source Undetermined

September 1, 2007
Cystic Fibrosis Now

Image of Dan Bessette, the child from the September 1989 cover of Science, a 19 year old college sophomore in 2003
References

Additional Source Information
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Slide 5: Science, September 1989
Slide 8: Knowles & Boucher 2002;109:571
Slide 9: Knowles & Boucher 2002;109:571
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Slide 14: Cystic Fibrosis Foundation Patient Registry Data. 2005
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