Pulmonary Vascular Disease in BPD

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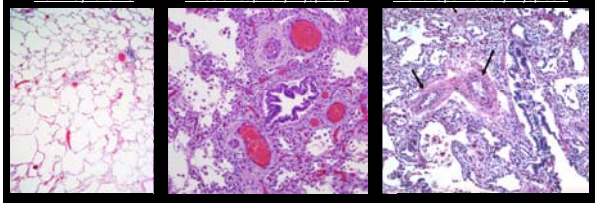
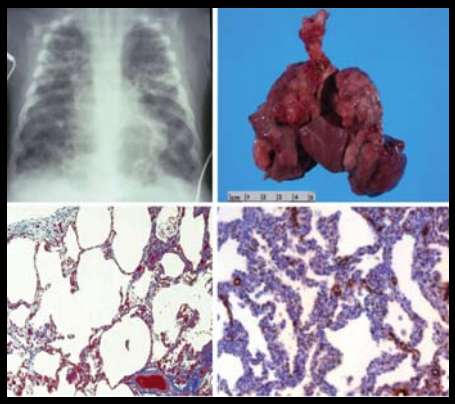
- Dr. Steve Abman has documented that he has no financial relationships to disclose or conflicts of interests to resolve.

Developmental Lung Diseases Associated with Pulmonary Hypertension

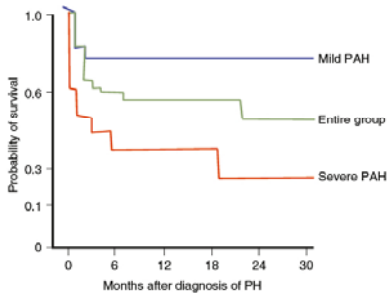
Down Syndrome | Alveolar Capillary Dysplasia | Bronchopulmonary Dysplasia



Bronchopulmonary Dysplasia (BPD)

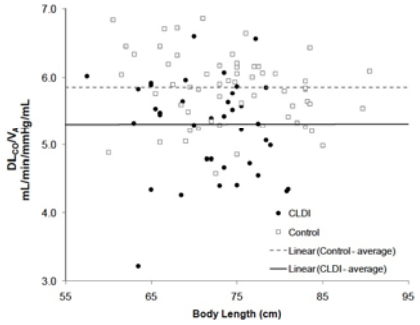


Late Pulmonary Hypertension is Associated with Poor Survival in BPD



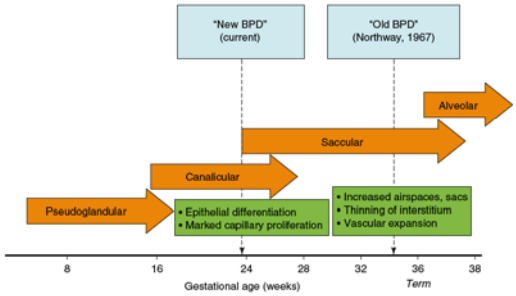
(from Khemani et al, 2007)

Reduced Lung Surface Area in Infants with Chronic Lung Disease

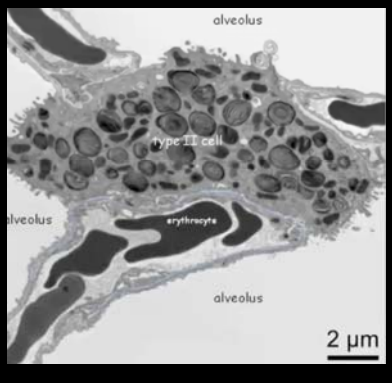


(Balinotti et al, AJRCCM, 2010)

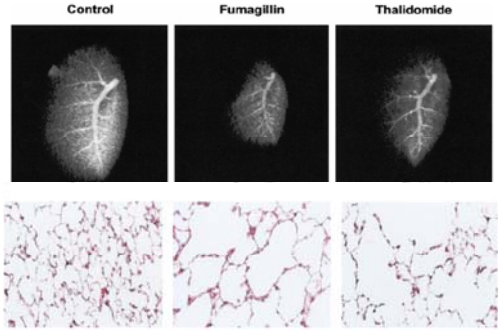
Lung Development and Preterm Birth



Endothelial - Epithelial Cell Interactions

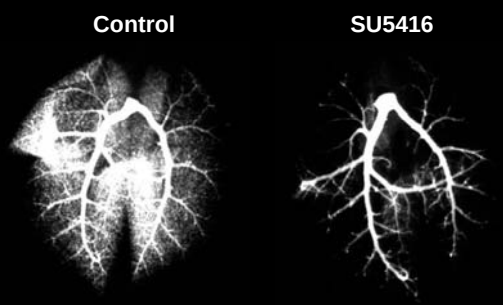


Disruption of Angiogenesis Impairs Alveolarization in the Developing Lung



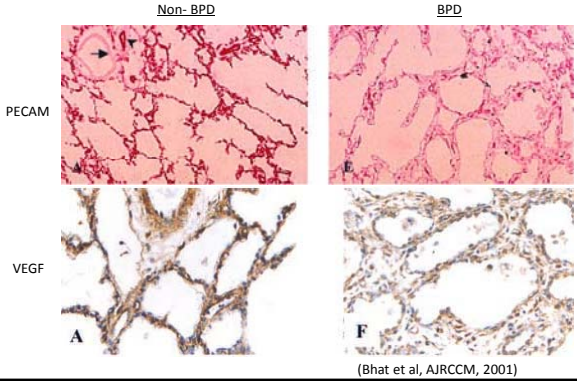
(Jakkula M et al Am J Physiol, 2000)

VEGF Receptor Inhibition Impairs Lung Vascular Growth in Neonatal Rats



(Jakkula M et al, Am J Physiol. 2000)

Decreased Angiogenesis and Vascular Endothelial Growth Factor in Human BPD



(Bhat et al, AJRCCM, 2001)

Pathogenesis of BPD

Epigenetic and Genetic Factors

Premature Birth

Prenatal factors
- Chorioamnionitis
- Fetal infection
- Preeclampsia, IUGR
- Smoking, drug use

Hyperoxia O_2^-

Inflammation O_2^-

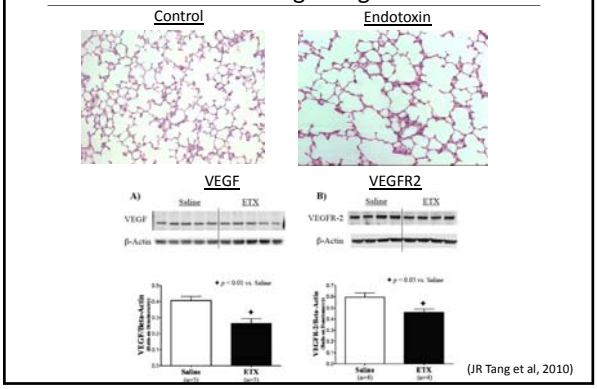
Infection O_2^-

Ventilator Induced Injury O_2^-

Disruption of growth factor signaling pathways

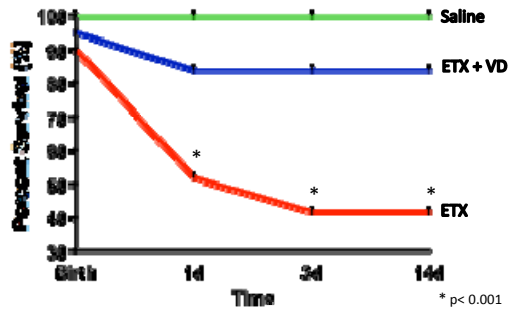
BPD
- Alveolarization
- Vascular Growth
- Lung Function

Intra-Amniotic Endotoxin Impairs Lung Structure and VEGF Signaling in Infant Rats



(JR Tang et al, 2010)

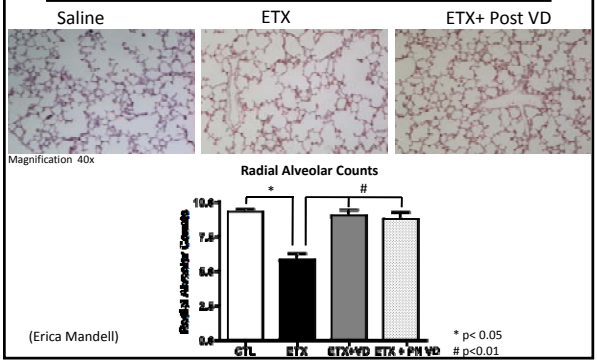
Antenatal Vitamin D Improves Survival in ETX - Exposed Rat Pups



* p< 0.001
ETX v ETX +VD

(Erica Mandell)

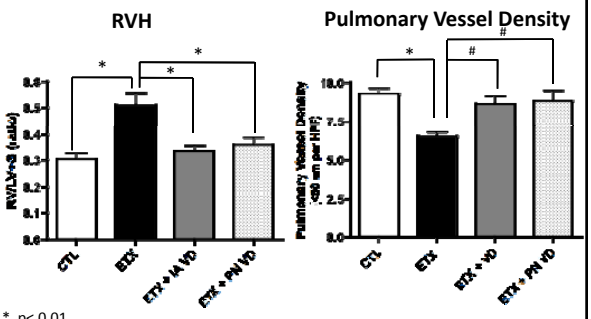
Vitamin D Treatment Improves Late Lung Structure after Antenatal ETX Exposure



(Erica Mandell)

* p< 0.05
# p<0.01

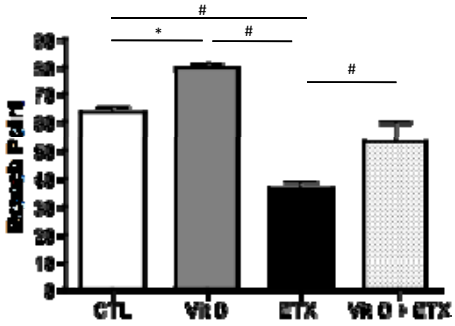
Vitamin D Decreases RVH and Preserves Pulmonary Vessel Density after ETX Exposure at Day 14



* p< 0.01
#p < 0.05

(Erica Mandell)

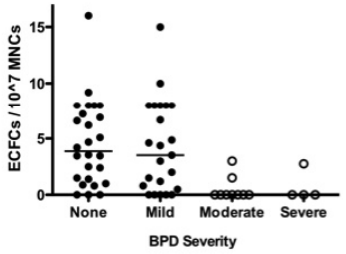
Vitamin D Increases Tube Formation in Fetal PAEC Exposed to ETX



(Erica Mandell)

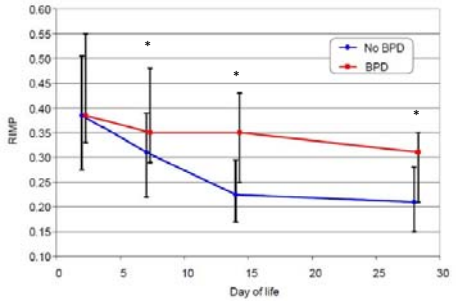
* p< 0.05
# p< 0.001

Cord Blood ECFC are Decreased at Birth in Preterm Infants who Develop BPD



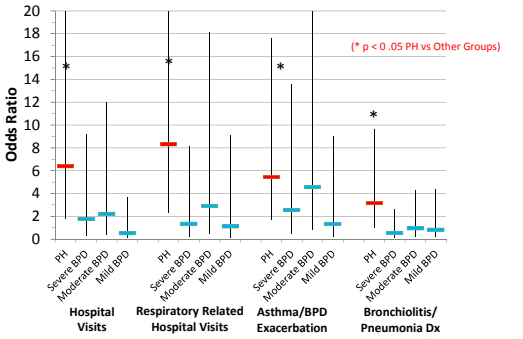
(Baker CD et al. *Eur Respir J,* 2012)

Lack of Decline in RIMP in Preterm Infants Who Later Develop BPD



(RIMP = RV index of myocardial performance) (Czernik C et al, PLoS One, 2012)

Diagnosis of Pulmonary Hypertension Increases Risk of Late Respiratory Morbidities Independent of BPD Severity



(Peter Mourani)

Pulmonary Vascular Disease in BPD

Abnormal Growth
- Impaired Angiogenesis
- Intrapulmonary Shunt Vessels
- Decreased Alveolarization

Abnormal Function
- High tone
- Abnormal Reactivity

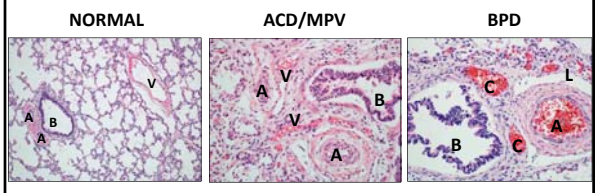
Abnormal Structure
- SMC hyperplasia
- Adventitial thickening
- Intimal occlusion (rare)

Decreased Lung Surface Area and Gas Exchange

- Prolonged oxygen therapy
- Altered distribution of blood flow with infection, stress
- Exercise intolerance
- Pulmonary Hypertension

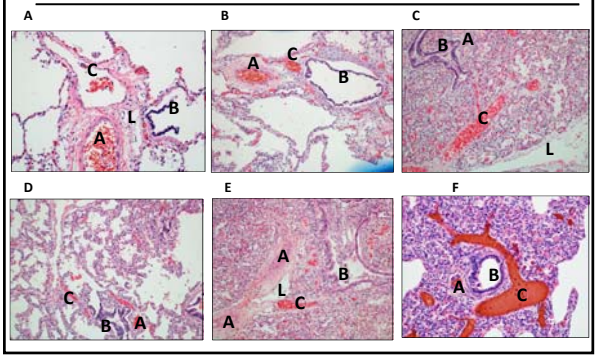
(Mourani PM, Abman SH. Curr Op Peds, 2012)

Histologic Evidence of Intrapulmonary Vascular Shunt Vessels in BPD

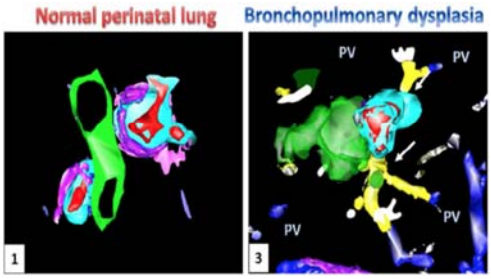


(Galambos C, Sims-Lucas S, Abman SH. *Ann Am Thorac Soc.* 2013)

Patterns of Abnormal Vasculature in the Distal Lung of Infants Dying with Severe BPD



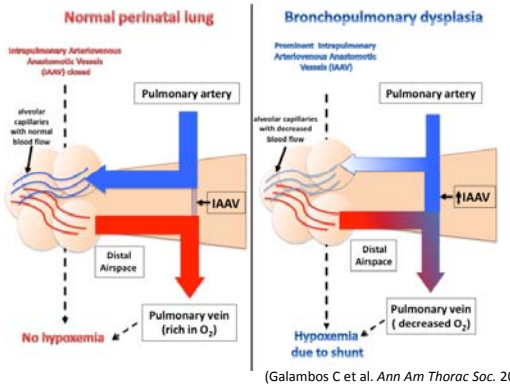
Persistent Fetal Intrapulmonary "Shunt Pathways" in Severe BPD



Artery: red	Lymphatic: pink
Veins: blue	Art. media: aqua
Airway: green	Vascular Channels: yellow

(Galambos C et al. *Ann Am Thorac Soc.* 2013)

Intrapulmonary Shunt Vessels in BPD



(Galambos C et al. *Ann Am Thorac Soc.* 2013)

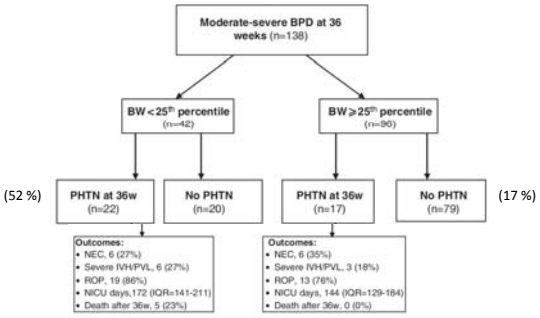
Issues in the Diagnosis and Management of Pulmonary Hypertension in BPD

- Whom to screen?
- How to screen?
- When to screen?
- What is the diagnostic evaluation?
- What is the role of cardiac catheterization?
- Which therapies are effective in BPD?

Whom to Screen?

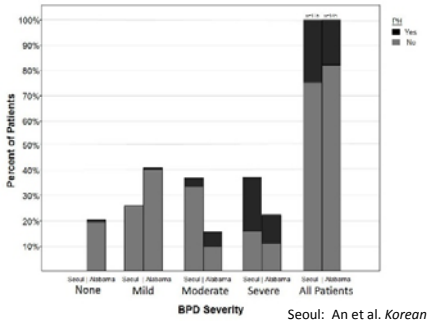
- Extreme prematurity (< 26 weeks)
- IUGR or pre-eclampsia
- Prolonged ventilator course
- Inability to wean FiO_2, lack of overall improvement with time, poor growth, recurrent "spells"
- Severity of BPD
- Or, All infants with BPD near term corrected age, even if clinically stable?

Low Birth Weight and Risk for Pulmonary Hypertension in BPD



(Check J et al, J Perinatol, 2013)

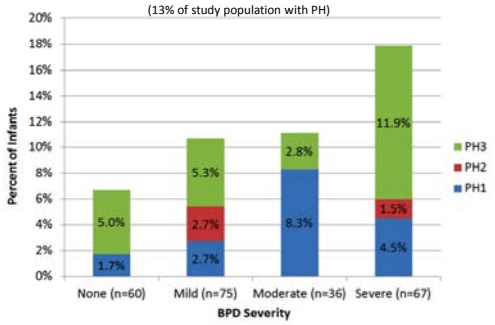
Pulmonary Hypertension and BPD: Association with Disease Severity



(Mourani PM, Abman SH. Curr Op Pediatr, 2013)

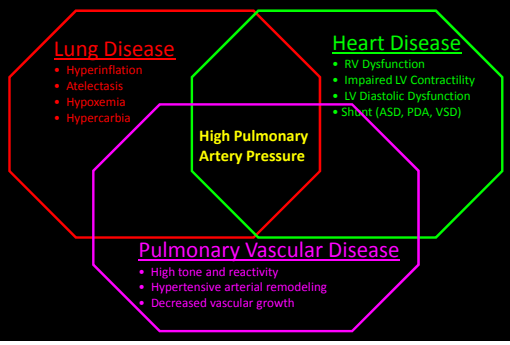
Seoul: An et al. *Korean Circ J,* 2010
Alabama: Bhat et al. *Pediatrics,* 2012

Relationship of Pulmonary Hypertension and Severity of BPD at 36 Weeks PCA

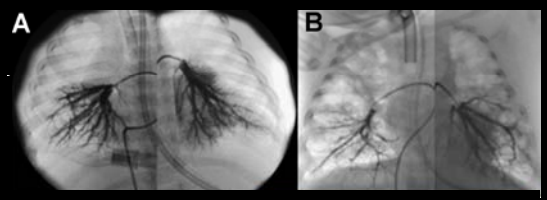


(PM Mourani et al, unpublished data)

Elements of Pulmonary Hypertension in BPD

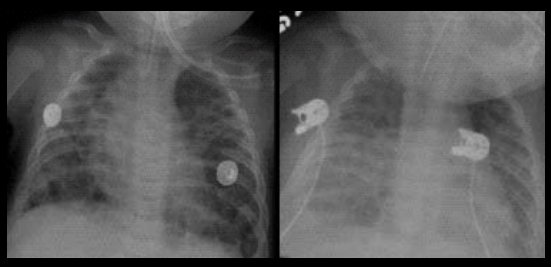


Pulmonary Vascular Development in BPD

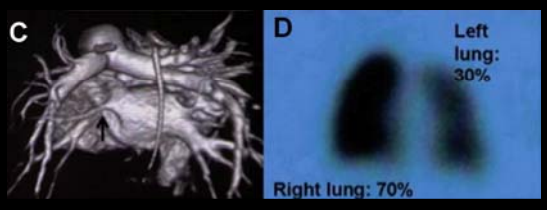


(del Cerro et al. Pediatric Pulmonol, 2013)

Left Ventricular Diastolic Dysfunction in BPD



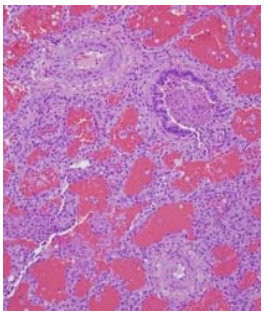
Pulmonary Vein Stenosis in BPD



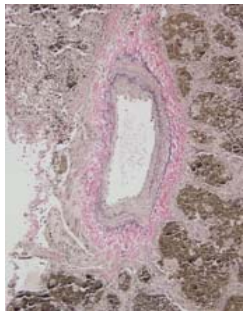
(del Cerro et al. Pediatric Pulmonol, 2013)

Severe Pulmonary Hypertension in a Preterm Infant with BPD and PVS

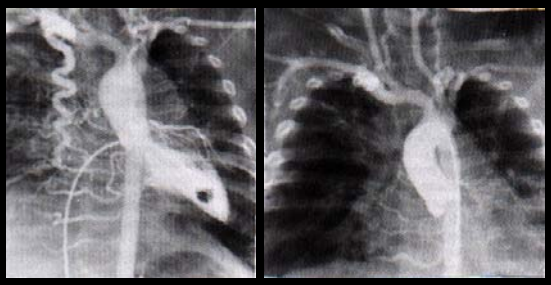
Pulmonary Artery Remodeling



Pulmonary Vein Remodeling



Increased Systemic to Pulmonary Collaterals in BPD



Associated Cardiovascular Lesions in BPD Infants with Pulmonary Hypertension

FINDING	% of PATIENTS
- PDA/ASD/PFO	50%
- Pulmonary Vein Stenosis	27%
- Aorto-pulmonary Collaterals	35%
- Left Ventricular End-Diastolic Pressure > 12 mmHg	54%

- Retrospective study of 29 patients
- 21 patients had CT scans, 14 had cath
- 66% with one associated findings

(del Cerro et al. Pediatric Pulmonol, 2013)

Course and Outcomes of BPD Infants with Pulmonary Hypertension

Clinical Feature	Values or Proportion
Age at diagnosis	4.5 months (median)
Diagnosed after NICU discharge	48%
Supplemental O2 therapy at diagnosis	59%
Mechanical Ventilation at diagnosis	28%
Echo at diagnosis (ratio of RVSP/Syst P)	70% (median)
Death	8/29 (28%)
PH-specific Drug Therapy	22/29 (76%)
Resolution of PH without Drug Therapy	3/29 (10%)
Required closure of shunt	6/29 (21%)
* Median duration of follow-up = 35 months	

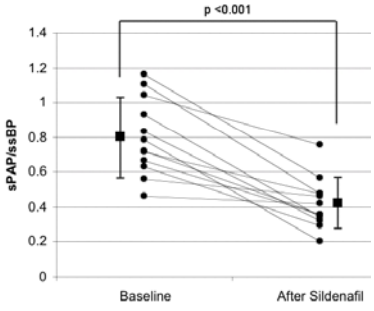
(del Cerro et al. Pediatric Pulmonol, 2013)

Summary and Recommendations

- All of these patients had moderate (24 %) or severe (76 %) BPD;
- Most patients had perinatal risk factors for BPD, including IUGR, preeclampsia, PPROM, chorioamnionitis, older maternal age;
- PH often late diagnosis, variable oxygen use;
- *Screen all patients with mod/severe BPD* with serial echocardiograms at 2-3, 4-6 and 10-12 months of age, especially with risk factors or prolonged oxygen course.

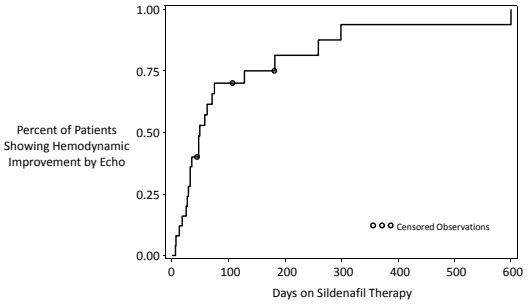
(del Cerro M et al, Pediatri Pulmonol, 2013)

Chronic Sildenafil Therapy for Late Pulmonary Hypertension in CLD



(Mourani PM et al, J Peds, 2009)

Clinical Response to Prolonged Sildenafil Therapy in BPD



(Mourani, J Pediatr, 2009)

Conclusions

- Pulmonary vascular disease (PVD) can be identified early in preterm newborns and is associated with:
  - an increased risk for developing BPD
  - higher mortality and late respiratory morbidities.
- Early endothelial cell injury disrupts angiogenesis and impairs alveolarization.
- Antenatal stress is sufficient to cause sustained abnormalities of postnatal lung growth.
- Prominent “fetal” intrapulmonary channels persist in severe BPD.
- Pulmonary hypertension and associated cardiovascular abnormalities modulate the clinical course and outcomes of BPD

Pediatric Heart Lung Center

Clinical Team

Lab Group