Asthma and Cystic Fibrosis

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What is Asthma?
What is Cystic Fibrosis?
What can these conditions tell us about lung biology and disease?
Case 1:

5 year old boy, born in Boston.
Coughs and wheezes frequently.
Several viral illnesses per year. First, and most severe episode, occurred when he was 7 months old.
Good growth and development.
Has patches of dry skin on elbows and cheeks.
Mother, father, and sister with similar symptoms.
Father smokes, but “only outside.”
Lives near Dudley MBTA station.
Case 2:

11 year old boy, born in Boston. Coughs and wheezes frequently, with bronchitis and pneumonias. Difficulty gaining weight; frequent constipation and abdominal pain. Nasal polyps noted. Other family members healthy. Visits relatives in Ireland and Scotland yearly. No smokers or environmental exposures.
Case 3:

19 year old woman, born in Boston.
Coughs only occasionally, wheezes with exercise.
Generally healthy, moderately overweight.
Frequent loose stools.
Mother morbidly obese; father healthy.
Noted to have “lung scarring” on chest X-ray, taken by Immigration Service when visiting family in Montreal.
Pediatric Asthma Morbidity
Burden of disease

- Most common chronic illness in childhood
  - Highest-ranking condition causing hospitalization
  - 87% had unscheduled physician visits in the prior year

- Number one chronic illness causing school absence
  - 3x the school absences of children without asthma
  - 40% of patients have disturbed sleep 1–2 nights per week

- 78% of parents report a negative impact on family
  - 36% of parents missed work in the prior year
Asthma: intermittent obstruction to air flow induced by a variety of stimuli in a susceptible individual.

Genetic: strong family history

Immunologic: inflammation

Environmental: irritants and allergens

Infectious: viral infections and inflammation

Mechanical: obstruction to airflow
Asthmatic Inflammation

Asthma is a chronic inflammatory disorder

Airway Inflammation leads to:

- Hyperresponsiveness - responses to triggers
- Obstruction - usually fully reversible
- Symptoms - cough, wheeze, dyspnea

While symptoms are easily appreciated, symptoms are not the fundamental aspect of asthma

The “Tip” of the Iceberg

Symptoms

- Airflow obstruction
- Bronchial hyperresponsiveness
- Airway inflammation

TITANIC
Airway Inflammation in Childhood Asthma

Thickening of basement membrane, leads to proliferation of smooth muscle and reduced airway lumen.

Barbato, AJRCCM, 2003
What causes a reduction in airway lumen?
- inflammation
  infection, usually viral
  irritation, such as gastric acid
  allergic, autoimmune
  systemic illness or disease
What causes a reduction in airway lumen?

- inflammation
  - infection, usually viral
  - irritation, such as gastric acid
  - allergic, autoimmune
  - systemic illness or disease

Chronic airway inflammation and constriction may become irreversible with time, as the lung responds to inflammation with proliferation of smooth muscle around the airway.
Why is constriction of the airways a bad thing?

Resistance to laminar flow within the connecting airways is dependent on several properties of the lung (Poiseuille’s law)

\[ R = \frac{8 \eta l}{\pi r^4} \]

- \( n \) viscosity
- \( l \) length
- \( r \) radius
Why is constriction of the airways a bad thing?

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If the radius is halved, the resistance increases 16-fold!
How is asthma diagnosed?

- **history**: wheezes with colds
- **physical exam**: wheeze, cough, signs of allergy
- **laboratory evaluation**:
  - Chest X-ray
  - Pulmonary Function Tests (PFT)
  - Peak Expiratory Flow Rate (PEFR)
- **lab tests**:
  - immune function
  - allergic component
  - sweat test (CF)
Asthma Severity Scoring

- Mild Intermittent
- Mild Persistent
- Moderate Persistent
- Severe Persistent
**Pediatric Asthma Guidelines**

Goals of asthma therapy

- Minimal – ideally NO – symptoms during the day or at night
- Minimal – ideally NO – asthma episodes
- Minimal use (<1x/day) of short-acting beta-agonist
- PEF ≥80% of personal best (if used)
- Minimal – ideally NO – adverse effects from medications
- NORMAL ACTIVITIES

*American Academy of Allergy, Asthma & Immunology; American Academy of Pediatrics: NAEPP / NHLBI / NIH*
Challenges in Treating Childhood Asthma

- May be difficult to make a "definitive" diagnosis in very young children
  - Lack of objective measurement
  - Lack of subjective awareness of symptoms

- Underdiagnosis of asthma is a frequent problem in children
Control of Factors Contributing to Asthma Severity

- Allergens
- Environmental triggers
- Exercise
- Can asthma be prevented?
Challenges in Treating Childhood Asthma

Environmental control measures

- Reduce tobacco (and other) smoke exposure
- Reduce allergen exposures
  - Dust mites: Encase pillows & mattress
  - Pets: Remove from home (or bedroom)
  - Cockroaches: Remove food and garbage
  - Molds: Reduce indoor humidity
- Reduce airborne irritants: Fumes, etc.
Pharmacologic Therapy

• Goals of therapy
• Step-wise approach to asthma management
• Follow-up recommendations
Challenges in Treating Childhood Asthma
Selecting appropriate medications

Quick-relief medications
- Short-acting beta-agonists
- Inhaled anticholinergics
- Systemic corticosteroids

Long-term control medications
- Corticosteroids
- Cromolyn sodium, nedocromil
- Long-acting inhaled $\beta_2$-agonists
- Theophylline
- Leukotriene modifiers
Effects of Inhaled Corticosteroids on Inflammation

Pre– and post–3-month treatment with budesonide (BUD) 600 mcg b.i.d.

Central Role of Leukotrienes in Asthma

- Decreased Mucus Transport
- Cationic Protein Release, Epithelial Cell Damage
- Increased Mucus Secretion
- Eosinophil Influx
- Sensory Nerves (C-Fibers)
- Contraction and Proliferation
- Airway Smooth Muscle

LTD$_4$

Edema

Blood Vessel

Inflammatory Cells (e.g., Mast Cells, Eosinophils)

Effects of Corticosteroids on Inflammatory Cells

- Epithelial cell
- Neutrophil
- Basophil
- Mast cell
- Smooth muscle cell
- Dendritic cell
- Macrophage
- Monocyte
- Eosinophil
- Neuron
- B cell
- Smooth muscle cell
- Myofibroblast

Mediator release modified

Corticosteroids affect the release of various mediators from different cell types, including cytokines, chemokines, and adhesion molecules.
Do children outgrow asthma?

MARTINEZ, JACI, 1999
Description of Cystic Fibrosis

“Cystic Fibrosis of the Pancreas and its Relation to Celiac Disease: A Clinical and Pathologic Study”

Dorothy H. Anderson, M.D.


“The chief pathologic changes were as follows:

1. The acinar tissue of the pancreas was replaced by epithelium-lined cysts containing concretions…

2. The lungs showed bronchitis, bronchiectasis, pulmonary abscesses arising in the bronchi…”
Cystic Fibrosis

- Most common lethal inherited disease in Caucasians (25,000 in US)
- Incidence: 1:2500 births (4% carriers)
- Clinical manifestations: progressive bronchiectasis, chronic cough and sputum production, dyspnea, respiratory failure
- Standard therapy: chest physical therapy, inhaled mucolytics, antibiotics, and oral pancreatic enzyme replacement
- Median survival (years):
  - Enzyme supplements
  - Improved antibiotics
  - General care and nutrition

![Graph showing median survival over time from 1940 to 2000]
Organs affected by CF

- Airways
- Liver
- Pancreas
- Small intestine
- Reproductive tract
- Skin (sweat gland)
CFTR: Cystic Fibrosis Transmembrane Regulator

Gene cloned in 1989 by studying large families with CF

Located on chromosome 7, spanning 188,700 bp; 27 exons

Many mutations now identified:
  over 800 individual mutations that cause CF

“Hot-spot” for mutation - possible role in pathogenesis?

Most common in Northern Europe:
  delta-F 508 homozygous, caused by a triplet nucleotide deletion
Localization of CFTR expression

- **Epithelial (high)**
  - Pancreatic ducts
  - Salivary/sweat ducts
  - Male genital ducts
  - Kidney tubules

- **Epithelial (low)**
  - Lung
  - Jejunum/colon

- **Potential other**
  - Fibroblasts, organelles

- **Respiratory epithelium**
  - (Exocrine tissues)
Infection and inflammation lead to airway obstruction.
Correlates of pulmonary disease progression: Bronchiectasis
Pathogenesis of CF lung disease

- CF Gene Mutations
- CFTR Dysfunction
- Ion Transport Abnormalities
- Altered Airway Secretions
- "Vicious Cycle": Inflammation → "Vicious Cycle" → Infection
- Tissue Damage
Predicted structure of CFTR (Cystic Fibrosis Transmembrane conductance Regulator)
CF pathophysiology: role of CFTR
CF: a heterozygote advantage?

- Clinical picture of CF reported world-wide
- Highest gene frequency found in Northern Europe (approximately 1 in 25)
- Persistence of a “lethal” gene:
  - genetic drift
  - recurrent random mutations
  - heterozygote advantage (increased fertility or survival benefit)
- Selective advantage of 2% occurring 23 generations ago could explain high observed incidence of CF
Principal infectious causes of infant mortality
(ca 500-1500 AD)

- Plague
- Smallpox
- Typhus
- Endemic tuberculosis
- Epidemic cholera

Rodman and Zamudio, Med Hypoth 1991; 36:253
CF: a heterozygote advantage

Fluid accumulation in mouse small intestine in response to infusion of cholera toxin

Gabriel et al, Science 1994, 266:107
CFTR genotype

Basic defect

Symptoms

Modifier genes

Environmental factors
CFTR Mutations in Other Diseases

- Congenital bilateral absence of vas deferens (CBAVD)
- Obstructive azoospermia
- Chronic obstructive pulmonary disease (COPD)
- Diffuse bronchiectasis
- Allergic broncopulmonary aspergillosis
- Chronic pseudomonas bronchitis
- Chronic bronchial hypersecretion
- Chronic sinusitis
- Pancreatitis
- Asthma
Genotype-Phenotype Correlations

Genotype

Sweat gland: GOOD
Pancreas: GOOD
Lung: BAD

CFTR Mutation and Clinical Consequence

Severity scale

Normal

CBAVD, COPD, pancreatitis, etc.

PS CF PI

Typical mutations

Atypical mutations
CF lung disease

CF Gene Mutation
CFTR Dysfunction
Abnormal Ion Transport
Viscous Secretions

Chronic Inflammation
Infection
Pulmonary Insufficiency
Lung Damage
Premature Death
Molecular Consequences of CFTR Mutations

<table>
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<tr>
<th>Normal</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
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<tbody>
<tr>
<td>No synthesis</td>
<td>Block in processing</td>
<td>Block in regulation</td>
<td>Altered conductance</td>
<td>Reduced synthesis</td>
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<td>Missense</td>
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New therapies for CF

Abnormal Gene → Abnormal Protein → Altered Ion Transport → Infection & Inflammation → Organ Destruction

Abnormal Gene
- Abnormal Gene

Abnormal Protein
- Abnormal Mucus Secretion

Altered Ion Transport
- Altered Ion Transport
- Abnormal Mucus Secretion

Infection & Inflammation
- Infection
- Inflammation

Organ Destruction
- Organ Destruction
- Respiratory Failure

Genetic therapy
- tgAAVCF
- Liposomes
- Receptor-mediated Gene transfer

Molecular therapy
- Gentamicin
- Phenylbutyrate
- Genistein
- 7,8 Benzoflavones
- CPX
- Curcumin

Ion Transport
- INS37217
- Moli1901 (Duramycin)
- Mucolytic
- Nacystelyn

Molecular therapy
- Gentamicin
- Phenylbutyrate
- Genistein
- 7,8 Benzoflavones
- CPX
- Curcumin

Infection
- TOBI efficacy study
- TOBI nebulizer study
- P113D
- IB367
- RSV vaccines
- PA1806
- Macrolides

Inflammation

Organ Destruction
- Organ Destruction
- Respiratory Failure

Transplantation

Destruction
Gene replacement therapy

✓ Rationale: abnormal gene leads to production of abnormal CFTR

✓ Available therapies:
  ✓ none

✓ Potential therapies:
  ✓ viral vectors
  ✓ non-viral methods
CFTR molecular therapy

ν Rationale: abnormalities in CFTR lead to defective processing, regulation, or conduction

ν Available therapies:
  ν none

ν Potential therapies:
  ν replace missing CFTR protein
  ν “chaperone” CFTR to apical membrane (i.e. ΔF508)
  ν activate defective CFTR
  ν suppress stop-codon mutations with antibiotics, such as gentamicin
Airway secretions and clearance
Pulmozyme® (rhDNase) improves CF sputum pourability

**N-acetyl L-cysteine (Mucomyst)**

- Mucolytic
- Anti-inflammatory
- Antiprotease
- Antioxidant
TOBI: inhaled tobramycin antibiotic

✓ Specific and potent antibiotic against pseudomona bacteria
✓ Inhaled delivery system reduces systemic toxicity
✓ Usually combined with other antibiotics
✓ Can be delivered at home, reducing exposure to other bacteria
Airway inflammation in CF:
Neutrophil dominated
Anti-inflammatory therapy: Effect of ibuprofen on FEV1

Lung Transplantation

- Final therapeutic option
- Technical and surgical hurdles manageable
- Decision when to transplant remains difficult
- 5-year survival is approximately 50%
- Limited availability of organ donation
- Challenge is in long term treatment of immunosuppression and rejection
Therapeutic Approaches to CF

Abnormal Gene → Abnormal Protein → Altered Ion Transport → Infection & Inflammation → Organ Destruction

Abnormal Mucus Secretion → Tissue Destruction → Respiratory Failure

Genetic therapy: - tAAVCF* - Liposomes - Receptor-mediated Gene transfer

Molecular therapy: - Gentamicin - Phenylbutyrate - Genistein - 7,8 Benzoflavones - CPX - Curcumin*

Ion Transport: - INS37217* - Moli1901 (Duramycin)

Mucolytic: - Nacystelyn*

Infection: - TOBI efficacy study* - TOBI nebulizer study - P113D - IB367 - RSV vaccines - PA1806 - Macrolides

Transplantation: - Acute and chronic rejection

Long term immunosupression

Inflammation: - DHA (Lumarel) - Protease inhibitors - BIIL 284* - Tyloxapol - GSH, Immunocal - Interferon gamma
Future Studies and Treatments

- Improved nutrition, antibiotics, and support
- Role of early diagnosis through newborn screen
- Gene therapy
- Stem cell therapy
- Improved transplantation treatments
- Modifying genes
- Understanding of cellular role of CFTR protein
What do Asthma and CF have in common?

- Genetic basis
- Broad spectrum of clinical presentation
- Expression of symptoms related to other factors
- Airway inflammation
- Similar treatments: anti-inflammatory medications
- Modifying genes
How do Asthma and CF differ?

- Genetic basis: single gene versus many
- Tissue and organs affected
- Airway inflammation
- Different treatments: antibiotics and nutrition
- Different progression of disease
- Modifying genes

- However, basic science advances may shed light on both diseases
Acknowledgements

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BALF neutrophil counts in CF

Molecular therapies for CF
Therapeutic approaches to CF lung disease

Gene therapy
- Defective gene
- Defective protein (CFTR)

ATP, UTP
- Abnormal epithelial ion transport
- Amiloride
- Na+
- CF

Domase alfa
- Gelsolin

Airway clearance techniques

Viscous intraluminal secretions

Release of DNA and F-actin from degraded cells

"Vicious Cycle"

Oral, aerosol, and IV antibiotics
- Immunoglobulin G

Immunostimulants

Corticosteroids
- Ibuprofen

Antiproteases

Chronic bacterial infection

Accumulation of inflammatory cells and release of proteolytic enzymes

Irreversible lung injury

Lung transplantation
Introduction to Cystic Fibrosis

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