Children’s Interstitial and Diffuse Lung Disease
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Outline
• Case
• Introduction to child
• Difference between child and adult ILD
• Description of common forms of child
• Treatment
• Conclusion

Case: History
• Full term infant, discharged from nursery
• Admission for respiratory distress at 7 weeks
  • Continued desaturation events ➔ mechanical ventilation
  • Refractory to treatment
• Family history
  • Paternal uncle who died of “pneumonia” at 6 months
  • Paternal grandfather who died of “lung disease”
Case: Initial CT scan

![CT scan image]

Case, Continued

- Unable to extubate → tracheostomy with chronic ventilation
- Ventilator wean over time, off by age 3
- Respiratory hospitalizations every 1-2 years
- Decannulated and room air at age 6
- DNA testing age 5: G182R mutation in SFTPC

Biopsy

- Diffuse alveolar proteinosis with lipid/iron laden macrophages
- Type II cell hyperplasia
- Septal widening
Outline

• Case
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• Difference between chILD and adult ILD
• Description of common forms of chILD
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What is chILD?

• Children’s Interstitial and Diffuse Lung Disease
• Diverse group of rare pulmonary disorders
• In the absence of known causes of lung disease, patients with at least 3 of the following:
  • Respiratory symptoms
  • Respiratory signs
  • Hypoxemia
  • Diffuse abnormality on chest imaging
• Pathology can be in airway, airspace (alveolar), and/or interstitium

Deterding 2007, Van Hook.
AJRCCM 2006;174A244

Airway: Bronchiolitis Obliterans
Airspace: Pulmonary Alveolar Proteinosis

Interstitial: Capillaritis

When do I need to think about chILD?
Symptoms:
• Cough
• Wheeze
• Exercise intolerance/shortness of breath
• Retractions

Signs:
• Retractions
• Crackles
• Clubbing
• Abnormal chest wall (barrel, pectus excavatum, pectus carinatum)

Testing:
• Low saturations
• Abnormal chest imaging
• Abnormal pulmonary function tests

Nota Bene
• A normal lung exam does not mean normal lungs!
• ~40% of patients in a North American review of children aged 2-18 years who underwent lung biopsies for chILD had NORMAL lung exams (Fan et al 2016)

Clinical-pathological Classification Scheme

I. Disorders of Infancy
- Diffuse developmental disorders
- Growth abnormalities
- Specific conditions of unknown/poorly understood etiology
- Surfactant dysfunction disorders and related abnormalities

II. Primary lung disorders of the immunocompetent host
- Infections and post-infectious processes
- Disorders related to environmental agents
- Aspiration syndromes
- Eosinophilic pneumonias
- Nonspecific interstitial pneumonia
- Idiopathic pulmonary hemosiderosis
- Others

III. Disorders related to systemic disease processes
- Immune-mediated disorders
- Storage disease
- Sarcoidosis
- Langerhans Cell Histiocytosis
- Malignant infiltrates
- Others

IV. Disorders of the immunocompromised host
- Opportunistic infections
- Disorders related to therapeutic intervention
- Disorders related to solid organ, lung, and bone marrow transplantation and rejection syndromes
- Diffuse alveolar damage of undetermined etiology
- Lymphoid infiltrates related to immune compromise (non-transplanted patients)

V. Vascular disorders masquerading as interstitial lung disease
- Arterial hypertensive vasculopathy
- Congestive vasculopathy and veno-occlusive disease
- Lymphatic disorders
- Pulmonary edema
- Thromboembolic disease
- Unclassified
- End-stage disease
- Non-diagnostic
- Inadequate tissue
- Insufficient information

Deutsch et al 2007, Langston and Dishop 2009
Workup for chILD: Patient specific

- Imaging
  - usually high resolution CT chest with inspiratory and expiratory views
- Pulmonary function testing
  - Spirometry
  - Lung volumes
  - Diffusion capacity
  - 6-minute walk
- Infant PFTs
- Genetic testing
  - Gene specific
  - Panel
  - Whole exome
  - Whole genome
- Echocardiogram
- Swallow study

ATS Guidelines: neonatal

ATS Guidelines: infancy
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How is chILD different from ILD in adults?

IPF slides courtesy of Dr. Joyce Lee, University of Colorado School of Medicine
Interstitial Lung Disease (adults)

- Heterogeneous group of disorders (>100) classified together because of similar clinical, radiographic, physiologic and/or pathologic manifestations
- Not just the interstitium – peripheral airway and alveolar involvement as well
- Common clinical presentation
  - Dyspnea, abnormal imaging studies, restrictive pulmonary physiology, increased A-a gradient

Children are not small adults

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>0.13* variable</td>
</tr>
<tr>
<td>Dominant Pathology findings</td>
<td>UIP</td>
</tr>
<tr>
<td>Specific Entities</td>
<td></td>
</tr>
<tr>
<td>Growth Abnormalities</td>
<td>Yes</td>
</tr>
<tr>
<td>NEHI</td>
<td>Yes</td>
</tr>
<tr>
<td>P.I.G.</td>
<td>Yes</td>
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<tr>
<td>SP-B Mutations</td>
<td>Yes</td>
</tr>
<tr>
<td>Bronchiolitis Obliterans</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Yes</td>
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*OJRD. 2009;4:26
#AJRCCM 1994;150:967

Kids: NEHI
Surfactant dysfunction
Growth

Adults: Idiopathic pulmonary fibrosis
Sarcoidosis
Hypersensitivity pneumonitis
Bronchiolitis obliterans
Rheumatologic associated disease
CLINICAL CLASSIFICATION

INTERSTITIAL LUNG DISEASE

Exposure-related:
- Occupational
- Environmental
- Avocational
- Medication

Other:
- Sarcoidosis
- Vasculitis/Diffuse alveolar hemorrhage (DAH)
- Langherhans cell histiocytosis (LCH)
- Lymphangioleiomyomatosis (LAM)
- Pulmonary alveolar proteinosis (PAP)
- Eosinophilic pneumonias
- CVID
- Inherited disorders
- Chronic aspiration
- Inflammatory bowel disease
- IgG4 disease

CTD
- Scleroderma
- RA
- Sjogrens
- MCTD
- Myositis
- IPAF

Idiopathic
- Interstitial pneumonia (IIP)
- Pulmonary fibrosis (IPF)
- Desquamative interstitial pneumonia (DIP)
- Acute interstitial pneumonia (AIP)
- Usual interstitial pneumonia (UIP)/IPF

Estimated Relative Distribution of Specific Interstitial Lung Diseases (ILDs) in the United States.

Re-evaluation of the pathology (1990s)

LUMPERS
- Interstitial lung disease
- Non-specific interstitial pneumonia (NSIP)
- Lung fibrosis due to arthritis
- Desquamative interstitial pneumonia (DIP)
- Acute interstitial pneumonitis (AIP)
- Usual interstitial pneumonia (UIP)/IPF

SPLITTERS

Courtesy of Dr. Joyce Lee
Differentiating disease predicts prognosis

**LUMPERS (1950-1990)**

**Splitters (2000)**

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**Idiopathic Pulmonary Fibrosis (IPF)**

- One of the most common causes of lung fibrosis
- Usual interstitial pneumonia (UIP) pattern
- Men more than women
- Former smokers
- Disease of the aging population
- Average survival from diagnosis: 3-5 years
- 40,000 deaths per year

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**IPF Clinical Course**

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Back to chILD and wrap up

An overview of chILD types
Surfactant Deficiency-not chILD

- Prematurity
  - 50% of 26-28 weekers
  - 30% of 30-31 weekers
- Lack of surfactant production → increased surface tension → edema and poor compliance → respiratory acidosis → vascular leak → hyaline membranes
- Prevent by prolonging gestation and antenatal steroids
- Treat with surfactant and respiratory support

SFTPC Mutation
Neuroendocrine cell hyperplasia of infancy: NEHI

- Fan clinical criteria
  - Under 1 year
  - Tachypnea
  - Failure to thrive
  - Hypoxemia
  - No clubbing
  - No wheeze when well
  - No cough when well
  - Barrel chest
  - Retractions
  - Crackles

- Infant PFTs: obstruction, air trapping, and tachypnea
- CT chest: lingular/RML perihilar ground glass
- Biopsy: bombesin stain positive for neuroendocrine cells
- Lower IL-1B, MIP-1B, IL8 in BAL (Popler et al)

Outcomes: vary widely

<table>
<thead>
<tr>
<th>Table 2. Age at death and outcome by category</th>
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</thead>
<tbody>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Extensive meningeal disease</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
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<tr>
<td>Vascular malformations</td>
</tr>
<tr>
<td>Arterial platelet</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Males with neurodevelopment of severe trauma</td>
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<td>Females with neurodevelopment of severe trauma</td>
</tr>
</tbody>
</table>

Deutsch 2007
Case 2:

- 10 year old with ALL status post HSCT
- Skin and ocular graft vs host disease

Pulmonary function tests

Bronchiolitis Obliterans

- BO (or OB)
- Fibrosing chronic obstructive disease
- Signs/symptoms:
  - Tachypnea, crackles, wheezing, hypoxemia
  - Indolent onset
Evaluation of BO

- Symptoms
- Pulmonary Function Tests (obstruction and airtrapping)
- HRCT
- Lung Biopsy

HRCT findings in BO

Biopsy Findings in BO (NOT the same as BOOP)

- Near complete obliteration
- Residual mucosal epithelium
- Subepithelial fibrosis
- Peripheral rim of smooth muscle
Bronchiolitis Obliterans

- **Etiology:**
  - *Post infectious* (adenovirus, measles, mycoplasma)
  - *Post transplant*: chronic graft vs host
    - Lung transplant
    - Hematopoetic stem cell transplant
  - Connective tissue disease
  - Toxin/drugs
  - Hypersensitivity
  - Aspiration
  - Stevens Johnson syndrome

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When to think about chILD

- Neonate with respiratory distress out of proportion to gestational age
- Infants with hypoxemia, poor weight gain, crackles when well, and recurrent infections
- Older children with unexplained respiratory signs and symptoms, especially after illnesses, transplant (lung or HSCT), and/or exposures

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When to think about chILD

- **Symptoms:**
  - Cough
  - Wheeze
  - Exercise intolerance/shortness of breath
  - Retractions
- **Signs:**
  - Retractions
  - Crackles
  - Clubbing
  - Abnormal chest wall (barrel, pectus excavatum, pectus carinatum)
- **Testing:**
  - Low saturations
  - Abnormal chest imaging
  - Abnormal pulmonary function tests
Treatment: disease specific

- Steroids?
  - P.I.G. (Deutsch and Young 2009)
  - chILD (Kurland et al 2013)
- IVIG?
  - Bronchiolitis obliterans
- Hydroxychloroquine?
  - ABCA3 (Williamson and Wallis 2013)
  - SFTPC (Rosen and Waltz 2005)
- Supportive care
  - Nutrition
  - Prevent aspiration
  - Respiratory support: oxygen, non invasive ventilation, invasive ventilation
  - Vaccines
  - Monitor for pulmonary hypertension

Treatment for chILD

- Antifibrotics? Trial with nintedanib (ofev) is underway for <18 years

?

VERY little literature on treatment.
The less one knows about a given condition, the more likely one is to try corticosteroids for it.

—a wise man who taught me most of what I know

Thank you!