Interstitial Lung Disease in Infants and Children
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DIFFUSE (INTERSTITIAL) LUNG DISEASE IN YOUNG CHILDREN
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The Problem of Classification
- Beyond the interstitium (path includes airways/airspace)
- Radiographic diffuse disease
- Adult Interstitial Lung Disease Classification
  - Different spectrum, frequency, path, outcome
  - Many idiopathic entities distinct to peds

CHILD Research Cooperative
- New attempt at classification
- Still a work in progress
- Hope to incorporate clinical/radiology/path going forward
- Radiographically diffuse lung disease

Broad categories
- Disorders of Infancy
- Disorders related to systemic disease
- Disorders of normal host
- Disorders of immunocompromised host
- Disorders masquerading as ILD

Disorders Related to Infancy
- Diffuse Developmental Disorders (FETAL)
- Growth abnormalities (Post-fetal alveolarization)
- Disorders of undefined etiology *
- Surfactant dysfunction disorders

Review of Embryology
- Pseudoglandular phase (6-16 weeks)
  - All lung elements form except alveoli
- Canalicular phase (16-26 weeks)
  - Lung tissue vascularized
  - Bronchioles and alveolar ducts form
- Terminal sacular phase (26 weeks to birth)
  - Type I and Type II pneumocytes form
- Alveolar phase (birth to 5 years)
**Diffuse Developmental Disorders (FETAL)**
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**Growth Abnormalities/Deficient Alveolarization**
- Primary (rare)
- Secondary (much more common)
  - Prenatal pulmonary hypoplasia
    - CDH and abdominal wall defects, Skeletal dysplasias, neuromuscular disorders prohibiting fetal breathing, chromosomal
  - Postnatal pulmonary hypoplasia-Chronic Lung Disease of Prematurity (BPD)
- Lobular simplification/alveolar enlargement
- Mortality 34%

**Radiology for these is Rare**
- Reduced lung volumes/increased pulmonary vascularity reported for CAD
- Many other etiologies to consider
- Need clinical picture
- CT not likely

**Disorders Related to Infancy**
- Acinar dysplasia (pseudoglandular or canalicular phase)
- Congenital alveolar dysplasia
- Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV)
- All show arrest of lobular development and reduced alveolar capillary density
- Term infants with hypoxia, PHTN unresponsive to ventilatory support

**Diffuse Developmental Disorders**
- Poorly understood
- Likely abnormality is a primary molecular mechanism of lung or pulmonary vascular development
- Mortality 100%
Four Stages
- RDS and its complications (PTX, PIE)
- Fine or coarse diffuse opacities
  - Air trapping, ATX, sequelae of PHTN on CT
- Bubbly appearance, cystic distortion, triangular opacities from deep pleural fissuring, subpleural bands, bronchiectasis
- Hyperexpansion, lower lobe air-trapping
Diffuse Developmental Disorders (FETAL)
- Growth abnormalities (Post-fetal alveolarization)
- Disorders of undefined etiology (PIG, NEHI)
- Surfactant dysfunction disorders (and associated conditions-CPI, infantile DIP)

Pulmonary Interstitial Glycogenosis (PIG)
- Mesenchymal cells in interstitium
- Histology: Vimentin positive
- Hypoxia, tachypnea in first six months of life
- Responds to steroids-favorable prognosis with rare mortality
- Diffuse markings, interspersed cystic change, hyperinflation, may mimic CLD of prematurity
- Infantile Cellular Interstitial Pneumonitis

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Neuroendocrine Cell Hyperplasia of Infancy (NEHI)
- Neuroendocrine cells in bronchioles
- Needs BOMBESIN stain for diagnosis
- Symptoms out of proportion to minor biopsy findings
- Rarely hospitalized, does not respond to steroids
- Characteristic radiographic appearance
  - RML/Lingula GGOS and diffuse air trapping

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Surfactant
- Type II pneumocytes
- Reduces surface tension
- Protein (10%) and phospholipids (90%)
- Hydrophobic proteins (SP-B and SP-C) help lipids form monolayer at air-liquid interface
- Membrane transporter (ABCA3)
- (GM-CSF receptors on macrophages and epithelial cells)

Histopathology
- Desquamative Interstitial Pneumonitis (DIP)
  - Alveolar macrophages
- Nonspecific Interstitial Pneumonitis (NISP)
  - Wide histologic spectrum
- Pulmonary Alveolar Proteinosis (PAP)
  - Lipoproteinaceous material, positive PAS
- Chronic Pneumonitis of Infancy (CPI)
  - Type II pneumocyte hyperplasia, increased macrophages, PAS positive globules

Surfactant Dysfunction Disorders
- Surfactant Protein B, C, ABCA3 mutations
- Unrecognized or poorly understood etiology, still defined by the histopathology
  - Congenital PAP
  - Chronic Pneumonitis of Infancy
  - DIP/NSIP
- These may disappear over time as the genetics become better understood
**SP-B deficiency**
- Full term infant with diffuse disease
- Histology: PAP
- Initially, resembles RDS clinically and radiographically
- Failure to resolve
- 100% mortality

**Premature infant with RDS**

**SP-B picture**

**ABCA3 mutation**
- Clinically may resemble SP-B (full term infant-RDS picture) or present in older children/young adults
- Fatal neonatal cases to chronic disease in older patients
- Histology: PAP, DIP, NISP
- Reported findings:
  - Ground glass
  - Septal thickening
  - Peripheral cysts

**4 year old female**

**16 year old male**
**Protein C deficiency**
- Wide range of onset, usually older children and adults
- Neonatal infections to chronic lung disease in adults
- May present fifth or sixth decade with pulmonary fibrosis
- Histology: NSIP, CPI
- GGOs and lung cysts, paraseptal emphysema, septal thickening

**Complex or undefined genetics for a histologic diagnosis**
- Congenital PAP:
  - Isolated Protein B, ABCA3 mutations
  - Unstable mRNA SP-B leading to SP-C processing abnormality
  - GM-CSF receptor mutation
  - Crazy paving

**Complex or undefined genetics for a histologic diagnosis**
- Chronic Pneumonitis of Infancy
  - Protein C
  - Unknown
  - Ground glass opacity sparing periphery
  - Very poor prognosis

**Take home**
- Be aware of broad categories
- Look at the clinical picture
  - CLD, CDH, Omphalocele, Downs, etc
  - Diffuse lung disease in a very sick neonate that does not fit smaller traditional differential diagnosis

**Take Home**
- PIG
  - Hyperinflation-Cysts-CLD picture
  - Suggest Vimentin stain
- NEHI
  - Distinct air-trapping
  - Suggest Bombesin stain
- Surfactant deficiencies
  - GGOs, crazy paving, scattered cysts
  - Suggest genetic testing (may avoid a biopsy)