Pulmonary Complications of Dyskeratosis Congenita

Don Hayes, Jr., MD, MS
Nationwide Children’s Hospital
The Ohio State University
Conflicts & Disclosures

• No conflicts of interests

• No relevant disclosures

• Funding
  – Chest Foundation
  – Cystic Fibrosis Foundation
  – NIH
  – Ohio Solid Organ Transplant Consortium
Lung Development

- **Embryonic**
  - Human: Weeks 3–7 (E9-13)
  - Rat: E9-12
  - Mouse: E9-12

- **Pseudoglandular**
  - Human: Weeks 5–17 (E13-18)
  - Rat: E13-18
  - Mouse: E12-17

- **Canalicular**
  - Human: Weeks 16–26 (E18-20)
  - Rat: E17-18
  - Mouse: E18-PN5

- **Sacular**
  - Human: Weeks 24–38 (E20-T)
  - Rat: T-PN28
  - Mouse: PN5-28

- **Alveolar**
  - Human: Weeks 36 to 3 years
  - Rat: 38 Weeks
  - Mouse: 22 Days

*E = Embryonic, PN = Postnatal, T = Term
Anatomy of the Respiratory System

- Nose
- Pharynx
- Larynx
- Trachea
- Bronchi
- Lungs
- Vasculature
- Interstitium
Lungs
Function of the Respiratory System

• Passageways to the lungs purify, warm, & humidify the incoming air
• Oversees gas exchanges between the blood & external environment
• Exchange of gasses takes place within the alveoli
Lungs

• Occupy most of the thoracic cavity
  – Apex is near the clavicle (collar bone)
  – Each lung is divided into lobes by fissures
    • Left lung – two lobes
    • Right lung – three lobes
Respiratory Divisions

- Primary bronchi
- Secondary bronchi
- Tertiary bronchi
- Bronchioli
- Terminal bronchioli
Bronchioles

- Smallest branches of the bronchi
- All but the smallest branches have cartilage
- Terminal bronchioles end in alveoli
Respiratory Zone

• Structures
  – Respiratory bronchioli
  – Alveolar duct
  – Alveoli

• Site of gas exchange
Alveoli

- Structure of alveoli
  - Alveolar duct
  - Alveolar sac
  - Alveolus

- Gas exchange takes place within the alveoli across the respiratory membrane
- Covered with pulmonary capillaries
Respiratory Membrane
Gas Exchange

• Gas crosses the respiratory membrane by diffusion
  – Oxygen enters the blood
  – Carbon dioxide enters the alveoli
• Macrophages add protection
• Surfactant coats gas-exposed alveolar surfaces
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age years</th>
<th>Features of DC trial</th>
<th>Aplastic anaemia</th>
<th>Telomere length</th>
<th>Gene, mutation</th>
<th>TERT, c.2264C&gt;T</th>
<th>Danazol, dexamethasone</th>
<th>HCT indication</th>
<th>Age at HCT years</th>
<th>HCT preparation, GWAID prophylaxis</th>
<th>At PAMR diagnosis</th>
<th>Age at last follow-up years</th>
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<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>L</td>
<td>Mild</td>
<td>VL</td>
<td>TERT, c.2264C&gt;T</td>
<td>p. R756C</td>
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<td>N/A</td>
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<td>2</td>
<td>27</td>
<td>None</td>
<td>Moderate</td>
<td>VL*.</td>
<td>RET/LL. c.2264C&gt;A</td>
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<td>p. T469K</td>
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<td>18</td>
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<td>VL</td>
<td>Compound int. PARN</td>
<td>p.19A</td>
<td>C</td>
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<td>NTR1, gene deletion</td>
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<td>N/A</td>
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<td>VL</td>
<td>DKCI, c.1223C&gt;T</td>
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<td>Aplastic anemia</td>
<td>HCT</td>
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<td>TIN2, c.846G&gt;A</td>
<td>p. R292H</td>
<td>Aplastic anemia</td>
<td>HCT</td>
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<tr>
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<td>HCT</td>
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<td>Chronic hypoxia</td>
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</table>

**Note:** The table provides detailed information on patients with aplastic anemia, their gene mutations, treatment, and clinical outcomes.
Pulmonary Arteriovenous Malformations (Pulmonary AVMs)
Causes shunting of blood – blood bypasses oxygen loading in the lung
Tests to Evaluate the Lungs

• Blood
  – pH, gas levels
• Pulmonary function testing
  – Spirometry, lung volumes, diffusion capacity
• Chest x-ray
• CT scan of the chest
• MRI of the chest
• Bronchoscopy
  – Lavage, washings, brushings
• Lung biopsy (bronchoscopy, surgical)
• V:Q scan
• Cardiac echocardiography
• Heart catheterization

Help identify shunts
## Pulmonary Function Testing

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Predicted</th>
<th>Pre Drug Measured</th>
<th>Pre Drug % Predicted</th>
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<tr>
<td>FVC</td>
<td>4.26</td>
<td>3.35 &lt;</td>
<td>79 &lt;</td>
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<tr>
<td>FEV1</td>
<td>3.63</td>
<td>2.53 &lt;</td>
<td>70 &lt;</td>
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<tr>
<td>FEV1/FVC</td>
<td>85</td>
<td>76</td>
<td>89</td>
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<tr>
<td>FEF25%</td>
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<td>6.29</td>
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<td>FEF50%</td>
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<td>3.76</td>
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<tr>
<td>FEF75%</td>
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<td>0.55</td>
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<tr>
<td>FEFmax</td>
<td>7.46</td>
<td>6.35</td>
<td>85</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>3.85</td>
<td>2.07 &lt;</td>
<td>54 &lt;</td>
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<td>Pimax/MIP</td>
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<td>PEmax/MEP</td>
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</table>

**Flow Volume**
- Flow: 4 7/5/2017 12:57 PM
- Flow (L/s)
- PEF
- Volume (L)
Chest x-ray
Closer View of Interstitial Lung Disease
CT Scan of Chest
Pulmonary AVMs on Catheterization
Our Research

Sue Reynolds, PhD
Director

Cynthia Hill, BA, ALAT
Lung Stem/Progenitor Cells

Injury & Infection Activate Airway Epithelial Stem Cells

Shaykhiev R. Eur Respir J 2015;46(4):894-7
Conclusions

• Lung disease is an evolving complication of dyskeratosis congenita
  – Clinical evaluation
    • Comprehensive team with expertise in this area
    • Screening echo to assess for pulmonary AVMs
    • Heart catheterization may be needed
  – Collaborative research
    • Identify ways to diagnosis it early
    • Understand why lung disease develops
    • Develop therapies to prevent or treat lung disease
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Patrick McConnell, MD
Stephen Kirkby, MD
Hemalatha Rangarajan, MD
Almost Done With Me! ☺

don.hayes@nationwidechildrens.org
In Loving Memory  (5-15-03 to 10-17-17)

"Fight lung disease we must."

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