Pediatric Pulmonary Hypertension

Sergio Bartakian, MD, FSCAI
Medical Director – Pediatric and Congenital Cardiac Catheterization
Assistant Professor, Division of Pediatric Cardiology
UTHSCSA, Department of Pediatrics

Disclosures

Sergio Bartakian, MD, FSCAI, has no relationships with commercial companies to disclose.

Learning Objectives

At the end of this presentation, the participant should:

• Have a better understanding of the current classification system for pediatric pulmonary hypertension (PH).
• Have an improved understanding of the presentation and basic evaluation / management guidelines for patients with PH.
• Have an appreciation for the importance of and the role for cardiac catheterization in the diagnosis and treatment of PH.

Pulmonary Hypertension Classification

Original

• Primary Pulmonary Hypertension
• Secondary Pulmonary Hypertension

5th World Symposium on PAH

• 1st - Geneva, Switzerland 1973
• 2nd - Evian, France 1998
• 3rd - Venice, Italy 2003
• 4th - Dana Point, CA, USA 2008
• 5th - Nice, France 2013
• 6th - Nice, France (March 2018)

Pulmonary Vascular Research Institute Task Force

• Annual PVRI World Congress meeting
  • 2014 Rome, Italy
  • 2015 Chicago, USA
  • 2016 Singapore
Pediatric PH Council

Familial PAH

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
   1.2.1. BMPR2
   1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3
   1.3. Drug- and toxin-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'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1''. Persistent pulmonary hypertension of the newborn (PPHN)

PAH-CHD

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Drug Induced PAH

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Pulmonary Hypertension Diagnostic Classification
Nice, France 2013

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1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1''. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   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

Main modifications to the previous Dana Point classification are in red.
Classification

- Officially adopted by:
  - Guidelines Committee of the Societies of Cardiology and Pulmonology
  - U.S. FDA and European Agency for Drug Evaluation for labeling purposes of new drugs approved for pulmonary hypertension

Multifactorial Causes of Pediatric Pulmonary Hypertensive Vascular Disease

Epidemiology

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

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

Tracking Outcomes and Practice in Pediatric PH (TOPP)

- The first multinational registry in pediatric pulmonary hypertension
- Launched January 2008
- Enrolled 450 children 3m-18y from 39 specialized centers from 22 countries in 4 continents.
- Objectives:
  - To describe the demographic and clinical characteristics of PH in children
  - To describe the effectiveness of medical treatment
  - Assess disease management patterns worldwide
- Designed to enable identification of any possible risk factors and the clinical course of disease progression
Global TOPP Registry: Group 3 PH In Pediatric Patients

- Most common Group 3 diagnoses:
  - BPD (26%)
  - ILD (24%)
- Chromosomal abnormalities, e.g. trisomy-21, reported in 13%


Pulmonary Hypertension
Definition

Pulmonary Arterial Hypertension

- Sustained elevation of mean pulmonary arterial pressure to > 25 mmHg
- With a mean pulmonary capillary and left atrial pressure < 15 mmHg at rest.
- Pulmonary vascular resistance > 3 woods units x m².


Pulmonary Arterial Hypertension
Diagnosis

I/FPAH vs APAH-CHD Pediatric PH Presenting Symptoms: REVEAL

Registry to Evaluate Early and Long-term PAH disease management
**Screening/Diagnostic Algorithm for Pediatric PH/PAH**

**Recommendation 2:** Cardiac catheterization is recommended before initiation of PAH-targeted therapy (I, B). Exceptions may include critically ill patients requiring immediate initiation of empirical therapy (I, B).

This recommendation places a high value in achieving a correct definitive diagnosis and the initiation of beneficial therapy and a lower value on the risks of the procedures.

**Recommendation 3:** Cardiac catheterization should include acute vaso-reactivity testing (AVT) unless there is a specific contraindication (Class I; Level of Evidence A).

This recommendation places a high value on avoiding the downsides of inappropriate drug selection for therapy and high-risk surgical intervention and places a lower value on the potential complications of cardiac catheterization.

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**Cardiac Catheterization**

- **CDH:** Evaluation for long-term PAH-specific therapy for PH in infants with CDH should follow recommendations for all children with PH, which include cardiac catheterization (Class I; Level of Evidence B). This recommendation places a high value on identifying contributing factors that can be identified and potentially treated as well as confirming PH before the initiation of PAH-specific therapies.

- **BPD:** Evaluation for long-term therapy for PH in infants with BPD should follow recommendations for all children with PH and include cardiac catheterization. This recommendation places a high value on identifying contributing factors that can be treated as well as confirming the severity and etiology of PH before the initiation of PAH-specific therapies.

- **SCD:** Children with SCD should undergo cardiac catheterization before the initiation of PAH-specific drug therapy (Class I; Level of Evidence C). This recommendation recognizes that off-label use of PAH-specific therapies can be harmful, burdensome, and costly and places a lower value on the harms of cardiac catheterization and AVT.

- **Congenital Heart Disease:** This recommendation places a high value on avoiding unnecessary postoperative complications and a lower value on ensuring that no patient who may benefit will be missed. It also places a lower emphasis on the risks of cardiac catheterization and AVT.
Goals for Cardiac Catheterization

1. Confirm the diagnosis and PH severity
2. Measure the response to pulmonary vasodilators (acute vasoreactivity testing [AVT]) before starting drug therapy
3. Evaluate the need for changes in therapy
4. Exclude/treat other factors contributing to disease
5. Assess operability in patients with CHD with systemic to pulmonary artery shunts, and
6. Assist in the determination of suitability for heart or heart-lung transplantation.


Positive Response to AVT

• 20% decrease in mPAP, and:
• an increase, or lack of a decrease in cardiac output, and:
• no change, or a decrease in the PVR/SVR ratio.

** NOT the same as definitions for adult PH:
- Decrease in mPAP >10 to <40 mm Hg with no change or an increase in cardiac output (Sitbon et al).

Typical PH Study

1. Suspected PH, no therapy initiated
   a. Baseline hemodynamics, room air
   b. Additional of 40-50% FiO2, wait 20 min, repeat hemodynamics
   c. Baseline hemodynamics with 40-50% FiO2
   d. Room air challenge
   e. Angiography
   f. Possible intervention if lesions identified

2. Positive PH screen echocardiogram, on O2 therapy
   a. Baseline hemodynamics with 40-50% FiO2
   b. Addition of iNO
   c. Room air challenge
   d. Angiography
   e. Possible intervention if lesions identified

3. Positive PH screen / history, on chronic PAH therapy (NOP)
   a. Baseline hemodynamics
   b. Addition of 40 ppm iNO to assess adequacy of NOP dosing
   c. Baseline hemodynamics
   d. Room air challenge only if on home O2 in addition to NOP therapy

AVT Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses reported</th>
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<tbody>
<tr>
<td>Inhaled nitric oxide</td>
<td>20-40 ppm</td>
</tr>
<tr>
<td>Inhaled iloprost</td>
<td>0.1 mg/kg for patients &lt;15 kg, 0.5 mg/kg for patients ≥15 kg</td>
</tr>
<tr>
<td>Inhaled prostacyclin</td>
<td>5-50 mcg/min</td>
</tr>
<tr>
<td>Inhaled imiprilide</td>
<td>1.35 mcg/kg (range: 0.1-2.0)</td>
</tr>
<tr>
<td>Inhaled nitroglycerin</td>
<td>50 mcg/kg</td>
</tr>
</tbody>
</table>
| Inhaled sildenafil | 20-200 mcg/kg dose 
| Intravenous pressor agents | 2-20 mcg/kg dose every 10-15 min |

AVT

Barst RJ, et al. Pediatr Cardiol. 2010
Sources of Error

Intervention

- Pulmonary artery stenosis
- Pulmonary vein stenosis
- APC embolization

Septal Communication

- Creation / Closure of a septal communications remains controversial and must be evaluated closely on a case to case basis
  - The decision to close a shunt is made along all the available information which is not solely dependent on the hemodynamics obtained during catheterization
  - Most centers, and current recommendations for shunt closure, suggest a PVR <4 is safe, >8 is a contraindication, and in between is center dependent, but caution advised.
  - In patients with septal communications and 2 ventricle anatomy, the presence of resting cyanosis (oxygen saturation <90%) predicts risk of elevated PVR and death after closure of the defect.
PH Treatment

• The prognosis of children with PAH has improved in the past decade owing to new therapeutic agents and off-label application of adult PAH specific therapies to children.

• Use of targeted pulmonary vasodilators in children is primarily based on experience with increasing evidence from an emerging number of pediatric clinical trials.

• Three primary endothelial based pathways of treatment.

PH Therapy

• Calcium Channel Blockers
  - Epoprostenol (IV/inh)
  - Treprostienil (subQ/IV/inh/PO)
  - Iloprost (inh)
  - Beraprost (long acting PO) available only in S. Korea and Japan
  - Tadalafil (PO, once daily) PDE5
  - Sildenafil (PO/IV) Inhibitors
  - Ambrisentan (ETA)
  - Bosentan (ETB)

PAH Treatment

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UHS Inpatient PH Therapy Options

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Outpatient PH Therapy Options

• Calcium Channel Blockers
  - Epoprostenol (IV/inh)
  - Treprostienil (subQ/IV/inh/PO)
  - Iloprost (inh)
  - Tadalafil (PO, once daily)
  - Sildenafil (PO/IV)
  - Ambrisentan (ETA)
  - Bosentan (ETB)

CCB Therapy

• Criteria:
  1. > 1 year of age
  2. No RV/LV failure
  3. WHO functional class I, II, or III
  4. For best results, must demonstrate a positive AVT (“responder”) according to combined REVEAL and Sitbon criteria.
  5. “Favorable hemodynamic profile”
  6. Verapamil contraindicated

**PDE5 Inhibitors**

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<tr>
<th>Generic Name</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
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<td>Approval</td>
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<td>2009</td>
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<td>Class</td>
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<td>PAH WHO Group I</td>
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<tr>
<td>Route</td>
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**ETRB**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Bosentan</th>
<th>Ambrisentan</th>
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</thead>
<tbody>
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<td>Selectivity</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;/ET&lt;sub&gt;B&lt;/sub&gt;</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;</td>
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<td>Dec 2001</td>
<td>June 2007</td>
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<tr>
<td>Class</td>
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<tr>
<td>Indications</td>
<td>PAH WHO Group I</td>
<td>PAH WHO Group I</td>
</tr>
<tr>
<td>Route</td>
<td>Oral</td>
<td>Oral</td>
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</tbody>
</table>

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**Chronic Therapy Options**

1. Patients with IPAH or FPAH and are > 1 y/o, with positive PVRT, and WHO class I-III, should be started on a calcium channel blocker therapy.

2. Those who do not respond to oxygen therapy with > 5 L/min, or do not meet criteria for PCCM/NHLBI 2015 guidelines should also be considered for calcium channel blocker therapy.

3. **Ambrisentan**: Infants < 1 year of age: 2.5 mg q daily.
   - Children > 1 year old but < 20 kg: 2.5 mg once daily, increase to 5 mg once daily after 1 week if no adverse SE.
   - 20 – 40 kg: 5 mg q daily, increase to 10 mg daily after 1 week if no adverse SE.
   - > 40 kg: 10 mg q daily
   - Must follow Liver function quarterly

4. **Bosentan**: Infants 5-15 kg: 15 mg q daily x 4 weeks, then increase to 15 mg twice daily
   - > 1 y/o but < 40 kg: 62.5 mg q daily x 4 weeks, then increase to twice daily
   - > 40 kg: 62.5 mg twice daily x 4 weeks, then increase to 125 mg twice daily
   - Must follow liver function monthly
   - Must enroll in TRACLEER study (medication provided free of charge and mailed to family monthly).

5. Those who are responders to iNO (PAH-CHD) should be started on therapy to target nitric oxide synthase pathway.

   a. **Tadalafil**: 1mg/kg/dose, once daily dosing (max 1.5 mg/kg/day, max 40mg/day)

   b. **Sildenafil**:<br>   - <20kg: 1mg/kg/dose, q 8 hour dosing (max 1.5 mg/kg/day or 20mg/dose)<br>   - >20kg: max 20mg q 8 hours

   - Repeat cardiac cath between 3-6 months depending on severity of PVD to optimize dosing / further management.

6. Those with positive PVRT who are responders to oxygen therapy, but do not completely normalize, and are non-responders to iNO trial, should be placed on continuous oxygen therapy, and started on ERB (Bosentan or Ambrisentan).

7. Those with positive PVRT who are responders to iNO but do not normalize completely should be considered for dual therapy with initiation of ERB in addition to sildenafil / tadalafil.

   - Repeat cardiac cath in 3-6 months.

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**Sildenafil Dosing**

Placebo adjusted percent change VO<sub>2</sub> peak

![Graph showing Sildenafil Dosing](image)

**Treprostinil Sub-Q / IV Delivery**

- **Advantages**
  - No central access needed (SQ)
  - Smaller infusion pump
  - Longer half life (4 hrs)
  - Stable at room temp for 48 hrs (IV), 72 hrs (SQ)
  - QOD mixing
  - No ice packs

- **Disadvantages**
  - Significant site pain (SQ)
  - Generally not used in Pediatrics; however use is increasing.
  - Cost - price comparison analysis (Nairne et al 2003) showed savings for SQ vs continuous Flolan IV infusion ($172k vs $106k annual) however compared 1:1 dosing.
Iloprost Inhalational System

- Compact, portable, lightweight system
- Breath actuated – consistent and accurate dosing
- Micro aerosol for deep pulmonary delivery
- 7-9x treatments / day
- Cost very prohibitive
- Significant waste

Prognosis

- Pre targeted PH therapy era:
  - Children with PAH died within 1-2 years of diagnosis
  - Adults had a median survival of 2-3 years
- With currently available therapies:
  - Children who respond to short-term vasodilator drug testing have a 5-year survival rate of 90% vs.
  - Non responders have a 5-year survival rate of 33%, though more recent data suggesting improved outcomes
- Death may occur from either:
  - Pulmonary hypertensive crisis
  - Heart failure
  - Arrhythmias

Prognosis

- PAH-CHD secondary to pulmonary vein stenosis / atresia is a particularly bad finding and typically has extremely poor prognosis.
- It is estimated that 10% of children with CHD who survive to adulthood will have PAH.
  - Decreasing numbers of patients with Eisenmenger syndrome giving way to increasing numbers of CHD survivors
- PH with sickle cell disease:
  - Adults: TRV >2.5m/s has shown to be consistent with 40% 3 yr mortality
  - Not yet shown to be prognostic in Pediatrics
- PAH-Scleroderma:
  - Prevalence well established (7-12%)
  - Prognosis very poor 1yr mortality 40%, compared to PAH (11%)
  - Early diagnosis and management may improve long term outcome

Prognosis

- PAH-HIV: stable 10 year prevalence
  - Pre HAART – 1 yr mortality 50%, Post HAART - 5 yr survival >70%
  - Interestingly, ~20% experience normalization of HD after several years of treatment

Summary

- Dyspnea and syncope are the most common presenting symptoms for pediatric PAH in the non-CHD population.
- The benefits of cardiac catheterization in the evaluation and management of PH far outweighs the perceived risks and is, under most circumstances, strongly recommended.
- Although newer therapies have significantly improved quality of life, there is still no cure for many forms of PH in children.
- Pediatric cardiology consult should be ordered as soon as there is any concern for the possibility of PH, particularly before initiation of any chronic therapy, if possible.

References