What’s New Since Nice 2013 in Pediatric PH?

**AWA/ATS Guideline**

Pediatric Pulmonary Hypertension

Guideline From the American Heart Association and American Thoracic Society

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**Original Article**

Executive summary. Expert consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension. The European Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK

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**Commentary**

Recommendations for the Use of Inhaled Nitrile Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension

Lisa E. Chamberlain, MD, FAAA; Jeffrey A. Rosenzweig, MD, FAAA; Brian Harfouche, MD, FAAA; Mary L. Morgan, MD, FAAA; Rachel K. Logan, MD, FAAA; Steven A. Needleman, MD, FAAA; Colleen D. Stephenson, MD, FAAA; Aaron S. Goldstein, MD, FAAA;彩色图像]
What’s New Since Nice 2013 in Pediatric PH?

- Expansion of PAH drug approval in children in US (n=1)!
- Expansion of use of interventional-surgical approaches for end-stage PAH in children
- Genetic discoveries relevant to pediatric practice
- New insights from pediatric specific registry data

Pediatric Patient Registries have been established and growing

- PPHnet (North America) ~1500 patients
- TOPP 1 and 2 registry (International) ~800
- Spanish registry ~225
- German registry ~200
- REVEAL pediatric ~200
- Total ~3000

Pediatric Definitions: Update?

PH = PAPm > 25mmHg was the same in children and adults
PAH = PAPm > 25mmHg with PAWPm < 15mmHg was the same

We discussed alignment with the adult definition:
- PAPm >25mmHg change to > 20mmHg
- Add PVRi > 3 U*m2
- Adding “in children over 3 months of age”

Task force debated over this change in pediatric definition

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Task Force PH/PAH definition considerations

**PRO**
- Common language
- Younger children with lower resting SBP may be included
- Borderline children under anesthesia at time of RHC may be included
- Includes PVRi (CHD)

**CON**
- Not sufficient data on PAPm of 21-24mmHg in children or subgroups
- Pediatric registries have not used this definition
- More useful to use a ratio of PAP/SAP in young children = >0.5 because SAP varies with age
New proposed pediatric PH and PAH definitions

PH = PAPm > 20mmHg and PVRi > 3U*m2

PAH = PAPm > 20mmHg and PAWPm <15mmHg and PVRi >3 U*m2 ...
in children over 3 months of age

Heritable PAH

- Known mutations: BMPR2, ALK1, ENG, CAV1, KCNK3, EIF2AK4
- TBX4 – described potential role in pediatric PAH and small patella syndrome, (Kerstjens-Frederikse WS, 2013)
- In one French Study – ACVRL 1 and TBX4 more common in children than adults, (Levy M, ERJ, 2016)
- Similar experience in US Cohort, (Zhu Circ Genom Precis Med. 2018;11)
- SOX 17 : transcription factor - ?CHD

Updated clinical classification (Nice 2018)

1. Pulmonary Arterial Hypertension
   1.1 Idiopathic PAH
      1.2 PAH with long-term response to Ca blockers
      1.3 Heritable PAH (Table 1)
      1.4 Drugs and toxins induced (Table 2)
      1.5 Associated with:
         1.5.1 Connective tissue disease (Table 3)
         1.5.2 HIV infection
         1.5.3 Portal hypertension
         1.5.4 Congenital heart diseases (Table 4)
         1.5.5 Schistosomiasis
         1.5.6 PAH with overt signs of venous/capillaries involvement (Table 5 & 6)
   1.7 PPHN Syndrome (Table P1)

2. PH due to left heart disease
   2.1 PH due to Heart Failure with preserved E.F.
   2.2 PH due to Heart Failure with reduced E.F.
   2.3 Valvular Disease
   2.4 Congenital Post-Capillary Obstruction (Table P2)

3. PH due to lung diseases and/or hypoxia
   3.1 Chronic obstructive Lung Diseases
   3.2 Interstitial Lung Diseases
   3.3 Other LD with restrictive/obstructive pattern
   3.4 Hypoxia without lung diseases
   3.5 Developmental Lung Disorders (Table P3)

4. PH due to pulmonary artery obstruction
   4.1 Chronic Thromboembolic PH
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5. PH with unclear mechanisms
   5.1 Haematologic disorders (Table 8)
   5.2 Systemic disorders (Table 8)
   5.3 Others
   5.4 Complex CHD (Table P4)

Comparison of Genetic Test Results in Adults and Children

FPAH

IPAH

N=178  N=79

N=130  N=25

Courtesy of Dr. Wendy Chung
Updated clinical classification (Nice 2018)

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Table 1. PPHN Syndrome - Associated Conditions

Idiopathic PPHN
Down syndrome
Meconium aspiration syndrome
Respiratory distress syndrome
Transient tachypnea of the newborn
Pneumonia/sepsis
Developmental lung disease (DLD)
Perinatal stress

Myocardial dysfunction (asphyxia, infection)
Structural cardiac diseases:
Hepatic and Cerebral arteriovenous malformations (AVMs)

Associations with other diseases
Placental dysfunction (PE, chorioamnionitis, maternal htn)
Metabolic disease
Maternal drug use or smoking

Table 4. Proposed Clinical Classification of PAH Associated with CHD

A. Eisenmenger Syndrome

B. Left to Right Shunts
   - Non-correctable
   - Correctable

C. PAH with co-incidental CHD

D. Post-operative PAH

Previous definition of PAH based on mean PAP > 25mmHg: PVR provides essential information for CHD patients
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Table P2. Congenital post-capillary obstructive lesions
- Pulmonary Vein Stenosis
  - Isolated
  - Associated (Bronchopulmonary dysplasia, prematurity)
- Cor triatriatum
- Obstructed total anomalous pulmonary venous return
- Mitral/aortic stenosis (including supra/sub valvular)
- Coarctation of the aorta

Pediatric PH by Nice Classification

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**Table P3. Developmental Lung Disorders**

- Bronchopulmonary Dysplasia
- Congenital Diaphragmatic Hernia
- Down Syndrome
- Alveolar Capillary Dysplasia with “Misalignment of Veins” (FOXF1)
- Lung Hypoplasia, Acinar Dysplasia
- Surfactant Protein Abnormalities
  - SPB deficiency
  - SPC deficiency
  - ABCA3
- TTF-1/Nkx2
- TBX4
- Pulmonary Interstitial Glycogenosis
- Pulmonary Alveolar Proteinosis
- Pulmonary Lymphangiectasia

**Pulmonary Vascular Disease in Down Syndrome (Trisomy 21)**

*Bush D et al. J Pediatr, 2017*

**TBX4 – associated disease**

**variable phenotype and age of presentation**

*Older child with IPAH*  
*Refractory PPHN*

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Table P4. Complex CHD

- Segmental Pulmonary Hypertension
  - Isolated pulmonary artery of ductal origin
  - Absent pulmonary artery
  - Pulmonary atresia with VSD MAPCAS
  - Hemitruncus
  - Other
- Single Ventricle
  - Unoperated
  - Operated
- Scimitar syndrome

Table of Pediatric IPAH/HPAH Risk

<table>
<thead>
<tr>
<th>LOWER RISK</th>
<th>DETERMINANTS OF RISK</th>
<th>HIGHER RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Presence of Symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt; 350 miles</td>
<td>WHO Functional Class</td>
<td>III, IV</td>
</tr>
<tr>
<td>I/L</td>
<td>WHO Functional Class</td>
<td>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>
<tr>
<td></td>
<td>Systemic CI &gt; 2.0 L/min/m²</td>
<td>Systemic CI &lt; 2.0 L/min/m²</td>
</tr>
<tr>
<td></td>
<td>Systemic venous saturation &gt;65%</td>
<td>Systemic venous saturation &lt; 60%</td>
</tr>
<tr>
<td></td>
<td>+ Acute Vasoreactivity</td>
<td>+ Acute Vasoreactivity</td>
</tr>
</tbody>
</table>

Survival stratified for AVT response status

- SR=Sitbon Responder
- NR=Non Responder
- RR=Reveal Responder

General: Consider Diuretics, Oxygen, Anticoagulation, Digoxin

Acute Vasoreactivity Testing

- Lower Risk
  - ERA or PDE-5i (oral)
  - Iloprost (inhaled)
  - Treprostinil (inhaled, USA)
- Higher Risk
  - Epoprostenol or Treprostinil (IV/SQ)
  - Consider Early Combination Therapy
  - ERA or PDE-5i (oral)

Atrial septectomy

Lung transplant

WSPH 2013
Pediatric IPAH/HPAH Treatment

- Expert Referral
- General: Consider Diuretics, Oxygen, Anticoagulation, Digoxin
- Acute Vasoreactivity Testing

Positive
- Improved + Sustained reactivity
  - Oral CCB
  - Lower Risk: ERA or PDE-5i (oral)
  - Consider combination therapy (sequential or upfront)

Negative
- Higher Risk: Epoprostenol or Treprostinil (IV/SQ)
  - Consider Early Combination
- Serial Reassessment***
- Atrial septostomy
- Potts Shunt
- Lung Transplant

Reverse Potts Shunt: Who and when and where in the algorithm?

- Described 14 years ago for severe PAH
- Some good long term responders
- High early mortality (12.5%)
- Need to better define indications / contraindications
- PePH observational registry
- rmgrady@wustl.edu

Pediatric PAH Risk factors, treatment goals and clinical end points

- Risk factor: For risk stratification
- Treatment goal: To evaluate treatment response
  - PEDIATRIC CLINICAL TRIAL DESIGN
  - Clinical End point: For trial design

- Clinically meaningful:
  - Clinical event relevant to the patient
  - Death, Transplant, Hospitalisation for PAH
  - Measures directly how a patient feels, functions or survives
  - Symptoms, Functional Class, Exercise testing, 6MWD, (ADL-)activities? (provided no negative impact mortality/morbidity)

- Surrogate:
  - Used as a substitute for a clinically meaningful endpoint
  - Changes induced by a therapy on biomarkers are expected to reflect the changes induced on the clinical endpoint in a clinically meaningful endpoint
Composite disease progression endpoint in paediatric PAH clinically meaningful and feasible for clinical research

- To describe the paediatric PAH population
- To describe the occurrence of individual and composite disease progression outcomes:

<table>
<thead>
<tr>
<th>Disease progression 1</th>
<th>Disease progression 2</th>
<th>Disease progression 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all-cause)</td>
<td>Death (all-cause)</td>
<td>Death (all-cause)</td>
</tr>
<tr>
<td>PAH-related hospitalisation*</td>
<td>PAH-related hospitalisation*</td>
<td>PAH-related hospitalisation*</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>Lung transplantation</td>
<td>Lung transplantation</td>
</tr>
<tr>
<td>Atrial septostomy</td>
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</tr>
<tr>
<td>WHO FC deterioration†</td>
<td>WHO FC deterioration†</td>
<td>WHO FC deterioration†</td>
</tr>
<tr>
<td>Initiation of i.v./s.c. prostanoids</td>
<td>Initiation of i.v./s.c. prostanoids</td>
<td>Syncope</td>
</tr>
<tr>
<td>(only first event)</td>
<td>(only first event)</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td>PAH worsening (symptoms)</td>
</tr>
</tbody>
</table>

Beghetti, AEPC 2016

First events predictive of long-term outcomes death and lung transplantation (multivariate)

- Common approach among regulators (requirements for approval)
- Use of targeted PAH therapy that does not have established benefit should not cause lack of equipose
- Extrapolation opportunities: adult PAH -> pediatric PAH
- Novel trial design / analysis: composite with ranked analysis
- Consensus on acceptable clinical endpoints (physicians/regulators)
- Potential clinically meaningful endpoints: TTCW, PROs, Functional Activity measurements (WHO-FC, 6MWD, Accelerometry)
- Potential surrogates
  - NT-pro-BNP
  - Not invasive hemodynamics (risk)
  - Imaging biomarkers

Beghetti, AEPC 2016

Events occurring first within the composite disease progression outcomes

Beghetti, AEPC 2016

RCT’s in Pediatric PAH Solutions
Conclusion

• In the past five years...
  • Approval of targeted PAH medication
  • Identification of genetic profile appears to be different in children
  • Registry data has grown substantially and may inform future clinical trial development

Future

• Growth of pediatric registry data to better characterize children with PAH
  • Pediatric-specific clinical trials
  • Genetic discoveries may translate into novel therapeutic approaches
  • More kids graduating into the adult PH clinics