### Pediatric PH

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Location</th>
<th>Country</th>
<th>Email</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
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<td>8</td>
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</tbody>
</table>
Recent Advances in the Diagnosis and Medical Management of Children with Chronic Pulmonary Hypertension

Dunbar Ivy, MD
Children’s Hospital Colorado
Disclosures

• The University of Colorado contracts with Actelion, Gilead, Pfizer, United Therapeutics for Dr Ivy to be a consultant
• Investigator Initiated grants: Gilead
• Steering Committee: GSK / Actelion
Natural History of IPAH: NIH Registry$^{1,2}$

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.

Pulmonary Hypertension

Definition and Classification
Pulmonary Arterial Hypertension

- Sustained elevation of mean pulmonary arterial pressure to > 25 mm Hg, with a mean pulmonary capillary and left atrial pressure < 15 mm Hg at rest
  - Pulmonary Vascular resistance > 3 Units X m²

Classification of PH: Dana Point 2008

1. Pulmonary Arterial Hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
      1.2.1. BMPR2
      1.2.2. ALK-1, endoglin (with or without HHT)
      1.2.3 Unknown
   1.3 Drugs and toxins induced
   1.4 Associated with:
      1.4.1. Connective Tissue Diseases
      1.4.2. HIV infection
      1.4.3 Portal Hypertension
      1.4.4 Congenital Heart Diseases
      1.4.5 Schistosomiasis
      1.4.6 Chronic Haemolytic Anemia
   1.5 PPHN

1' Pulmonary Veno Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis

2. Pulmonary Hypertension Due to Left Heart Disease
   2.1 Left Ventricular Systolic Dysfunction
   2.2 Left Ventricular Diastolic Dysfunction
   2.3 Valvular disease

3. Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental abnormalities

4. Chronic Thromboembolic Pulmonary Hypertension

5. Pulmonary Hypertension with Unclear Multifactorial Mechanisms
   5.1 Hematologic disorders: Myeloproliferative disorders splenectomy.
   5.2 Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Chromosomal or genetic syndromes

Pathological insults on growing lung

Developmental abnormalities
Lung hypoplasia

Other diseases and conditions

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
Classification of Pediatric PH In Combined Netherlands Cohorts: 1991 - 2005

Incidence of Pediatric PH In Combined Netherlands Cohorts: 1991 - 2005

Global TOPP Registry: Group 3 PH In Pediatric Patients

- Most-common Group 3 diagnoses
  - Bronchopulmonary Dysplasia (26%)
  - Interstitial Lung Disease (24%)
- Chromosomal abnormalities, e.g. trisomy 21, reported in 13%

N=456 children with confirmed PH diagnosed between January 2008 and February 2010 from 31 centers in 20 countries.
Survival in BPD-related PH

N=42 premature infants with BPD-related PAH

Pulmonary Arterial Hypertension

Diagnosis
I/FPAH vs APAH-CHD Pediatric PH

Presenting Symptoms: REVEAL

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CHD-PAH</th>
<th>I/FPAH</th>
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<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td>30%</td>
<td>53%</td>
</tr>
<tr>
<td>Presyncope/syncope</td>
<td>4%</td>
<td>36%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Chest pain/discomfort</td>
<td>3%</td>
<td>16%</td>
</tr>
<tr>
<td>Dizziness/lightheadedness</td>
<td>1%</td>
<td>15%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Edema</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Dyspnea at rest</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>No reported symptoms</td>
<td>3%</td>
<td>7%</td>
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N=199.
Screening/Diagnostic Algorithm For Pediatric PH/PAH

Secondary Test
- Polysomnography
- MRI/Pulmonary or CT angiography

Required Tests
- Echo / CXR / ECG
- Pulmonary function tests
- HRCT ± V/Q Scan

Rule Out
- CHD / Left-side heart disease
- Airway, parenchymal, connective tissue, neuromuscular, or chest wall/restrictive diseases
- ILD /Thromboembolic

Cardiac catheterization with acute vasodilator challenge

Screening/Diagnostic Algorithm For Pediatric PH/PAH: Associated Tests

Causative or exacerbating associated conditions

- Connective tissue disease
- HIV
- Hypercoagulability
- Liver disease
- Sickle cell disease

Disease severity / Stage

- Six-minute walk test
- Cardiopulmonary exercise testing (CPET)
- Modified NYHA Functional Classification

Pulmonary Arterial Hypertension

Treatment
PAH Treatment

Suggested Treatment Algorithm For Pediatric PAH

Acute Vasodilator Response During RHC

Yes

CCBs

Inadequate Response

Oral/Inhaled PAH Monotherapy
• ERAs
• PDE5 Inhibitors
• Inhaled Prostacyclins

No

Right Heart Failure

No

Yes

Suggested Treatment Algorithm For Pediatric PAH

Acute Vasodilator Response During RHC

- **Yes**
  - **CCBs**
  - Inadequate Response

- **No**
  - **Right Heart Failure**
    - **No**
      - **FC IV**
    - **Yes**

**Oral/Inhaled PAH Monotherapy**
- ERAs
- PDE5 Inhibitors
- Inhaled Prostacyclins

**Combination Therapy**

**Parenteral Prostacyclins**

Adapted from Abman SH, Ivy DD. *Curr Opin Pediatr.* 2011;23:298-304.
Suggested Treatment Algorithm For Pediatric PAH

Acute Vasodilator Response During RHC

Yes

- CCBs
  - Inadequate Response

No

- Right Heart Failure
  - No
    - Yes
      - FC IV

Oral/Inhaled PAH Monotherapy
- ERAs
- PDE5 Inhibitors
- Inhaled Prostacyclins

Combination Therapy

Parenteral Prostacyclins

Atrial Septostomy

Transplant

## Endothelin Receptor Antagonists

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Bosentan</th>
<th>Ambrisentan</th>
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<tr>
<td>Selectivity</td>
<td>$\text{ET}_A/\text{ET}_B$</td>
<td>$\text{ET}_A$</td>
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<tr>
<td>Approval</td>
<td>Dec 2001</td>
<td>June 2007</td>
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<td>Class</td>
<td>II, III, IV</td>
<td>II, III</td>
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<td>Indications</td>
<td>PAH WHO Group I</td>
<td>PAH WHO Group I</td>
</tr>
<tr>
<td>(Package Insert)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route</td>
<td>Oral</td>
<td>Oral</td>
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Survival At 1 Year with Bosentan

Long-term Bosentan in Children with PAH: Patient treatment patterns

- **Initiation of bosentan**
- **Observation period**
- **End of data collection**

**86 patients**
- (42: bosentan alone)
- (44: bosentan + prostanoid)

**34 patients received at least 1 additional PAH-specific drug**
- 25 patients alive on bosentan
- 43 patients discontinued bosentan for reasons other than death (2 of these died later on)

**52 patients remained on initial therapy**
- 11 patients died
- 7 patients lost to follow-up

FUTURE 1

An open label, multicentre study to assess the pharmacokinetics, tolerability, and safety of a paediatric formulation of bosentan in children with idiopathic or familial pulmonary arterial hypertension
Ambrisentan in Children: Safety

- 0/33 patients had AST/ALT elevations > 2x ULN while on ambrisentan
- 4 patients discontinued ABS due to: headache (1), sinusitis (1) or lack of clinical improvement (2)
- Other reported adverse events included: nasal congestion (8), leg edema (2), and headaches (2)

Takatsuki, Rosenzweig, Zuckerman, Brady, Calderbank, Ivy. *Pediatr Pulmonology* (in print)
Ambrisentan in Pediatrics

Takatsuki, Rosenzweig, Zuckerman, Brady, Calderbank, Ivy. *Pediatr Pulmonology* (in print)
## PDE5 Inhibitors

<table>
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<tr>
<th>Generic Name</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
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<td>Approval</td>
<td>2005</td>
<td>2009</td>
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<td>Class</td>
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<tr>
<td>Route</td>
<td>oral</td>
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STARTS-1 and -2

A randomized, double-blind, placebo controlled, dose ranging, parallel group study of oral sildenafil in the treatment of children, aged 1-17 years, with pulmonary arterial hypertension (PAH)

Placebo-adjusted Percent Change

\( \text{VO}_2 \text{ Peak} \)

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage Change (n)</th>
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<tbody>
<tr>
<td>Low (n=24)</td>
<td>3.81</td>
</tr>
<tr>
<td>Medium (n=26)</td>
<td>11.33</td>
</tr>
<tr>
<td>High (n=27)</td>
<td>7.98</td>
</tr>
<tr>
<td>Low/Med/High (n=77)</td>
<td>7.71</td>
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</table>

\( p = 0.056 \)

\( \text{VO}_2 \text{ Peak} \) (% change from baseline to Week 16) Comparison to Placebo (n=29) with 95% CIs

Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2

Hazard ratios for mortality were 3.50 (95% CI, 1.29–9.51) H vs L
Sildenafil in Failing Fontan Physiology

Oxyhemoglobin saturation (%)

Pre    Post
70
80
90
100
p=0.017

Mean PA pressure (mmHg)

Pre    Post
10.0
12.5
15.0
17.5
20.0
p=0.018

Tadalafil in Pediatric PAH

N = 33

Sildenafil 3.4+/−1.1 mg/kg/day to Tadalafil 1.0+/−0.4 mg/kg/day

## Prostanoids

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Epoprostenol</th>
<th>Treprostinil</th>
<th>Iloprost</th>
<th>EPO For Injection</th>
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<tr>
<td>Class</td>
<td>III, IV</td>
<td>All</td>
<td>III, IV</td>
<td>III, IV</td>
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<td>Indications (Package Insert)</td>
<td>PPH, SPH due to scleroderma</td>
<td>PAH WHO Group 1</td>
<td>PAH WHO Group 1</td>
<td>PPH, SPH due to scleroderma</td>
</tr>
<tr>
<td>Route</td>
<td>Continuous IV</td>
<td>Cont. SQ or IV Inhaled</td>
<td>Inhaled</td>
<td>Continuous IV</td>
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</table>
Idiopathic PAH in Children: Survival and Treatment Success with Chronic IV Epoprostenol

Treprostinil Subcutaneous Delivery

• **Advantages**
  - No central line
  - Smaller infusion pump
  - Longer half life

• **Disadvantages**
  - Significant site pain
  - Generally not used in pediatrics; however use increasing

IV Treprostinil Administration

- Requires higher dose (up to 2.5 times) as compared to Flolan
- Longer half life: 3-4 hours
- Stable at room temp for 48 hrs for IV and 72 hrs for SQ
- No Ice Packs
- Every other day mixing
- Antiplatelet effects and drug stability allow for slow infusions with smaller pumps

Iloprost Inhalation System

- Compact, portable, and lightweight inhalation system
- Advanced technology
  - Breath-actuated
  - Patient specific adaptation
  - Consistent and accurate dosing
  - Micro-aerosol for deep pulmonary delivery
- Treatments 7-9 X / Day
Treprostinil Inhalation System

- 4 Treatments per day
- 6 mcg / breath
- 3-9 breaths per treatment
- Equivalent to less than 15 ng/kg/min IV treprostinil

Krishnan, et al. *Am J Cardiol* (in print)
Pulmonary Arterial Hypertension

Survival
Survival UK Pulmonary Hypertension Service

Survival time (years)

Cumulative survival

Test for equality of survival distribution
Log rank 0.905, Breslow 0.199.

Haworth, S G et al. Heart 2009;95:312-317
Pediatric Survival from Diagnosis in At-Risk Population

Conclusions

- Dyspnea and syncope are common presenting symptoms of pediatric PH
- Accurate diagnosis and treatment of underlying disorders is critical for optimal management of PH
- Novel therapies adapted from adult randomized trials have benefited children
- Although therapy has improved quality of life, there is no cure for many forms of PH in children