New Paradigms in Diagnosis and Management of Cystic Fibrosis

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CF: Diagnosis and Management

- Review of cystic fibrosis
  - Pathophysiology
  - Epidemiology

- Clinical features and “red flags”

- Management
  - Maintenance
  - Complications
“Woe to the child that, when kissed on the forehead, tastes salty. He is bewitched and soon must die.”

--Proverb from northern European folklore
CF Basics

• Autosomal recessive

• Disease of **chloride transport** across mucosal surfaces

• **“Thick mucus”** leads to obstruction of:
  • Bronchioles
  • Sinus ostia
  • Biliary / cystic ducts
  • Intestines
  • Vas deferens
Manifestations of Cystic Fibrosis

**General**
- Growth failure (malabsorption)
- Vitamin deficiency states (vitamins A, D, E, K)

**Nose and sinuses**
- Nasal polyps
- Sinusitis

**Liver**
- Hepatic steatosis
- Portal hypertension

**Gallbladder**
- Biliary cirrhosis
- Neonatal obstructive jaundice
- Cholelithiasis

**Bone**
- Hypertrophic osteoarthropathy
  - Clubbing
- Arthritis
- Osteoporosis

**Intestines**
- Meconium ileus
- Meconium peritonitis
- Rectal prolapse
- Intussusception
- Volvulus
- Fibrosing colonopathy (strictures)
- Appendicitis
- Intestinal atresia
- Distal intestinal obstruction syndrome
- Inguinal hernia

**Lungs**
- Bronchiectasis
- Bronchitis
- Bronchiolitis
- Pneumonia
- Atelectasis
- Hemoptysis
- Pneumothorax
- Reactive airway disease
- Cor pulmonale
- Respiratory failure
- Mucoid impaction of the bronchi
- Allergic bronchopulmonary aspergillosis

**Heart**
- Right ventricular hypertrophy
- Pulmonary artery dilation

**Spleen**
- Hypersplenism

**Stomach**
- GERD

**Pancreas**
- Pancreatitis
- Insulin deficiency
- Symptomatic hyperglycemia
- Diabetes

**Reproductive**
- Infertility
  - (aspermia, Absence of vas deferens)
- Amenorrhea
- Delayed puberty
CF Epidemiology

- **Prevalence**
  - 30,000 in the US
  - 850 in NC (CF Registry)

- **Incidence:**
  - Caucasian 1 / 2,500 (approx 1 in 25 or 4% carrier)
  - Hispanic 1 / 9,500
  - African American 1 / 15,000
## Symptoms of Newly Diagnosed CF Patients

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>52%</td>
</tr>
<tr>
<td>Failure to thrive/malnutrition</td>
<td>32%</td>
</tr>
<tr>
<td>Steatorrhea &amp; malabsorption</td>
<td>27%</td>
</tr>
<tr>
<td>Meconium ileus</td>
<td>20%</td>
</tr>
<tr>
<td>Family history</td>
<td>15%</td>
</tr>
<tr>
<td>Neonatal screening</td>
<td>5%</td>
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</tbody>
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N = 864; CFF Patient Registry
Under the Microscope: CF Lung Disease

Normal Airway

CF Airway
Airway Mucous Plugging and Inflammation in CF
Cystic fibrosis is changing...

- CF being diagnosed younger
- Patients are living longer
- Adults with CF have fuller, more productive lives
- New treatments and options = improved longevity
Most CF now diagnosed by NBS

- CF Registry Annual Report, CF Foundation 2010
Patients with CF living longer

- CF Registry Annual Report, CF Foundation 2010
CF: No longer a childhood illness

- CF Registry Annual Report, CF Foundation 2012
Majority of Adults with CF

- Attend College
- Work at least full time

- CF Registry Annual Report, CF Foundation 2012
Adults with CF: Marriage and Fertility

- **Marital status**
  - 55% single
  - 40% married or living together
  - 5% separated or widowed

- **Can CF patients have children?**
  - Approximately 80% of CF females are fertile
  - Most (95%) of men are infertile due to absence of vas deferens
    - Testicular sperm aspiration (TESA) may be an option
When to suspect CF: Red Flags
"Wait a minute here, Mr. Crumbley... Maybe it isn't kidney stones after all."
When to suspect CF: Red Flags

- **Gastrointestinal** problems usually FIRST to appear during infancy

- **Respiratory** infections usually begin by one year

- Physical exam and radiographic features can prompt further investigation
Gastrointestinal: Red Flags

- **Meconium ileus**
  - May be associated with ileal atresia

- **Failure to thrive**
  - Usually EXCELLENT appetite
  - FREQUENT foul, greasy stools

- **Constipation**
  - Rectal prolapse – may be first sign of CF
Gastrointestinal: Red Flags

- Fat-soluble vitamin deficiencies (A,D,E,K)
  - **A**: Night blindness, dry eyes and skin
  - **D**: Osteoporosis
  - **E**: Reduced deep tendon reflexes, paresthesias
  - **K**: Bruising and bleeding
Gastrointestinal: Red Flags

- Distal intestinal obstruction syndrome (DIOS)
  - Recurrent abdominal pain and bowel obstruction

- Intussusception / Volvulus

- REMEMBER: Some patients with CF are pancreatic sufficient - without GI manifestations!
Respiratory: Red Flags

- Chronic, daily, productive cough

- All that wheezes is not asthma...
  - Less responsive to steroids, bronchodilators

- Frequent antibiotic courses
  - Recurrent pneumonia or rhinosinusitis
  - Symptoms may not completely improve on antibiotics or return after stopping
CXR findings are nonspecific

- Hyperinflation
- Peribronchial thickening
- Perihilar vascular prominence
- Areas of consolidation
- Lymphadenopathy
- Bronchiectasis (rarely seen on plain film)

- MAJORITY of children with CF have normal or nonspecific findings on CXR.
Chest CT findings more sensitive

- Peribronchial wall thickening
- Bronchiectasis "signet ring sign"
- Nodular or branching opacities
- Mucus plugging
Respiratory: Red Flags

- **Hemoptysis**
  - 9% of CF patients in a 5-year period \(^1\)
  - 4% will have life threatening hemoptysis \(^2\)

- **Pneumothorax**
  - 3% of CF patients will have pneumothorax in their lifetime \(^3\)

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\(^1\) J Cyst Fibrosis 2008; 7:301-306.
\(^3\) Chest 2005; 128:720-728.
Other: Red Flags

- **Dehydration**
  - Hyponatremic, hypochloremic metabolic alkalosis

- **Liver disease**
  - Elevated transaminases

- **Exam findings**
  - Clubbing
  - Crackles
  - Wheezing (especially upper lobes)

Source=http://knol.google.com/k/jerry-nick-m-d/cystic-fibrosis/UtI7gr91/HU2bIw# |Author=Jerry Nick, M.D.
Diagnosis of Cystic Fibrosis
Diagnosis of CF: Strategies

- **Universal screening**
  - Immunoreactive trypsinogen (IRT) with or without CFTR genotype on newborn screen
  - Different protocols by state
  - NC NBS started in 2007

- **Sweat chloride analysis** (gold standard)

- **Genotyping** (DNA analysis)

- **Nasal potential difference** (rarely used)
Newborn screening for CF

- First NBS in Victoria, Australia in 1989

- IRT – varies daily but typically + >90.
  - Marker of pancreatic damage
  - Elevated even in pancreatic sufficient CF patients

- Different algorithms
  - **IRT / DNA**: NC, VA, GA (90% of states)
    - Benefit: single sample
    - Approx 95% sensitivity
  - **IRT / IRT**: SC, TN, MD
    - Requires 2 samples
Newborn screening for CF

- False positives of elevated IRT
  - Neonatal stress – asphyxia and septicemia
  - hypoglycemia
  - Conditions with elevated trypsinogen
    - CMV infection
    - Trisomies
    - Intestinal obstructions – ileal and biliary atresia

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IRT/DNA Newborn Screen for CF

- IRT
  - normal
  - highest 5%

- CFTR DNA
  - 0 mutations → CF unlikely
  - 1 mutation → CF possible
  - 2 mutations → CF likely

- SWEAT CHLORIDE
Sweat chloride: the gold standard

- Most efficient >4 weeks of age
- Electrodes applied to skin
- Sweating stimulated by pilocarpine iontophoresis
- Sweat collected by gauze, weighed and chloride analyzed
- Should only done at labs accredited for sweat testing (ECU, DUKE, NCU)

http://www.cfmedicine.com/history/fifties.htm
Beyond the sweat test: Genotyping

- All patients with CF should have 2 CFTR mutations identified
  - CFTR full gene sequencing if needed

- All mutations are NOT created equal
  - Classes I-V based on severity of CFTR defect
  - Some mutations not associated with pancreatic insufficiency
  - 85% of patients, however, are pancreatic insufficient
Beyond the sweat test: Genotyping

- CFTR genotype is NOT the only predictor of severity
  - Environment
  - Socioeconomic factors
  - Disease complications
  - Lung microbiology

- “Cystic fibrosis modifier genes”
Treating CF in the 2010’s

- Basic treatments have not changed
  - Mucociliary clearance
  - Antibiotic therapy for infections
  - Preserve lung function
  - Pancreatic enzyme replacement

- New treatments are emerging
  - Inhaled antimicrobials
  - CFTR modulators
Airway Clearance is Essential

- Regular airway clearance recommended for all CF patients (2+ times per day)
- Enhancing the efficacy of the Mucociliary escalator
- No option is preferred, but exercise airway clearance
Mucous Clearance

- Adequate cough is first and foremost
  - Cough is impaired with chronic obstruction
  - Impairment with neuromuscular disorders
Mucous Clearance

Manual – Triad of 3

- Chest Physiotherapy
- Postural Drainage
- Adequate Suction
Airway Clearance is Essential

- Multiple options
  - Manual percussion and drainage
  - Positive end-expiratory pressure (PEP)
  - High frequency chest wall oscillation (Vest therapy)
  - Autogenic drainage
  - Huff cough
Mucous Clearance

- Hand-Held devices
Pulmonary Guidelines for 2013

- **Children over age 6**
  - Hypertonic saline (may cause bronchospasm)
  - High dose ibuprofen (if FEV₁ > 60% predicted)

- **Children over age 6 with chronic Pseudomonas**
  - Inhaled tobramycin
  - Oral azithromycin (controversy about risk for NTM)
  - Inhaled aztreonam

- **Children over age 6 with mod/severe disease**
  - Dornase alfa (DNase)

- **Children over age 6 with G551D mutation**
  - Ivacaftor
Enzyme Therapy for CF Airways Secretions – Dornase Alfa: Overview

Background
- Neutrophil-released DNA and F-actin ↑viscoelasticity and adhesiveness of CF sputum

Dornase alfa
- Recombinant human DNase I
- Breaks down extracellular DNA
- Transforms purulent CF sputum to free-flowing liquid in vitro
- Approved December 1993

Pulmonary Guidelines for 2013

- Not routinely recommended:
  - Inhaled corticosteroids,
  - Anticholinergics,
  - Leukotriene receptor agonists,
  - N-acetylcysteine,
  - Beta agonists
Ivacaftor – The CFTR Modulator

- New class of therapies, treat underlying CFTR defect
- Ivacaftor improves CFTR regulation at cell surface
- Approved for patients >6 yr with G551D mutation (5% of CF)
CFTR Modulation: Ivacaftor

Adapted from Welsh and Smith (1993) and modified from Claustres (RBM online, 2005)
Observed Benefits of Ivacaftor

- Increase in FEV1 by 10%
- Decreased time to next pulmonary exacerbation
- Weight gain from baseline
- Improved quality of life
- Reduction in sweat chloride
- WHAT about the cost???

B Ramsey et al. NEJM 365:1663-72 (2011)
Antibiotic options changing...

http://commons.wikimedia.org/wiki
File:Intravenous_charge_up.jpg
File:CFnebulizer.jpg
Respiratory Germs by Age (CF Registry 2010)

S. aureus > P. aeruginosa (until 18 yr)
New inhaled antibiotics for CF

2000: Tobramycin

2010: Tobramycin
       Aztreonam

2015+: Tobramycin
       Aztreonam
       Tobramycin powder
       Vancomycin
       Amikacin
       Levofloxacin
CF drug development pipeline

**CFTR Modulators**
- Ivacaftor (to patients) ➔ Improve CFTR function (G551D)
- VX-809 and Ivacaftor (Phase 3) ➔ Improve CFTR processing and function (df508)
- VX-661 and Ivacaftor (Phase 2)

**Inhaled anti-infectives**
- Aztreonam (to patients) ➔ Pseudomonas
- Levofloxacin (Phase 3)
- Amikacin (Phase 3) ➔ Pseudomonas, NTM
- Vancomycin (Phase 2) ➔ MRSA
- Pseudomonas, NTM
- MRSA
New Guidelines for 2014

- CF Infection control guidelines
  - Contact precautions: gown and gloves for all CF patients (new recommendation in 2013!)
  - Unrelated CF patients should not be within 6 feet of each other
CF Foundation Guidelines

- Patients should be followed in an accredited CF Center

- Multidisciplinary CF team
  - MD
  - Nurse
  - Respiratory Therapist
  - Nutritionist
  - Social Worker
CF Foundation Guidelines

- CF Center visits at least 4x per year
  - Spirometry (FEV1) and respiratory culture every visit (sputum or deep pharyngeal)
  - Annual labs (CMP, LFT’s, coagulation factors, fat-soluble vitamins, IgE)
  - Annual chest-x-ray
  - Nutrition assessment at least annually
  - Social work assessment at least annually
Cystic Fibrosis in NC

- Per CF Foundation, all patients should be followed in an accredited CF Center

- Durham – Duke
- Chapel Hill – UNC
- Winston Salem - WFU
- Charlotte
- Asheville
- ECU – in progress

Large portion of eastern NC > 100 miles from any CF Center
Life would be infinitely happier if we could only be born at the age of eighty and gradually approach eighteen........

Mark Twain