



Pulmonary Hypertension Neonates and Children

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Why Pulmonary Hypertension (PH)

- PH is associated with high morbidity and mortality especially without treatment
- Great mimicker, need high index of suspicion to identify. Frequently late diagnosis
- Etiologies are related to heterogenous group of disease including multiple organ systems
- Tools for treatment are available to ease the burden of the disease and sometimes cure

- **Objectives**
- Learn to identify the disease
- Identify high risk groups in the pediatric patients for proper referral
- Get familiar with the tools available for treatment

What is Pulmonary Hypertension/ Definition

- **Precapillary**
- Mean PAP > 20 mmHg in children > 3 months of age at sea level (2024, World symposium PH, Barcelona)
- PVR index > 3 WU.m² with PCWP < 15 mmHg (2024, WSPH),
- PVR > 2 WU with PCWP < 15 mmHg (2022, European society of cardiology and pulmonary, 2024 WSPH, Barcelona),
- **Post capillary**
- Mean PA pressure > 20 mmHg,
- PCWP > 15 mmHg. Normal PVR
- In combined precapillary and postcapillary PVR is abnormal
- Annual incidence in USA children 4.8- 8.1 per million children

Updated Classification of PH WSPH, Barcelona 2024

- **PAH Group I**
- **1.1. Idiopathic PAH**
- **1.1.1 Long responder to calcium channel blockers**
- **1.2. Heritable PAH**
- 1.3 Associated with . Drug- and toxin-associated PAH
- 1.4. Associated with
- 1.4.1. Connective tissue disease
- 1.4.2. HIV infection
- 1.4.3. Portal hypertension
- 1.4.4. **Congenital heart disease**
- 1.4.5. Schistosomiasis
- 1.5. PAH long-term responders to calcium channel blockers
- 1.6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- **1.6. Persistent PH of the newborn syndrome**

Updated classification of PH

- *PH due to left heart disease Group II*
 - 2.1. Heart Failure
 - 2.1.1 with preserved LVEF
 - 2.1.2. with reduced LVEF
 - 2.1.3 Cardiomyopathies
 - **2.2. Valvular heart disease**
 - **2.2.1 Aortic valve disease**
 - **2.2.2 Mitral valve disease**
 - **2.2.3 Mixed valvar disease**
 - **2.3. Congenital/acquired cardiovascular conditions leading to postcapillary PH**
- *PH due to lung diseases and/or hypoxia Group III*
 - 3.1. COPD/Emphysema
 - 3.2. Interstitial lung disease
 - 3.3. Combined pulmonary fibrosis and emphysema
 - 3.4 Other parenchymal lung disease
 - 3.5 Non parenchymal restrictive lung disease
 - 3.5.1 Hypoventilation
 - 3.5.2 Pneumonectomy
 - 3.6. Hypoxia without lung disease/ high altitude
 - **3.7. Developmental lung disorders**

Developmental lung disease associated with PH

- **Bronchopulmonary dysplasia**
- • **Congenital diaphragmatic hernia**
- • Alveolar capillary dysplasia with “misalignment of veins” (FOXF1)
- • Lung hypoplasia, acinar dysplasia
- • Surfactant protein abnormalities
- • Surfactant protein B deficiency
- • Surfactant protein C deficiency
- Some include DS in this group and others in group 5
- • ABCA3
- • TTF1/NKX2-1
- • TBX4
- • Pulmonary interstitial glycogenesis
- • Pulmonary alveolar proteinosis
- *Rosenzweig EB, et al. Paediatric pulmonary arterial hypertension: Updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53(1):1801916;*

Updated classification of PH

- *PH due to pulmonary artery obstructions Group IV*
- 4.1. Chronic thromboembolic PH (CTEPH)
- 4.2. Other pulmonary artery obstructions
- *PH with unclear and/or multifactorial mechanisms Group V*
- 5.1. **Hematologic disorders**
- 5.2. Systemic and metabolic disorders
- 5.3 Metabolic disorders
- 5.4 Chronic renal failure with or without hemodialysis
- 5.5 Pulmonary tumor thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis
- 5.7. **Complex congenital heart disease**

Pediatric Pulmonary Hypertension Classification

- 1. Prenatal or development 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 syndrome
 - 7. Pediatric lung disease
 - 8. Pediatric thromboembolic disease
 - 9. Pediatric hypobaric hypoxic exposure
 - 10. Pediatric pulmonary vascular disease associated with other system disorders
- Cerro MJ, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ. 2011;1(2):286-298.*

Work up

- Extensive work up involves
- EKG/ Echocardiogram
- Cardiac catheterization with vasoreactivity testing
- CXR, Chest CT/ VQ scan
- Cardiac MRI/MRA
- Stress test/ 6 min walk test
- PFT
- BNP/ NTpro BNP
- Lung biopsy
- **Evaluate for**
- Lung disease/ heart disease
- OSA
- Aspiration
- Thromboembolic disease / Coagulopathy
- Connective tissue disease
- Porto-pulmonary hypertension
- Genetic work up
- HIV
- Sickle cell disease and other hemoglobinopathies

Symptoms

- Non-specific deceptive symptoms that lead to delay in diagnosis
- 1. Cyanosis
- 2. Failure to thrive
- 3. Tachypnea
- 4. Dyspnea
- 5. Decreased exercise tolerance
- 6. Decreased endurance
- 7. Feeding difficulties
- 8. Asthma not responding to proper treatment as expected
- 9. Dizziness
- 10. Hemoptysis
- 11. Chest pain
- 12. Edema
- 13. Irritability in neonates
- 14. Syncope
- Biggest hurdle in making the diagnosis is not considering it

Physical Examination

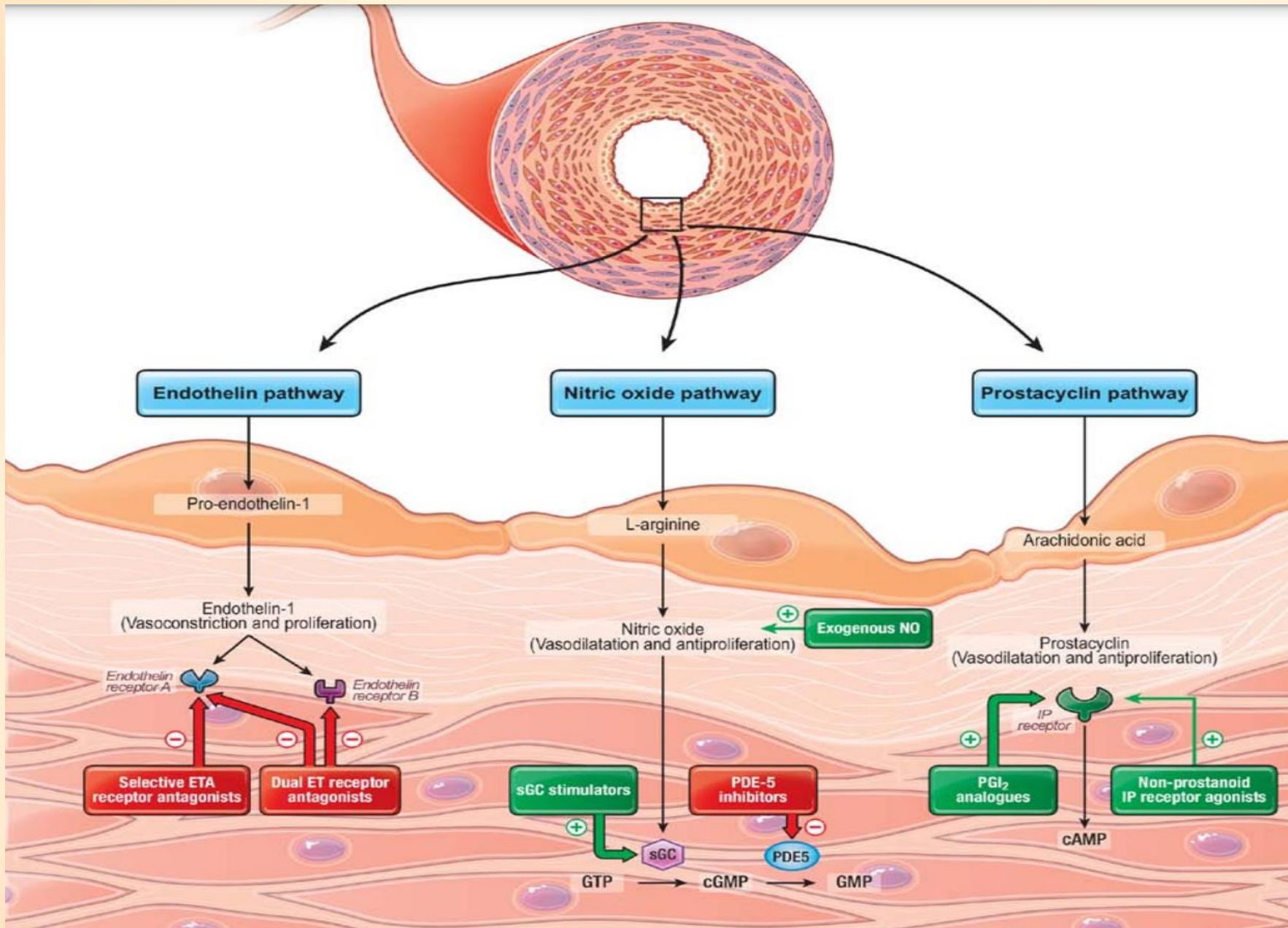
- Loud single S2
- Right ventricular heave
- Regurgitant murmur at LLSB (TR murmur)
- Diastolic murmur over the LUSB (PR murmur)
- Hepatomegaly, peripheral edema due to RV failure
- Signs of congestive heart failure due to decreased cardiac output

Goals of treatment

- Induce pulmonary arterial vasodilatation
- Unload the RV and support it
- Optimize cardiac output to avoid coronary ischemia and heart failure
- Improve prognosis
- Alleviation of signs and symptoms or provide clinical improvement
- Improve quality of life

PH Treatment

- Oxygen is indicated since prolonged periods of hypoxemia predispose to PH especially in lung disease. Sometimes night-time oxygen use
- Address underlying cause if determined such as chronic aspiration, OSA, Thromboembolic disease, severe laryngomalacia etc...
- Once the underlying conditions are addressed consider PH medical therapy
- Adult PH has extensive research targeted therapies based on classifications. This area is not developed in the pediatric population.
- Anticoagulation is used on individual cases
- In pediatric age group most therapies are based on expert opinion and experience which makes the disease more challenging



Medical Treatment

Targets the three pathways of pulmonary hypertension.

Humpert M, et al; Advances in the therapeutic advances in patients with pulmonary arterial hypertension; Circulation. 2014;130:2189-2208

Nitric oxide pathway

- Works through increasing cyclic guanosine phosphate (cGMP) in smooth muscles
- NO is smooth muscle relaxer and arterial vasodilator
- NO pathway medications
 - Nitric oxide
 - Sildenafil,
 - Tadalafil,
 - Riociguat

NO signaling pathway medications/ Sildenafil

- Phosphodiesterase 5 inhibitors. Inhibits breakdown of cGMP in endothelial cells
 - *Tettey, A.; Therapy for Pulmonary Arterial Hypertension: Glance on Nitric Oxide Pathway. Front. Pharmacol. 2021, 12, 3159*
- STARTI trial evaluated different dosage of sildenafil in patients with pulmonary arterial hypertension 1-17 years of age. All doses showed improved outcomes with no measured difference between the dosages
- STARTII the extension to START I
- Improvement in survival noted in all classes but unexplained mortality in the higher dose as compared to the lower dose
 - *Barst, R.J.; et al. A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Oral Sildenafil Citrate in Treatment-Naive Children with Pulmonary Arterial Hypertension. Circulation 2012, 125, 324–334.*
 - *Barst, R.J et al.; STARTS-2 Investigators. STARTS-2: Long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation 2014, 129,1914–1923.*
- Sildenafil remain s off label use 0-17 years of age

NO signaling pathway medications/L- Citrulline

- L- Citrulline
- The amino acid precursor of NO substrate
- Preliminary studies are favorable but still ongoing research
- Appears to be safe option
- Dose determination and safety profile trials in premies started in 2023

NO signaling pathway medications/ Tadalafil

- Phosphodiesterase 5 inhibitor with longer half life
- Tadalafil is well tolerated in pediatric age group
- *Shiva, A. et al;. Oral Tadalafil in Children with Pulmonary Arterial Hypertension. Drug Res. 2016, 66, 7–10.*
- *Small, D. et al;. Pharmacokinetics and safety of tadalafil in a paediatric population with pulmonary arterial hypertension: A multiple ascending-dose study. Br.J. Clin. Pharmacol. 2019, 85, 2302–2309.*
- *Takatsuki, S.; et al. Initial Experience With Tadalafil in Pediatric Pulmonary Arterial Hypertension. Pediatr.Cardiol. 2012, 33, 683–688.*
- In a small study 35 patients Tadalafil is suggestive of improvement in PH children 1-17 years of age
- *Ivy, D. et al; The LVHV Study Group. Efficacy and safety of tadalafil in a pediatric population with pulmonary arterial hypertension: Phase 3 randomized, double-blind placebo-controlled study. Pulm.Circ. 2021, 11, 1–8.*

Riociguat

- Increase cyclic GMP by direct stimulation of soluble GMP (sGMP) and independent of NO. Increases sGMP sensitivity to NO. It works synergistically with NO hence useful in cases of low NO
- Approved in adults to treat PH particularly thromboembolic disease
- A small pediatric trial conducted in Europe with favorable results
- A clinical trial is underway in pediatric age group but suffering from difficulty in recruitment

Endothelin I pathway ET1

- All agents are oral, no IV or inhaled
- There is upregulation of ET1 in the lungs of PH patients
- ET1 has complex effect through 2 receptors
- ETA activation causes vasoconstriction
- ETB activation causes vasodilatation through increasing NO
- ET1 stimulate smooth muscle cell growth and promote pulmonary vascular remodeling

Endothelin I pathway/ Bosentan

- Bosentan dual ET receptor antagonist
- Safe and tolerated in children
- Known hepatic toxicity and teratogenic side effects
- Hepatic toxicity, dose dependent and reversible in most cases with decrease in the dose
- Teratogenic effects requires very cautious handling especially in pregnant women
- FDA approved for use in children > 3 years

- *Berger, R.M.; et al. FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the pediatric Formulation of bosentan in pulmonary arterial hypertension. Int. J. Cardiol. 2016, 202, 52–58.*
- *Hislop, A.; Haworth, S.G. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur. Respir. J. 2011, 38, 70–77.*
- *Ivy, D.D. et al ; Long-Term Outcomes in Children With Pulmonary Arterial Hypertension Treated with Bosentan in Real-World Clinical Settings. Am. J. Cardiol. 2010, 106, 1332–1338. 84.*
- *Sitbon, O.; et al. Bosentan for the treatment of pulmonary arterial hypertension associated with congenital heart defects. Eur. J. Clin. Investig. 2006, 36, 25–31.*

Endothelin I pathway/ Macitentan

- Macitentan non selective ET1 receptor antagonist
- Approved in adults.
- Decreased hepatic toxicity as compared to Bosentan
- Does not affect the serum level of sildenafil if used in combination
- Some evidence of safety and efficacy in children
- *Schweintzger S, et al; Safety and efficacy of the endothelin receptor antagonist Macitentan in pediatric pulmonary hypertension. Cardiovasc Diagn Ther. 2020 Oct;10(5):1675-1685*

Endothelin I pathway/Ambrisentan

- Selective ETA antagonist
- Some favorable evidence in pediatric age group
- *Takatsuki, S.; Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension. Pediatr. Pulmonol. 2013, 48, 27–34.*
- *Ivy D; Long-term safety and tolerability of ambrisentan treatment for pediatric patients with pulmonary arterial hypertension: An open-label extension study., RMFBEurJ Pediatr. 2024 May;183(5):2141-2153.*

Prostacyclin PGI₂

- Independent of NO
- Decrease PGI in patients with PH
- Works via prostacyclin synthase in smooth muscles and increases smooth muscle intracellular cyclic adenosine monophosphate (cAMP)
- PGI inhibit vascular proliferation and can protect pulmonary modeling
- Prostanoids are synthetic prostacyclins.
- This class contain non prostanoids such as Selexipag
- Present in inhaled, oral, subcutaneous and IV forms
- Scant information in preterm, term and pediatric age group but reports are favorable

Prostacyclin Pathway Medications Used in Children

Name	Trade Name	Mode of administration	Type of medication
Iloprost	Ventavis	inhaled	Synthetic prostacyclin analog
Epoprostenol	Flolan Veletri	IV	synthetic prostacyclin
Treprostinil	Remodulin Tyvaso	S/C, IV Inhaled	prostacyclin vasodilator
Selexipag	Uptravi	Oral	prostacyclin receptor agonist

Calcium Channel Blockers (CCB)

- Specific use in PH restricted to patients who are vasoreactive and responsive to CCB
- Should not be used without testing in the cath lab for vasoreactivity
- A trial of nitric oxide is first done. If responsive, then a trial of CCB is carried on in the cath lab
- CCB work by blocking the influx of calcium to smooth muscles resulting in vasodilatory effects
- Contraindicated in children less than one year and in patients with RV failure and advanced symptoms
- CCB responders have favorable prognosis in patients with PAH

Vasoreactivity Definition

- **Sitbon criteria mostly adults**
- defined as decrease in PAP ≥ 10 mmHg to achieve PAP < 40 mmHg with unchanged or increase in cardiac output
- **Barst pediatric criteria**
- Decrease of at least 20% in the mean pulmonary arterial pressure (mPAP)
- Unchanged, increased, or $<10\%$ decreased cardiac index (CI), and
- Unchanged or decreased pulmonary to systemic vascular resistance ratio

Medical treatment in pediatric group

- Many tools are available to treat pulmonary hypertension but what is approved in pediatric population is scarce
- European Medicine agency (EMA) approved sildenafil (bodyweight ≥ 8 kg and >1 year old) and Bosentan > 3 years of age
- Food and drug administration (FDA) approved Bosentan for chronic use in PH children > 3 years of age
- NO is FDA approved for treatment of PPHN. NO is not FDA approved in BPD treatment
- Other than the above all medication usage is off label

Non medical treatment/ ASD

- Creation of an intraatrial septal defect usually in the cath lab
- A stent is usually placed to ensure patency
- The idea is to increase cardiac output through creating a right to left shunting. It also would help the RV as pop off.
- Cardiac output is maintained at expense of saturation(Blue PH is better than grey PH)

Non medical treatment/ Reverse POTs shunt

- Creating a communication between the proximal descending aorta and the LPA. Valved conduit are used to direct a rt to left shunting
- Palliative procedure and does not cure the disease however some patients have clinical improvement and decrease in the use of continuous prostanoids
- Pots shunt complicates lung transplant and increase perioperative mortality. There are associated bleeding complications. This has to be discussed with the family before proceeding

Transplant

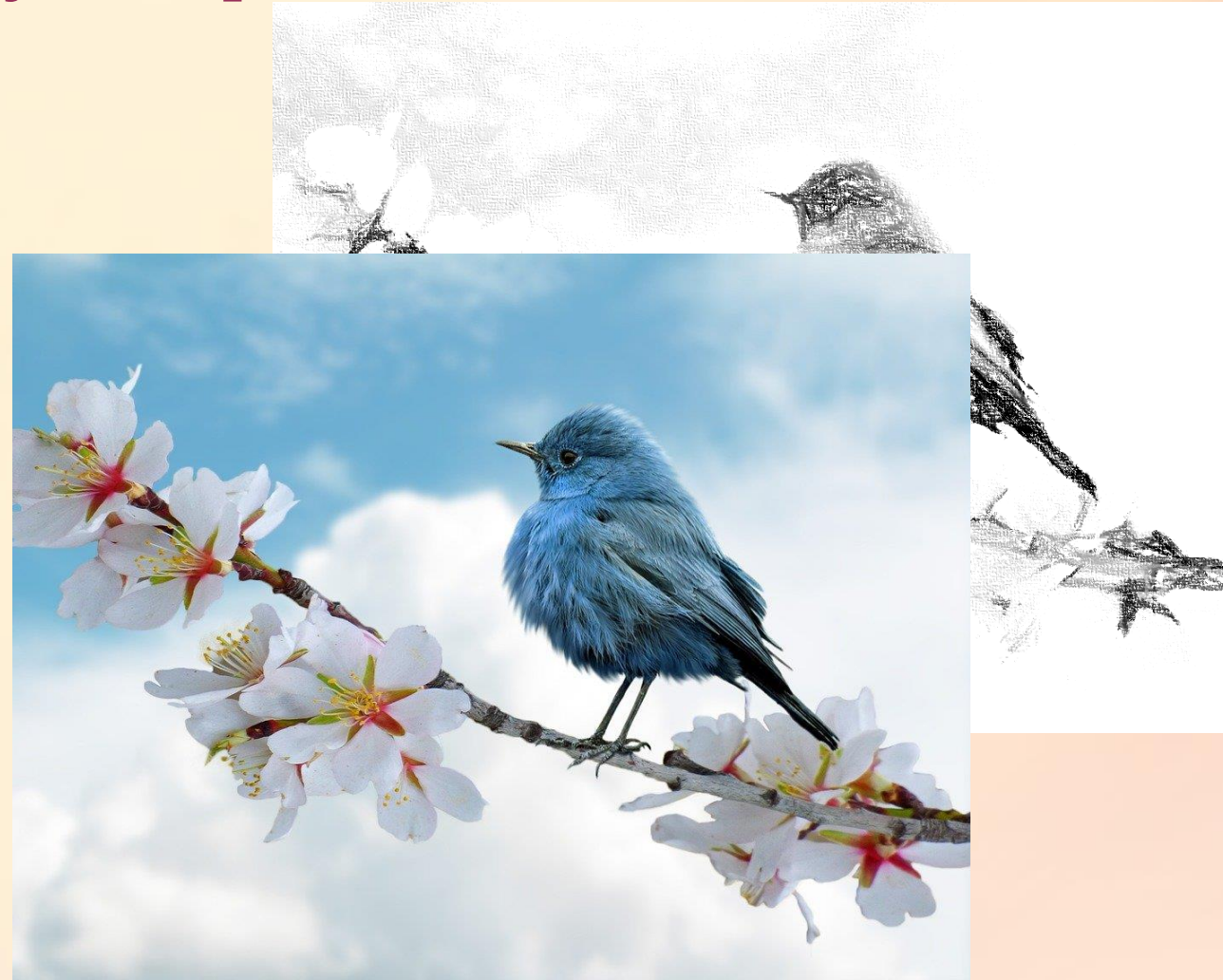
- Lung transplant or heart and lung transplant if heart failure developed secondary to pulmonary hypertension is the last effort to treat pulmonary hypertension
- Outcome of lung transplant have been improving
- ECMO can be used as a bridge to transplant, but increased mortality is seen if patients are on ECMO prior the procedure so discussions with the family about transplant should be done early preferably before heart failure develops in progressive disease
- Few centers perform pediatric lung transplantation and even fewer do neonatal and toddler lung transplant

Acute management of PH crisis

- Oxygen
- Nitric oxide 25% are non responder
- Inhaled illoprost 25% are non responders
- IV sildenafil
- Milrinone for synergistic effects with NO
- IV/SC prostanoids
- Sedation and paralysis in severe cases
- Minimal stimulation
- Avoid hypoxemia and hypercarbia

Prognosis: There is Always Hope

- The prognosis of PH is disease dependent.
- Contrary to the adult disease, some PH related diseases in pediatric age group improve with age or completely resolve.



Idiopathic Pulmonary Hypertension

- Sporadic disease
- Very rare in pediatric age group with female predominance
- Very bad prognosis in pediatric age group
- Disease of exclusion ie extensive work up for PH should be done particularly in age group before the diagnosis is made
- In pediatric age group is associated with thyroid abnormalities, lower air way obstruction and elevated ANA
- *Satoh M, Aso K, et al. Autoimmune thyroid disease in children and adolescents with idiopathic pulmonary arterial hypertension. Circ J. 2010;74(2):371-374*
- *Rastogi D, et al. Lower airway obstruction, bronchial hyperresponsiveness, and primary pulmonary hypertension in children. Pediatr Pulmonol. 2004;37(1):50-55*

Familial Pulmonary Hypertension

- 6-12% of idiopathic PH is genetic. As more genes are described, idiopathic PH category is decreasing.
- BMPR2 is the most common mutation explaining up to 80% of cases. Mode of inheritance is autosomal dominant with variable penetrance
- All genetic mutations described so far are inherited as autosomal dominant with exception of EIF2AK4 (GCN2) which is associated with pulmonary venoocclusive disease and pulmonary capillary hemangiomatosis (autosomal recessive)

Familial Pulmonary Hypertension

- **TGF- β receptor superfamily**
- - BMPR2 : 80% of familial cases
- - ALK1: Familial HHT
- - Endoglin : Familial HHT
- - SMAD9
- EIF2AK4 (GCN2), Associated with pulmonary capillary hemangiomatosis (PCH) and pulmonary venoocclusive disease (PVOD).
- TBX4 T-Box 4, Small patella syndrome
- KCNK3 Encodes TASK-1, A K channel
- CAV1 Encodes caveolin-1
- ATP13A3 ATPase 13A3
- GDF2 Growth differentiation factor 2/BMP9
- SOX17: SRY-box 17 associated with PH in CHD
- AQP: Aquaporin 1
- *Austin ED, et al The genetics of pulmonary arterial hypertension. Circ Res. 2014;115(1):189-202.*

Congenital Diaphragmatic hernia

- PH can develop at any stage of the disease
- Multifactorial related to lung hypoplasia, abnormal lung vasculature, abnormal pulmonary artery and pulmonary veins development. The hyper-muscularized vasculature leads to constriction and PH.
- Dysregulated signaling pathways that lead to endothelial dysfunction affecting pulmonary remodeling.
- Diaphragmatic hernia PH can be very severe.
- Prognosis in CDH is directly related to occurrence of PH and its degree
- *Geggel, R. L. et al. Congenital diaphragmatic hernia: arterial structural changes and persistent pulmonary hypertension after surgical repair. J. Pediatr. 107, 457–464 (1985)*
- *Wynn, J. et al. Outcomes of congenital diaphragmatic hernia in the modern era of management. J. Pediatr. 163, 114–119.e1 (2013). 4*

Congenital Diaphragmatic Hernia

- MRI done during fetal life can help with predicting the degree of pulmonary hypoplasia and secondary pulmonary hypertension
- Survival has improved due to advances in neonatology, respiratory management , surgical repair and tools for treatment of PH
- Most cases of PH resolve. The long term occurrence of PH range from 8% to 38%. Prognosis improves if patients survive beyond the neonatal stage.
- Factors associated with long term PH includes use of ECMO, nitric oxide and duration of mechanical ventilation
- *Wong M, et al. Pulmonary hypertension in congenital diaphragmatic hernia patients: Prognostic markers and long-term outcomes. J Pediatr Surg 2018;53:918-24. 23*
Kraemer US, Leeuwen L, Krasemann TB, et al. Characteristics of infants with congenital diaphragmatic hernia who need follow-up of pulmonary hypertension. Pediatr Crit Care Med 2018;19:e219-26.
- American heart association and American Thoracic society recommend long term follow up of CDH patients by a PH specialist
- *Abman SH, et al. Pediatric pulmonary hypertension. Circulation 2015;132:2037-99. 31*

Diaphragmatic hernia PH treatment

- Management of acute phase includes nitric oxide and oxygen
- ECMO may be needed to provide clinical stability
- Avoid prostanoids if possible as they cause platelets deactivation and the patient will require surgery
- In severe cases and trying to avoid ECMO, consider keeping the PDA open to augment cardiac output
- After surgical repair, longer term therapy is indicated if PH persists

Pulmonary Hypertension in BPD

- Besides dysplasia of bronchopulmonary vasculature and abnormal airway, BPD is associated with pulmonary vascular disease and pulmonary hypertension
- PH in BPD is associated with abnormal vascular remodeling and rarefaction of pulmonary vasculature resulting in increased PVR
- *Lignelli, E., . Recent advances in our understanding of the mechanisms of lung alveolarization and bronchopulmonary dysplasia. Am. J. Physiol. Lung Cell. Mol. Physiol. 317, L832–L887 (2019).*

PH in BPD

- ~ 8-42 % of patients with BPD especially moderate or severe BPD develop PH. Mortality is up to 45% within 2 years of diagnosis
- *Weismann, C. G. et al. Pulmonary hypertension in preterm infants: results of a prospective screening program. J. Perinatol. 37, 572–577 (2017).*
- *Mourani, P. M. et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am. J. Respir. Crit. Care Med. 191, 87–95 (2015).*
- As compared to patients without PH, patients with BPD and PH are at increased risk for tracheostomy, neurodevelopmental delay, feeding difficulties, frequent hospital admission, delayed growth and need for supplemental oxygen.
- *Lagatta, J. M. et al. The impact of pulmonary hypertension in preterm infants with severe bronchopulmonary dysplasia through 1 year. J. Pediatr. 203, 218–224.e3 (2018).*
- **Young adults** born with very low birth weight (< 1500 gm) and average gestation age of 28 weeks are at increased risk of PVD and PH
- *Goss, K. N. et al. Early pulmonary vascular disease in young adults born preterm. Am. J. Respir. Crit. Care Med. 198, 1549–1558 (2018).*

BPD and PH: Who is at higher risk

- Disrupted lung development whether in utero or after birth
- Immaturity (gestational age, birth weight)
- Male sex
- Adverse intrauterine environment: Maternal vascular disorders (e.g. pre-eclampsia, oligohydramnios, maternal diabetes)
- Intrauterine growth restriction (IUGR) or small-for-gestational age (SGA)
- Higher level of neonatal respiratory support ($\geq 3-7$ days) – Mechanical ventilation or supplemental oxygen exposure, persistent respiratory support and use of JET ventilator
- Infections: sepsis, tracheitis
- Length of stay, Use of steroids
- *Ambalavanan 2011; Bose 2009; Durrmeyer 2012; Hansen 2010; Laughon ADC 2011; Laughon AJRCCM 2011; Wai 2016; Greenberg 2022, Nagiub 2017, Sheth 2020*

BPD and PH/ When to suspect

- Severe respiratory compromise in any preterm infant < 28 weeks gestation
 - BPD at corrected age of 36 weeks, (Infants who had PH at 7 days of life are at higher risk of PH associated with BPD)
 - Prolonged oxygen requirement
 - Poor growth
 - Suboptimal clinical improvement
 - Requiring continuous pulmonary support, interventions and treatment
 - Abnormal cardiac markers such as BNP or NT pro BNP
- *Mourani, P. M. et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am. J. Respir. Crit. Care Med. 191, 87–95 (2015).*
 - *Hansmann, G. et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J. Heart Lung Transplant. 38, 879–901 (2019).*
 - *Although there are no clear indications on whom to follow long term after discharge, using the above as a guideline can help with identification and proper treatment*

BPD- PH/ Diagnosis

- Echocardiogram in addition to the clinical picture remain the basis for the diagnosis of PH.
- Supportive evidence come from cardiac markers mostly NT pro BNP or BNP which help in diagnosis and in tracking, however
- Echocardiogram will not be able to quantitate a shunt if it is present
- Echocardiogram may fail to identify severity
- Echocardiogram may underdiagnose or over-diagnose PH although the correlation with cardiac catheterization is relatively good. The estimation of PAP is not as accurate
- *Nawayato H et al, Clinical utility of echocardiography in former preterm infants with Bronchopulmonary dysplasia. Vol 33 issue 3, P378-388, March 2020*

BPD- PH diagnosis

- CT scan is indicated mostly to assess lung parenchyma, presence of thromboembolic disease, or vascular abnormalities including pulmonary vein stenosis
- MRI
- Increasingly used in PH BPD
- Helps with estimation of shunt and pulmonary perfusion
- Helps assess the RV function and size,
- Detects presence of PH through different parameters such as AO/PA ratio and septal configuration
- Advances in MRI were developed to assess interstitial and parenchymal lung disease in developing lungs
- *Kato, S. et al. Prognostic value of cardiovascular magnetic resonance derived right ventricular function in patients with interstitial lung disease. J. Cardiovasc. Magn. Reson. 17, 10 (2015).*

BPD- PH diagnosis

- The gold standard for diagnosis remains cardiac catheterization.
- It is rare that cardiac catheterization is required to make the diagnosis of BPD- PH
- It is acceptable to start treatment without cardiac cath which will be deferred especially if risks outweigh benefits especially in premies
- Cardiac catheterization is indicated if left sided obstructive lesion such as pulmonary vein stenosis is present
- Cardiac catheterization is indicated if second or third agents are required or if worsening of the clinical picture with treatment; however, the clinical instability may impede this in premature infants

BPD and PH/ Treatment

- Treatment of PH associated BPD starts with optimization of the respiratory support and lung recruitment
- Avoid invasive ventilation if possible: bubble CPAP
- Avoid atelectasis as it worsens the perfusion mismatch
- Diuretic use: different school of thought Lasix vs diuril
- Optimize nutritional needs to maintain growth
- Oxygen saturation is set at a higher target of > 93% in suspected PH and > 95% in confirmed PH
- Sedation to avoid BPD spells ie PH crisis

BPD- PH/ Treatment

- No medication is FDA approved to treat pulmonary hypertension, emphasizing the need for clinical research in BPD.
- All medications used are off label use based on expert opinion and experience
- Treatment include targeting the 3 pathways of pulmonary hypertension
- Treatment of BPD- PH is associated with improved outcome up to 95% survivor in 2 years F/U
- *Kadmon, G. et al. Pulmonary hypertension specific treatment in infants with bronchopulmonary dysplasia. Pediatr. Pulmonol. 52, 77–83 (2017).*
- It is reasonable to start sildenafil for the treatment of BPD- PH.
- Need for further therapies, it is recommended that the patient is under the care of PH specialist
- IV/ Oral medication may increase the VQ mismatch leading to decreased oxygenation since chronic lung disease is characteristic of disease
- This is not seen with inhaled agents.

Pulmonary Hypertension in Down syndrome/ Etiology

- Multifactorial
- Developmental lung disease including lung hypoplasia, microvascular developmental abnormalities, alveolar developmental abnormality and persistence of double capillary
 - Bush D, Abman SH, Galambos C. Prominent intrapulmonary bronchopulmonary anastomoses and abnormal lung development in infants and children with Down syndrome. *J Pediatr* 2017; 180: 156–162.
- High incidence of CHD
- Upper air way obstruction due to OSA
- PPHN has higher incidence in PPHN

Pulmonary Hypertension in Down Syndrome

- Unknown life-long incidence of pulmonary hypertension but the estimates range are around 28% that increases to 45% in the presence of congenital heart disease. The recurrence rate was the same for patients who developed PPHN and patients who did not develop it
- PH develop commonly in the first year of life with an incidence 6- 37.5% in Down syndrome with CHD
- *Mourato FA et al 2014. Bush D et al 2018, Espinola-Zavaleta N et al 2015, Cua CL et al 2007*
- DS patients have 3.83 odd ratio of dying with PH as compared to general population.
- *Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet. 2002;359(9311):1019-1025.*
- DS patients represent 5- 17% of PH patients in Pediatric PH registries
- *. Marín MJ del et al, 2014; van Loon RLE et al,2011; Moledina S et al, 2010*

Pulmonary Hypertension in Down Syndrome (DS)

- PH is a lifelong risk in DS
- In the first year of life is associated with PPHN and CHD
- In older patients it is respiratory symptoms and LV diastolic dysfunction especially in the presence of obesity, or other comorbidities such as OSA, hypothyroidism, sedentary life-style, and parenchymal lung disease, tracheostomies and aspiration .
- There is a delay in diagnosis of PH in DS in part related to developmental delay including difficulty in performing 6 minutes test or verbalizing symptoms
- Many of these patients underwent routine echo testing but detection of PH ranged widely between providers suggesting the need for PH specialist to do the screening

Pulmonary Hypertension DS

- PH is the main predictor of adverse cardiovascular outcome in adults with PH

- *Hayes SA, Kutty S, Thomas J, Johnson JT, Yetman AT. Cardiovascular and general health status of adults with Trisomy 21. Int J Cardiol 2017;241:173–6.*

- Resolution of early PH in DS was estimated as 43% at 3 years in a cohort of patients

- This is similar to resolution of PH in group I PH (43 % at 3 years) while resolution of PH in group III is higher at 60%

- *Hoper et al. Pediatric pulmonary hypertension with Down syndrome: results from the pediatric pulmonary hypertension registry. J Pediatr 2023, January 252, 131- 140.*

- *Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037–99.*

PH in DS/ Treatment

- Identify the underlying comorbidities and address them
- Medical treatment is otherwise similar to other patients with PH including PD5 inhibitors and ERAs

Persistent Pulmonary hypertension of the New Born (PPHN)/ Definition

- Failure to transition from high fetal PVR to a lower PVR after birth. This usually present shortly after birth causing hypoxemia
- Incidence ~ 2/1000 newborn, highest at term or early preterm
- *Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics. (2000)105:14-20.*
- *4. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. Pediatrics. (2017)139:e20161165.*

PPHN/ Mechanism

- High PVR in utero secondary to fluid filled lungs, low oxygen tension and low pulmonary blood flow (PBF) with resultant vasoconstriction and suppression of NO and prostacyclin production
- In late gestation vasculature acquires ability to respond to vasodilators through maturation of the endothelium and smooth muscles thus preparing for the changes after birth
- After birth PVR decreases drastically due to increased oxygen tension, and production of NO and PGI
- Ventilation irrespective of oxygenation contributes to the decrease PVR as well
- This results in reorganization of pulmonary vasculature with thinning of smooth muscles
- Clearing of the pulmonary fluid in the first few hours of life and during uterine contraction also aides in decreasing PVR
- Failure of this process results in PPHN

PPHN Etiologies

- **Idiopathic PPHN**
- 10-20% of all PPHN
- Normal lung parenchyma with abnormal remodeling of pulmonary vasculature
- **Lung parenchyma disease**
- Vasoconstricted pulmonary bed
- Pneumonia, meconium aspiration, and RDS

PPHN Etiologies

- **Abnormal Transition at Birth**
- Impaired pulmonary vasodilatation
- Transient tachypnea of new born (TTN)
- Hypoxia/ Perinatal stress
- **Developmental lung disease**
- Hypoplastic pulmonary vasculature
- Congenital diaphragmatic hernia, Down syndrome, Oligohydramnios
- *Martinho S, Persistent Pulmonary Hypertension of Newborn: Front pediatr 2020 July 24, 8:342*

PPHN risk factors

- Maternal drug intake :SSRI or NSAID intake
- Maternal comorbidities: overweight, diabetes and smoking
- Delivery: C section
- ?Maternal Asthma
- Maternal Race highest in African American lowest in Hispanic
- Gestation age highest in later preterm and early term neonates
- Highest in SGA and LGA
- Highest in males
- *Steurer MA, (2017), Hernandez D (2007), Heubreychts KF (2015), Van Marter LJ (2013)*

PPHN/ Treatment and F/U

- Optimize oxygenation and Ventilation
- NO is FDA approved for treatment of PPHN
- Beyond NO, medication use is based on expert opinion and experience.
- Short term follow for PPHN is indicated after discharge
- Long term follow up is unknown. Experts in the field acknowledge the different etiologies and the need for a subgroup to continue longer term follow up but it is not well defined yet

PH secondary to congenital heart disease

- **Heterogenous group includes**
- 1. Eisenmenger Syndrome
 - Untreated large shunt that leads to severe elevation in PVR
- 2. Left to right shunts
 - Correctable
 - Non correctable
- 3. PH in the presence of small shunt that does not explain the PH
 - Usually follows a natural course similar to PAH
- 4. Repaired heart disease with persistent PH or PH that developed after repair
 - Progressive disease with worse prognosis than PAH.
- 5. CHD without initial shunt such as d TGA repaired in neonate

PH in complex heart disease with pulmonary vascular disease

- Segmental pulmonary hypertension
 - - Absent pulmonary artery (pulmonary artery of ductal origin)
 - - Pulmonary atresia VSD
 - - Hemitruncus
- Multifactorial
 - - Scimitar syndrome
- Single ventricle
 - - Unoperated with unobstructive pulmonary flow
 - - Fontan circulation

Patient I /neonate with rt diaphragmatic hernia

- Echocardiogram showed pulmonary hypertension with hypoplasia of the right pulmonary artery. Flow from the rt pulmonary veins could not be confirmed
- CT scan showed hypoplasia of the right bronchus. The right side of the chest was occupied by the liver with fusion of lung tissue and liver. A sliver of right lung present and patient had scimitar syndrome with sequestration
- Patient started on nitric oxide with optimization of respiratory status and transitioned to oral sildenafil
- Surgery declined repair since no intestines were seen in chest

Patient I

- A full term newborn transferred to NICU level IV for respiratory failure and cyanosis with discrepancy between the upper and lower extremities saturation
- Chest X ray showed right diaphragmatic hernia
- An echocardiogram was ordered
- At age of 6 months had clinical deterioration with right sided heart failure while still on sildenafil.
- Patient was referred for ASD closure with a fenestration
- Patient did well clinically but had persistence of pulmonary hypertension
- At age of 2 years she underwent transcatheter occlusion of the feeder to the sequestered lung because of reports about improvement in PH with feeder occlusion
- No change in PH seen after the procedure

Patient I

- Continued to do well until she had COVID infection which she tolerated but had worsening of pulmonary hypertension subsequently
- She was changed to Tadalafil and Ambrisentan for ease of administration and improving compliance.
- She continues to do well



Patient II/ Patient with suspected myocarditis

- The 6 years old patient that presented to the ER with hypotension, hemodynamic compromise, cyanosis and chest pain following a URI. Elevated biomarkers
- In PICU, I R/O myocarditis and suspected severe PH secondary due to massive PE based on echo findings
- CT scan showed bilateral thrombus almost completely occluding the branch pulmonary arteries
- Patient underwent transcatheter thrombectomy but developed recurrent thrombosis. She was treated with Tpa but also recurred
- The recurrent thrombosis was deemed as secondary to autoimmune process due to its relentless nature. She was successfully treated with steroids and anticoagulation.
- She was discharged from hospital and did well clinically; but she continues on anticoagulation and is under care of hematology and cardiology

Patient III/ Syncope in a toddler

- A 2 years old presented to the ER with syncopal episode. She had one prior episode 2 months ago that was discussed with pediatrician and attributed to breath holding spells. The current episode was severe and required that the family perform CPR
- I read the echocardiogram as pulmonary hypertension in absence of CHD etiology unclear
- Patient placed on nitric oxide until stable then nitric oxide was weaned to discontinue in order to perform cardiac catheterization and check for vasoreactivity to calcium channel blockers
- Patient coded with the removal of last 1 ppm of nitric oxide ECMO called but patient successfully recovered and returned to Nitric oxide

Patient III

- I decided to tentatively treat the patient and forget vasoreactivity. We kept the child sedated
- She was started on Sildenafil and the dose adjusted. She was successfully weaned off nitric oxide. Echo still showed signs of PH. She coded when sedation was weaned.
- Bosentan was added for hope that she is an ERA responder. She showed improvement in echo findings but still evidence of PH
- IV flolan was started then successfully changed to remodulin. The dose was titrated under echo guidance. Sedation was weaned and the patient underwent cardiac catheterization which showed normal PVR on triple therapy

Patient III

- I did an extensive work up including genetic work up and whole exon sequence all of which were negative
- I recommended creation of an ASD in the cath lab. The family refused and requested a second opinion. She was transferred to Cincinnati Children.
- Cincinnati Children revisited the diagnosis of idiopathic PH and started weaning Remodulin. The patient coded. The dose was returned. The IV Remodulin was changed to subcutaneous and patient discharged home without an ASD
- 4 months later, she was taken to the cath lab for reassessment. The intubation was little rocky and the patient coded in the cath lab. She was recovered and an ASD was created with stent placement.
- 2 ½ years after diagnosis, she continues on triple therapy of PH and oxygen but is considered for lung transplantation. She remains very volatile.

Patient IV/ Extreme premie

- A 21 weeks gestation male patient was delivered by emergency C section due to HELLP syndrome in the mother with seizures and renal insufficiency
- The newborn was resuscitated and intubated in the delivery room.
- Echocardiography done at few days if life showed severe pulmonary hypertension.
- He was started on nitric oxide but did not respond
- He was taken off nitric and started on inhaled iloprost.
- He showed some improvement but remained critical and the family were told about the very poor prognosis
- Sildenafil IV was started and the newborn turned a corner with the combination

Patient IV extreme premie

- He was weaned off inhaled iloprost and remained on sildenafil and oxygen.
- He did relatively well with routine echocardiogram screening
- At around 32 weeks gestation, he had a PH crisis and was started on nitric oxide. Echo showed worsening of his PH. Bosentan was added. Inhaled iloprost was added and the dose of nitric was weaned as the dose of inhaled iloprost increased. He did well and underwent tracheostomy and G button placement. His respiratory settings improved. He was transferred to a rehabilitation facility on respiratory. His dose of iloprost was weaned 1 ½ yr later but he required frequent admissions with URI symptoms. Cardiac catheterization done after recovery showed PVR index of 4 wu on sildenafil and bosentan. He was put back on iloprost



Patient V/ Down syndrome with CHD

- A patient with Down syndrome and prematurity at 32 weeks gestation was admitted to NICU
- Echocardiogram done showed ASD and VSD
- Around 40 weeks gestation, she showed evidence of pulmonary overcirculation; so she was treated with diuresis. Her respiratory status did not improve. and she remained intubated
- At 42 weeks gestation, her shunt was purely left to right so she was taken for closure of ASD, VSD. She did well postoperatively. She was extubated but remained oxygen dependent
- Echo showed pulmonary hypertension

Patient V/ Down syndrome with non complex CHD

- She was started on sildenafil and did very well just with dose adjustment for growth.
- Cardiac catheterization confirmed the PH
- Around 2 years of age, her PH started to worsen. This was atypical for her so I repeated her blood work although it was done one month prior and was normal.
- Results of CBC came positive for leukemia. She tolerated treatment and recovered.
- Her sildenafil was discontinued at 3 years of age and she is monitored closely

Patient VI / Complex heart disease

- A 14 years old with pulmonary atresia, collaterals s/p repair, with residual ASD had history of pulmonary hypertension since infancy.
- She has been maintained on sildenafil by her cardiologist but referred to PH clinic with symptomatic RV failure and saturation low 70s- Low 80s on oxygen. She was very symptomatic with very limited 6 min walk test.
- Her mother aware of her condition just requested that her daughter live to attend the PROM
- Bosentan was added to the treatment with some improvement but one year later she recurred.
- Oral selexipeg was added to her regimen and bosentan was changed to ambrisentan and sildenafil to tadalafil

Patient VI / Complex heart disease

- Her symptoms improved. Her saturations increased to the low 90's and she was happy able to do routine daily activities and travelled
- One or 2 years later, she deteriorated so selexipeg was changed to s/c remodulin.
- The transfer was not smooth as she developed left ventricular diastolic dysfunction with the increase in her cardiac output.
- I treated diastolic dysfunction and was able to up titrate remodulin to maintain saturations > 90.
- She was referred to adults for heart/ Lung transplant. The concern was the developmental delay in the child who had 11 years old mental status.
- After meeting with the transplant team, the family declined transplant and decided to proceed with medical therapy

Patient VI / Complex heart disease

- She went to the PROM with her beau and the mother was all grateful. The child was very happy
- A couple of years later, she died suddenly at home
- After her demise, I spoke to the family, and they were still very grateful that she had few good years and was able to enjoy her last years

Patient VI

- A 14 years old female patient with history of prematurity and pulmonary hypertension who was discharged home on oxygen but outgrew her oxygen needs the first year of life
- She was seen in pulmonary for reactive airway disease. However, her symptoms did not improve with adequate asthma treatment.
- Patient referred to PH clinic and echo done showed PH
- Cardiac cath confirmed PH and she was started on sildenafil.
- Her echo normalized but the patient continued to complain about generalized fatigue
- CT scan of chest done was consistent with sarcoidosis which we attributed the fatigue to.
- The pulmonary hypertension was considered is still related to chronic lung disease as sarcoidosis related PH occur in advanced cases but we referred her to our adult colleagues because of sarcoidosis

Conclusion

- PH in children although rare is present in pediatric age group and requires high index of suspicion to recognize
- Identifying high risk group in pediatric patients facilitate the suspicion for PH and proper referral
- Treatment is dependent on expert opinion and experience. Frequently we have to think outside the box when deciding a regiment for treatment
- Active on going research is going to standardize the treatment, but we are still very far from this target



Questions?

