Paediatric PAH in the current era

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Paediatric PAH in the current era & A Gap Analysis

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Disclosures

I have the following financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity:

• The University of Colorado contracts with Actelion, Bayer, Lilly, and United Therapeutics for which I am a consultant

• UC Contract: Steering Committee Actelion / Bayer / Lilly / United Therapeutics

• Funding from NIH / FDA

I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Outline

- Definition and Classification
- Epidemiology
- CHD
- BPD
- Survival
- Guidelines for Treatment of PAH
Pulmonary Arterial Hypertension

Definition and Classification
5th WSPH Consensus Definitions: Right-heart Catheterization Confirmed

<table>
<thead>
<tr>
<th>Pulmonary Hypertension (PH)</th>
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<tbody>
<tr>
<td>Mean pulmonary artery pressure (mPAP)</td>
<td>≥25 mm Hg</td>
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<td>Mean pulmonary artery pressure (mPAP)</td>
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<tr>
<td>and</td>
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<tr>
<td>Mean pulmonary artery wedge pressure (PAWP)</td>
<td>≤15 mm Hg</td>
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<th>PH Hemodynamic Definition</th>
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<td>Pulmonary vascular resistance (PVR)</td>
<td>&gt;3 Wood units</td>
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5th WSPH: Classification of Pulmonary Arterial Hypertension by Etiology

- **Group 1 Pulmonary Arterial Hypertension (PAH)**
  - Idiopathic (IPAH)
  - Heritable (HPAH)
    - BMPR2
    - ALK-1, Endoglin, SMAD9, CAV1, KCNK3
    - Unknown
  - Drugs and toxins induced
  - Associated with
    - Connective Tissue Diseases
    - HIV Infection
    - Portal Hypertension
    - Congenital Heart Diseases
    - Schistosomiasis

- **Group 1’ Pulmonary Veno Occlusive Disease (PVOD) and/or Pulmonary Capillary Hemangiomatosis (PCH)**
- **Group 1” Persistent pulmonary hypertension of the newborn (PPHN)**

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5th WSPH: Clinical Classification of Other Forms of Pulmonary Hypertension

- **Group 2** -- Pulmonary Hypertension Due to Left Heart Disease
  - Left Ventricular Systolic Dysfunction
  - Left Ventricular Diastolic Dysfunction
  - Valvular disease
  - Congenital / acquired left heart inflow / outflow tract obstruction
- **Group 3** -- Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental lung disease
- **Group 4** – Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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• Group 4 -- Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

5th WSPH: Developmental Lung Diseases Associated With Pulmonary Hypertension

- Congenital diaphragmatic hernia
- Bronchopulmonary dysplasia
- Alveolar capillary dysplasia (ACD)
- ACD with misalignment of veins
- Lung hypoplasia ("primary" or "secondary")
- Surfactant protein abnormalities
  - SPB deficiency
  - SPC deficiency
  - ATP-binding cassette A3 mutation
  - Thyroid transcription factor 1/Nkx2.1 homeobox mutation
- Pulmonary interstitial glycogenosis (PIG)
- Pulmonary alveolar proteinosis (PAP)
- Pulmonary lymphangiectasia

Group 5 – Pulmonary Hypertension with Unclear Multifactorial Mechanisms

- **Hematologic disorders**: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
- **Systemic disorders**: Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculitis, **Down Syndrome**
- **Metabolic disorders**: Glycogen storage disease, Gaucher disease, thyroid disorders
- **Others**: Segmental PAH, tumoral obstruction, fibrosing mediastinitis, chronic renal failure

Multifactorial Etiology in Pediatric Pulmonary Hypertensive Vascular Disease

In utero pulmonary vascular disease: Transposition of the Great Arteries

Maeno, Y. V. et al. Circulation 1999;99:1209-1214
The broad schema of 10 basic categories of Pediatric Pulmonary Hypertensive Vascular Disease

1. Prenatal or developmental pulmonary hypertensive vascular disease
2. Perinatal pulmonary vascular maladaptation
3. Pediatric cardiovascular disease
4. Bronchopulmonary dysplasia
5. Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7. Pediatric lung disease
8. Pediatric thromboembolic disease
9. Pediatric hypobaric hypoxic exposure
10. Pediatric pulmonary vascular disease associated with other system disorders

Pulmonary Hypertension

Epidemiology
Annual Incidence Rates for Pediatric PAH

Year of diagnosis

Pulmonary Arterial Hypertension

Survival
Predicted survival according to the NIH equation. Predicted survival rates were 69%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively. The numbers of patients at risk were 231, 149, 82, and 10 at 1, 2, 3, and 4 years, respectively. *Patients with primary pulmonary hypertension, now referred to as idiopathic pulmonary hypertension.

Survival in the Current Era Using Off-Label Therapy (Denver/Dutch/NY)

Survival by WSPH Group

Pulmonary Arterial Hypertension

CHD-PAH
Table 3: Updated Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease*

1. Eisenmenger syndrome
   Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.

2. Left-to-right shunts
   - Correctable†
   - Noncorrectable
   Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.

3. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease
   Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.

4. Post-operative PAH
   Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

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Children classified according to the Nice-CHD-classification
Denver Dutch New York

Co-morbidities (n=60/134)
- Down (30)
- Noonan (3)
- DiGeorge (1)
- Turner (1)
- Robinow (1)
- VACTERL (1)
- Undefined Syndrome (3)
- Lung (8)
- HHT/GSD/ABCA3

Non-classifiable
- TAPVR
- Scimitar/ IPADO
- TGA +/- VSD

Pulmonary Arterial Hypertension

Lung Disease Associated PH
Pulmonary Arterial Hypertension

BPD
Survival in BPD-related PAH

N=42 premature infants with BPD-related PAH

Pulmonary Vein Stenosis
Pulmonary vein stenosis of ex-premature infants with pulmonary hypertension and bronchopulmonary dysplasia, epidemiology, and survival from a multicenter cohort

N=39

Pulmonary Arterial Hypertension

Guidelines for Treatment of PAH
## WSPH 2013 - Consensus Pediatric IPAH/HPAH Treatment Algorithm

### Higher risk vs. Lower Risk Factors

<table>
<thead>
<tr>
<th>LOWER RISK</th>
<th>DETERMINANTS OF RISK</th>
<th>HIGHER RISK</th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Progression of Symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Growth</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>I,II</td>
<td>WHO Functional Class</td>
<td>III,IV</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP / NTproBNP</td>
<td>Significantly elevated</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td>Rising level</td>
</tr>
</tbody>
</table>

- **Severe RV enlargement/dysfunction**
- **Pericardial Effusion**

<table>
<thead>
<tr>
<th>Systemic CI &gt; 3.0 L/min/m² mPAP/mSAP &lt; 0.75</th>
<th>Hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic CI &lt; 2.5 L/min/m² mPAP/mSAP &gt; 0.75</td>
<td>PVRI &gt; 20 WU*m²</td>
</tr>
</tbody>
</table>

RAP > 10mmHg

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Echocardiographic Predictors


Increased risk of transplant or death

1. FAC <15.5%
2. TAPSE z-score <-4.3
3. RVED z-score >4.8
4. RVESi <18.4
Treatment goals in Paediatric Pulmonary Arterial Hypertension

Ploegstra, et. al., European Respiratory Journal 2014 44: 1616-1626
3D Echocardiographic Evaluation of Right Ventricular Function and Strain: a Prognostic Study in Paediatric Pulmonary Hypertension

EDV: 337.7 ml
ESV: 272.5 ml
SV: 65.2 ml
EF: 19.29 %
RVLS (Septum): -5.31 %
RVLS (Frewall): -6.09 %

All patients (n = 96)  Event free (n = 78)  With event (n = 18)
Death, Transplant, IV Prostacyclin, PAH hospitalization, Potts, BAS
3D Echocardiographic Evaluation of Right Ventricular Function and Strain: a Prognostic Study in Paediatric Pulmonary Hypertension

![Graph showing diagnostic performance of various parameters]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Cut-off</th>
</tr>
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<tbody>
<tr>
<td>3D EDVi (mL/m²)</td>
<td>0.76</td>
<td>55</td>
<td>91</td>
<td>102</td>
</tr>
<tr>
<td>3D ESVi (mL/m²)</td>
<td>0.76</td>
<td>72</td>
<td>87</td>
<td>54</td>
</tr>
<tr>
<td>3D Svi (mL/m²)</td>
<td>0.62</td>
<td>66</td>
<td>64</td>
<td>37</td>
</tr>
<tr>
<td>3D EF (%)</td>
<td>0.83</td>
<td>90</td>
<td>67</td>
<td>43</td>
</tr>
<tr>
<td>2D Septal RVLS (%)</td>
<td>0.62</td>
<td>61</td>
<td>64</td>
<td>-15</td>
</tr>
<tr>
<td>2D Free wall LS (%)</td>
<td>0.68</td>
<td>48</td>
<td>93</td>
<td>-16</td>
</tr>
<tr>
<td>2D TAPSE (mm)</td>
<td>0.68</td>
<td>60</td>
<td>57</td>
<td>14</td>
</tr>
<tr>
<td>2D FAC (%)</td>
<td>0.80</td>
<td>97</td>
<td>57</td>
<td>32</td>
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3D Echocardiographic Evaluation of Right Ventricular Function and Strain: a Prognostic Study in Paediatric Pulmonary Hypertension
Expert Referral

General: Consider Diuretics, Oxygen, Anticoagulation, Digoxin

Acute Vasoreactivity Testing

Positive + > 1 y.o.

Oral CCB

Improved / Sustained reactivity

Lower Risk

ERA or PDE 5i (oral)
Treprostinil (oral/inhaled)
Iloprost (inhaled)
Selexipag

Reassess consider early combo-therapy

Higher Risk

Epoprostenol or Treprostinil (IV/SQ)
Consider Early Combination ERA or PDE-5i (oral)

Atrial septostomy
Potts Shunt ?
Lung Transplant