8 WK OLD FEMALE WITH DIFFICULTY FEEDING AND SUBSEQUENT RESPIRATORY DISTRESS

CLINICAL PATHOLOGICAL CASE CONFERENCE
JULY 25, 2014

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History of Present Illness

Chief complaint: constipation and difficulty gaining weight

HPI: 8 wk female with history of ex-34 wk prematurity, and “unilateral polycystic kidney” presents with complaint of feeding difficulties, constipation, and poor weight gain.

Feeding history:

- PO intake had decreased in past week associated with tachypnea and crying 15 min after feedings

Additional History

Born at 34 wks GA via C/S for NRFHR after PTL

BW 2790 gm (6.15 lbs, 90%). Apgars 8, 8.

Initially born “edematous” and after birth, weight dropped to 4 lbs.

Transferred to NICU for desaturations to the 80’s

Maternal Hx: 30 yo Hispanic G1P1

Pregnancy Hx: polyhydramnios, “flu”

Family Hx: negative

Immunizations: up to date

NICU Course

Stayed in NICU for 3 wks

Nasal cannula x 2 days, then room air

Received platelets for thrombocytopenia

Multiple cysts in the left kidney, no hydronephrosis, and normal right kidney

ECHO revealed small ASD (with left to right shunting) and "small PDA"

Karyotype normal

Sepsis work-up negative

Initial NBS abnormal, but repeated NBS normal

Pertinent Exam Findings

Wt 3800 gm (~50%)

Lt 54.5 cm (~90%)

HC 36 cm (~50%)

T 36.9 | P 160 | BP 74/49 | RR 32 | Sats 97-100% on RA

Healthy, NAD, fussy but consolable

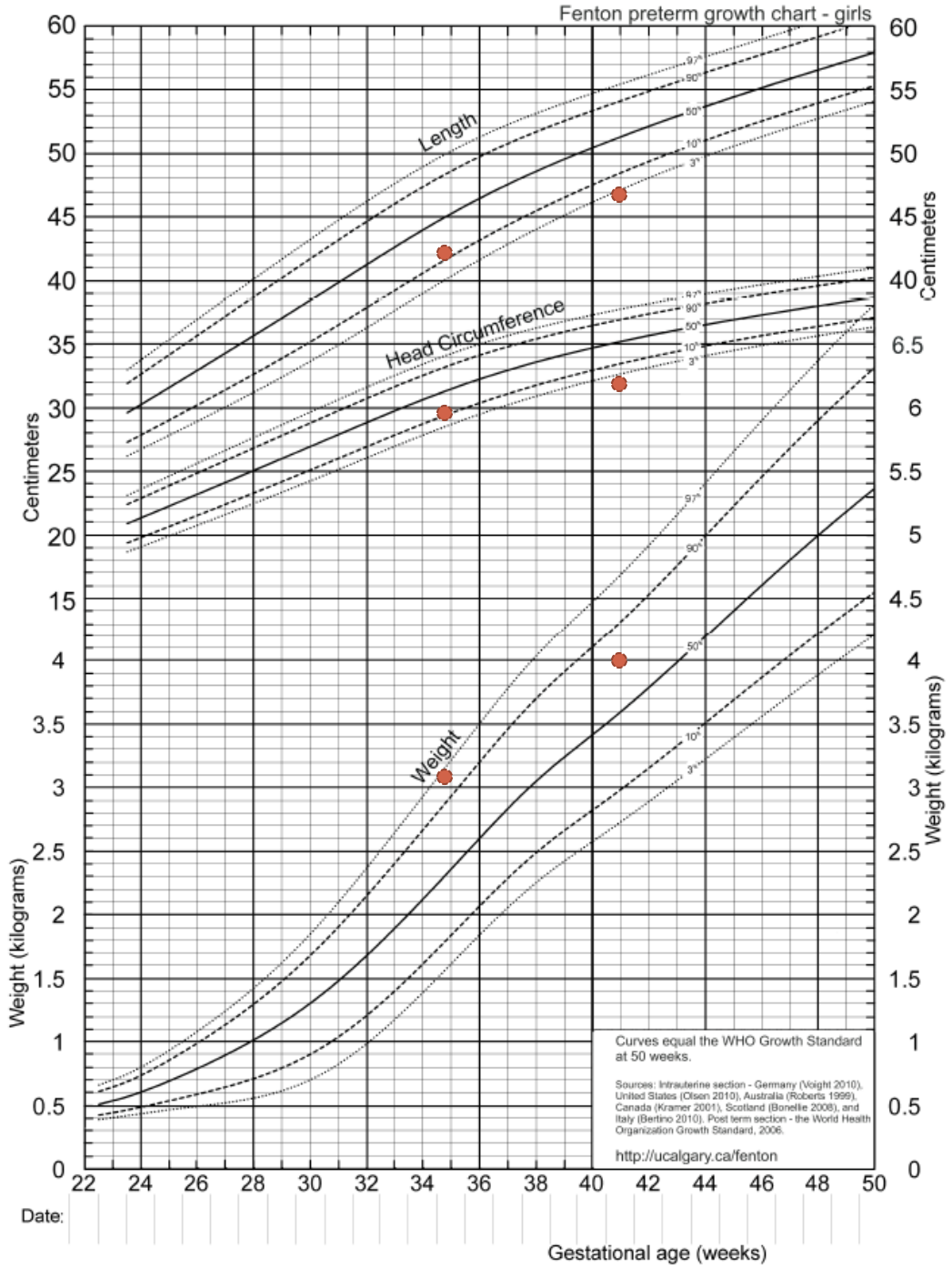
HEENT normal

CTAB, no rales, rhonchi or wheezes

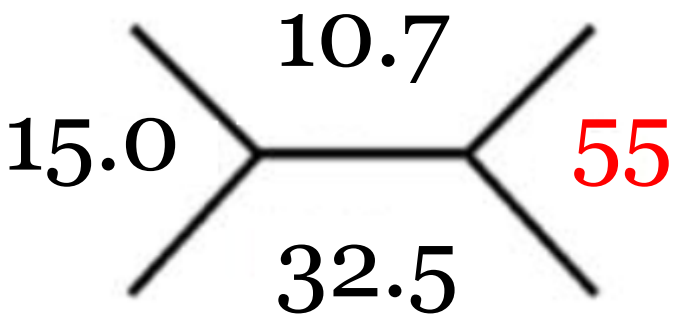
RRR, normal S1 and S2, 1/6 systolic murmur at the LLSB

Soft, NT, mildly distended without HSM

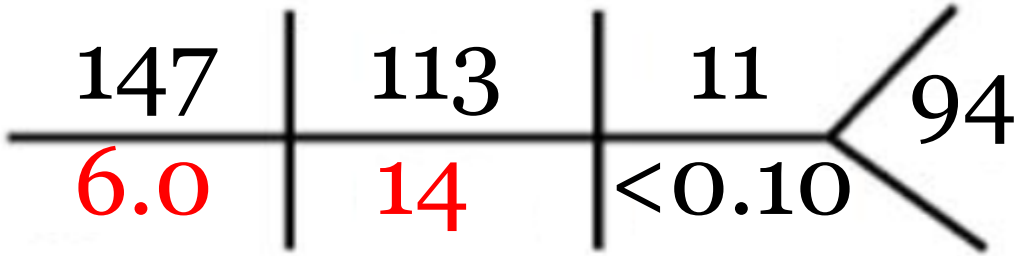
Normal to mildly hypotonic, mild head lag, moves all extremities, full range of motion


Fenton preterm growth chart - girls
Length
Head Circumference
Weight
97th
90th
50th
10th
3rd
Centimeters
Weight (kilograms)
Curves equal the WHO Growth Standard at 50 weeks.
Sources: Intrauterine section - Germany (Voigt 2010), United States (Olsen 2010), Australia (Roberts 1999), Canada (Kramer 2001), Scotland (Bonellie 2008), and Italy (Bertino 2010). Post term section - the World Health Organization Growth Standard, 2006.
http://ucalgary.ca/fenton
Date:
Gestational age (weeks)

Lab Work



N25
L68
M4
Bands 3



AST 33, ALT 13, CA 9.8, Tbili 1.2
ESR 8

Echo

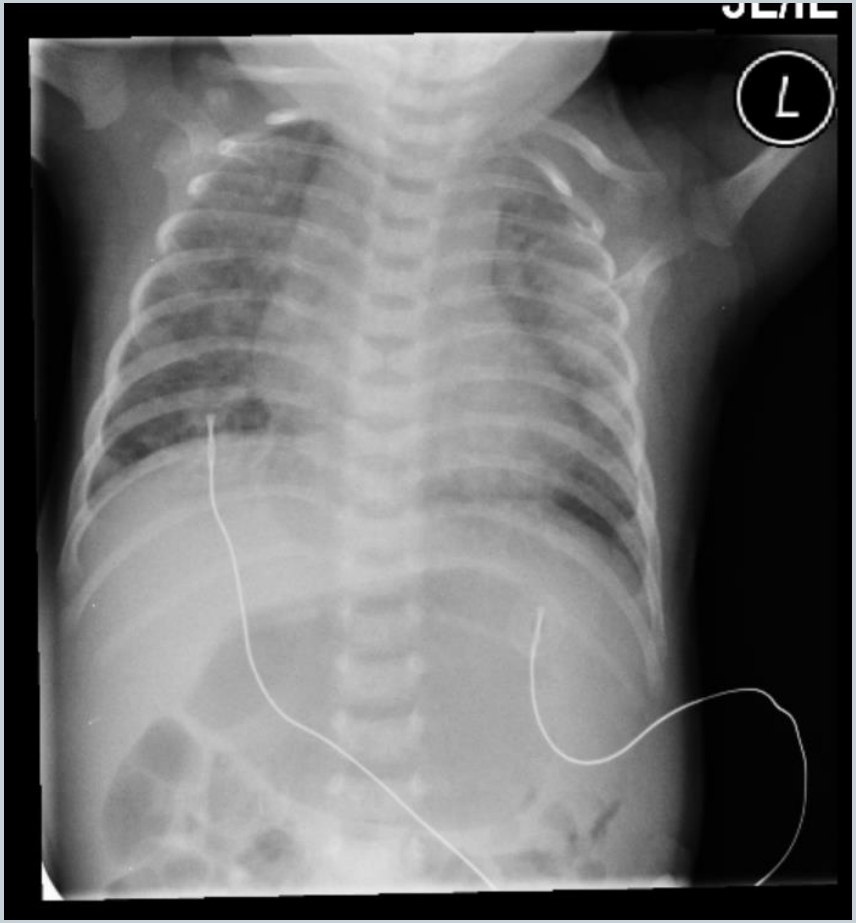
- Moderate right ventricular hypertension/pulm artery hypertension
- Moderate to large PDA (bidirectional)
- Normal biventricular systolic function (EF 80.5%)
- Tricuspid regurgitent velocity estimated pulmonary artery pressure at 66 mmHg plus central venous pressure (systolic blood pressure was 90 mmHg at time of Echo)
- Aorta was normal

Pulmonology consulted for “pneumonia”

Pertinent exam findings:

T 36.9 | P142 | BP 84/37 | RR 50-70 | Sats 99-100% RA

- Lungs: crackles throughout lung fields
- Heart: tachycardic, normal S1 and S2, 3-4/6 systolic murmur at LUSB radiating throughout anterior chest and radiating throughout lung fields, no rub or gallop



Transferred to PICU for desaturations and increased work of breathing

PCR +enterovirus/rhinovirus

CT surgery recommended PDA evaluation after recovery from rhinovirus bronchiolitis with consideration of directionality of PDA

Renal U/S showed atrophic left kidney, possibly duplex with multicystic dysplastic kidney appearance of the lower pole. Right kidney was normal.

Transferred to PICU again and intubated for increased tachypnea and lethargy

CBG: pH 7.35 | pCO_2 60 | HCO_3 33 | BE 7.0 | pO_2 46

CXR: Increased moderate pulmonary opacities, hyperexpanded lungs, normal heart size

ECHO:

- Normal LV size and function
- Normal size of L & R atria
- At least 2 pulmonary veins (lower L & R) empty in the L atrium, suggestion of pulmonary vein obstruction
- Moderate PDA though PDA was not ideally profiled on this study

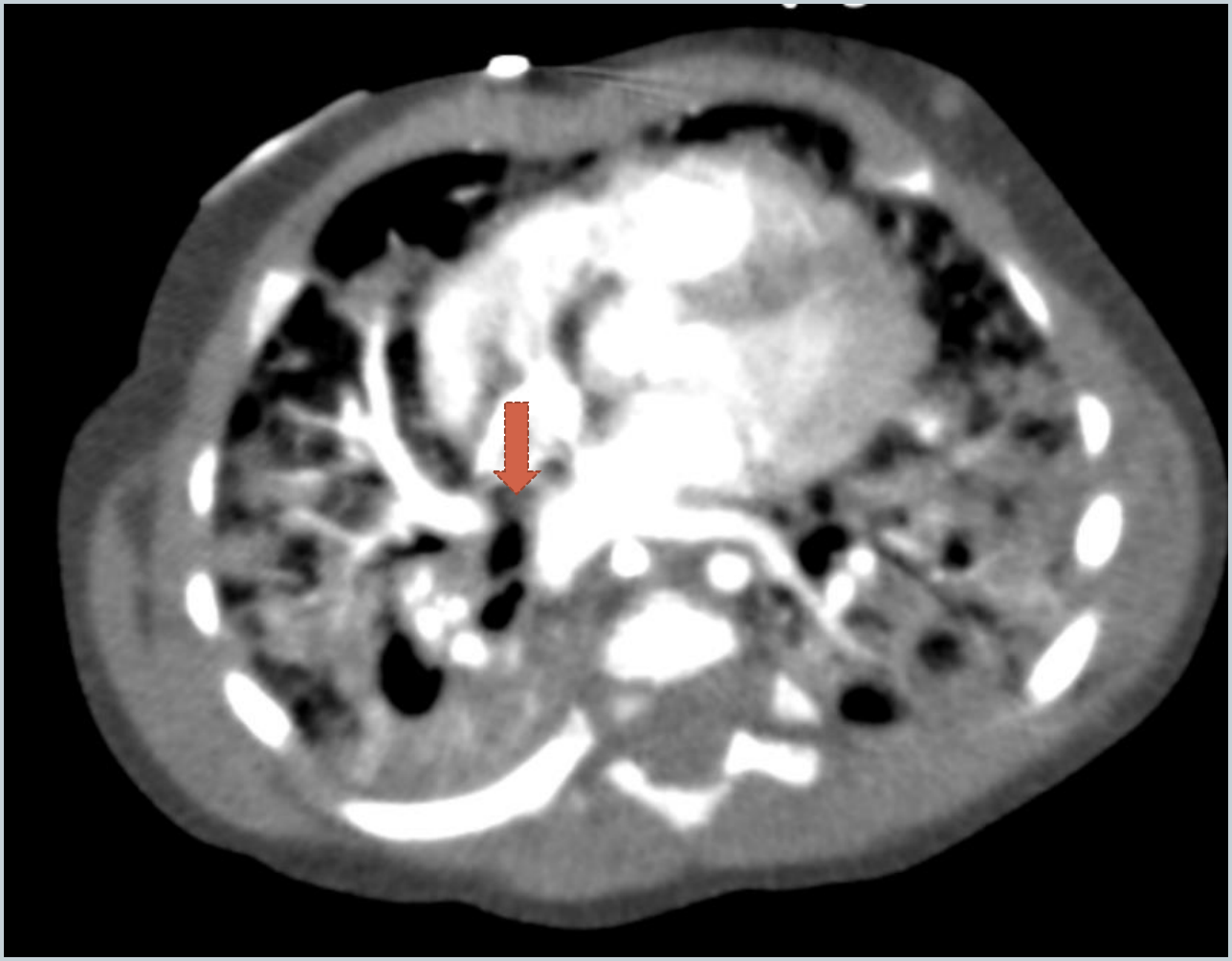
CTA of Chest completed

Radiographic Imaging

SON C. NGUYEN, MD
PEDIATRIC RADIOLOGY

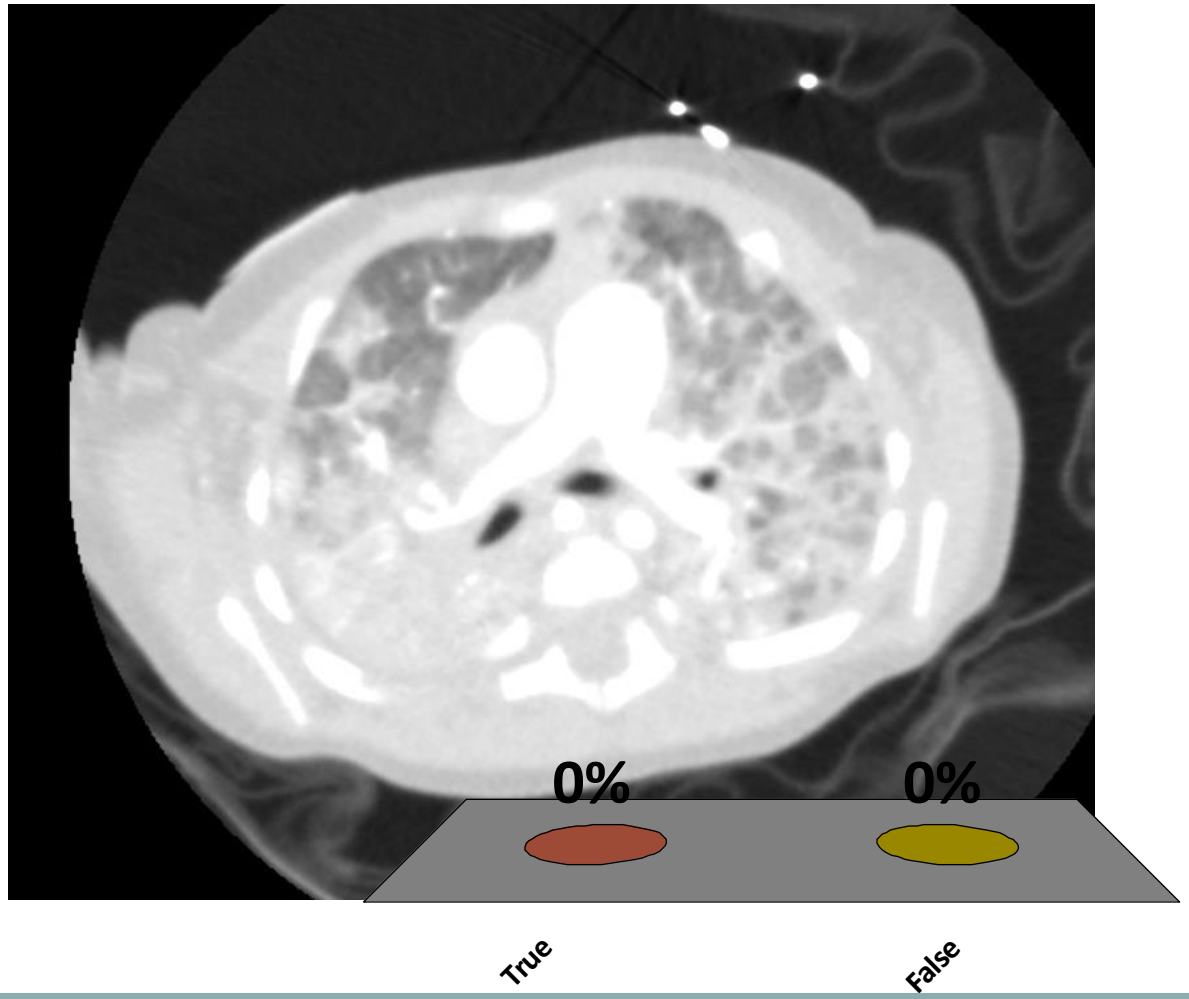
CTA Chest

CTA of Chest



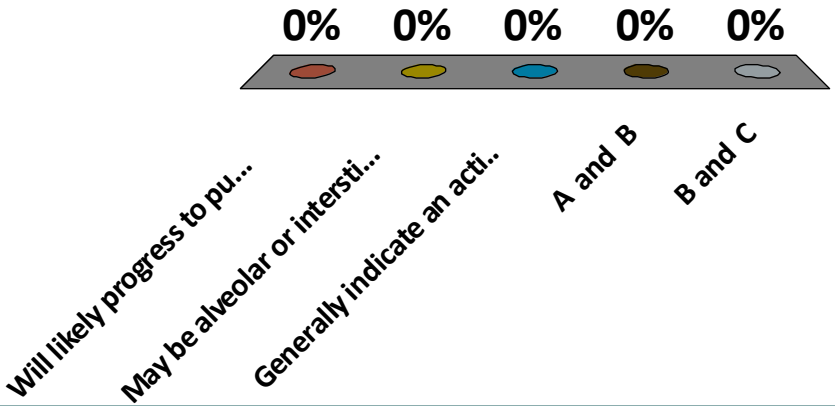
Ground glass opacities obscure underlying bronchovascular structures

A. True
B. False



Ground glass opacities

A. Will likely progress to pulmonary fibrosis
B. May be alveolar or interstitial
C. Generally indicate an active and potentially reversible process
D. A and B
E. B and C

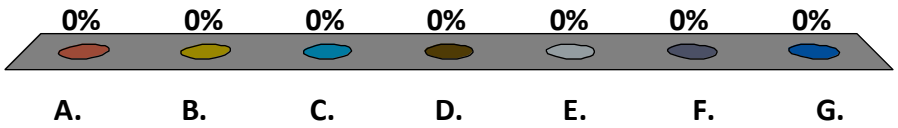


Answer: E (B and C)

- Ground-glass opacities may reflect an alveolar or interstitial process (B)
- 60-80% reversible (C)

What is the most likely cause for the patient's respiratory distress?

A. Acute respiratory distr
infectious etiology
B. Uncorrected patent du
C. Chronic aspiration due
D. Chronic lung disease o
E. Interstitial lung diseas
F. Underlying congenital
G. Underlying metabolic

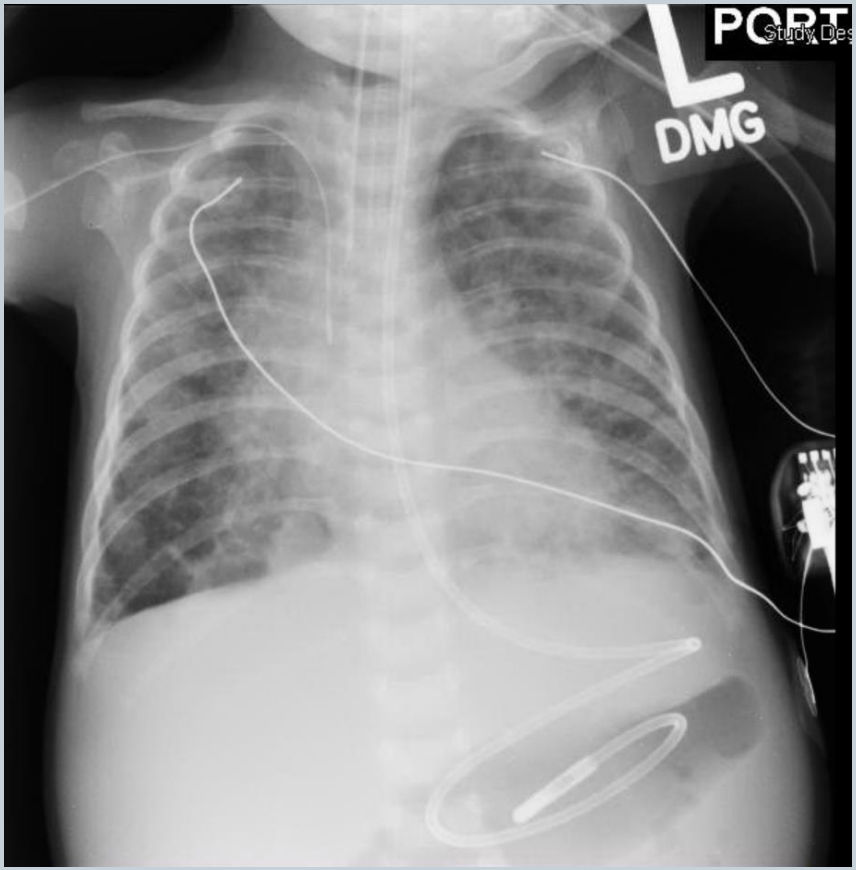


Differential diagnosis

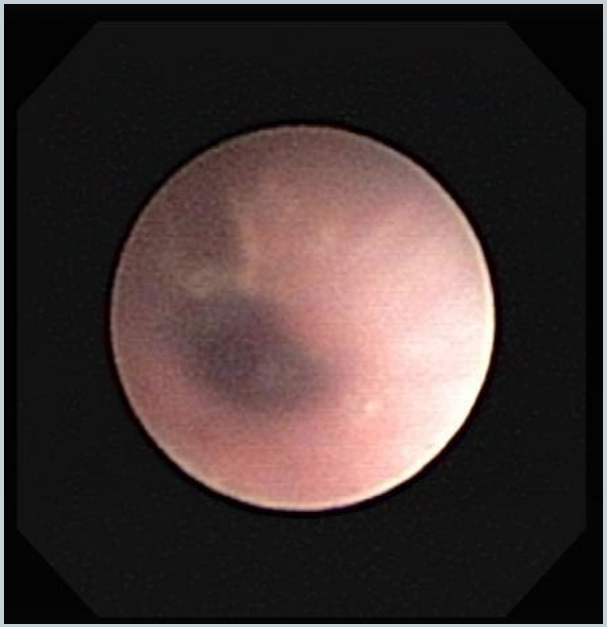
- Infectious
- Cardiac
- Childhood interstitial lung diseases:
  - Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD-MPV)
  - Lung growth disorders
  - Pulmonary interstitial glycogenosis
  - Neuroendocrine cell hyperplasia of infancy (NEHI)
  - Genetic disorders of surfactant dysfunction – genetic mutations in SFTPB, SFTPC, ABCA3, and NKX2.1/TTF1
- Aspiration syndromes
- Bronchiolitis obliterans
- Hypersensitivity pneumonitis
- Systemic disease processes
- Disorders masquerading as interstitial disease – arterial, venous or lymphatic abnormalities masquerading as interstitial lung disease

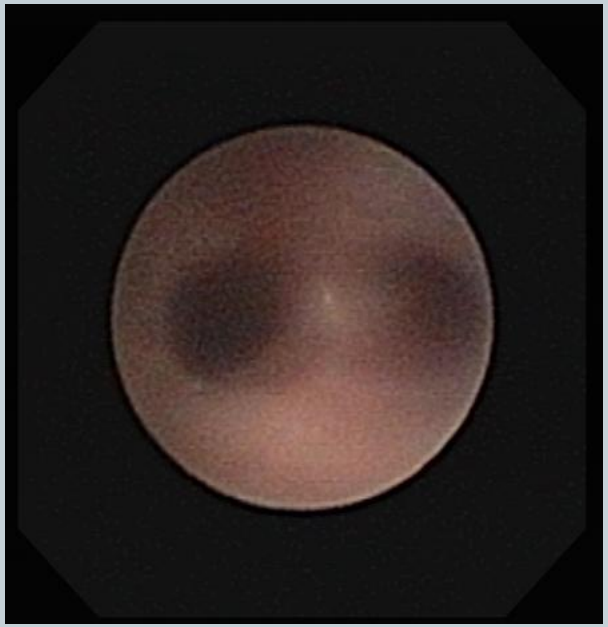
Bronchoscopy and BAL with brush biopsy performed

- BAL cytology:
  - WBC 567 (79% segs, 11% lymphs, 9% monos, 1% eos)
  - No malignant cells, no viral inclusions
  - Many inflammatory cells
  - Positive lipid laden macrophages
  - Negative for iron-laden macrophages (only rare or weakly positive)
- Bronchial brush biopsy sent to CHLA for electron microscopy
- Genetic analysis sent for surfactant protein B deficiency, surfactant protein C deficiency, and ABCA3-related surfactant deficiency



Bronchoscopy #1





Findings:

1) blood-tinged mucus plugs most notable in the RUL
2) severe airway inflammation
3) moderate friability throughout, especially between the left lingula and the LLL

Cardiology Perspective

BRANDY HATTENDORF, MD, FAAP, FACC, FASE
INTERIM DIRECTOR OF PEDIATRIC CARDIOLOGY
DIRECTOR OF NONINVASIVE PEDIATRIC CARDIOLOGY

Transferred to Cedar-Sinai for cardiac catheterization and possible intervention

Fluoroscopy of chest showed severe bilateral interstitial lung disease

PDA was closed with a vascular plug

Transeptal approach used to access the left atrium with an (intentional) small atrial septal defect left post procedure

- Cardiac index was normal
- Initial Qp:Qs measured was 1.2:1
- Saturations: SVC=57%, PA=61%, Aortic=83%; On 100% oxygen: PA=61%, Aortic=91% indicating significant lung disease
- Pressures: PA: 74/44, mean 58, aortic 82/46, mean 64 (concurrent measurements), RA pressure: mean 7 mmHg
- LV: 91/3-10 with no gradient on pullback across the valve, transverse arch or descending aorta.
- Right upper pulmonary vein gradient: 11

After pulmonary vein angioplasty and closure of the ductus:

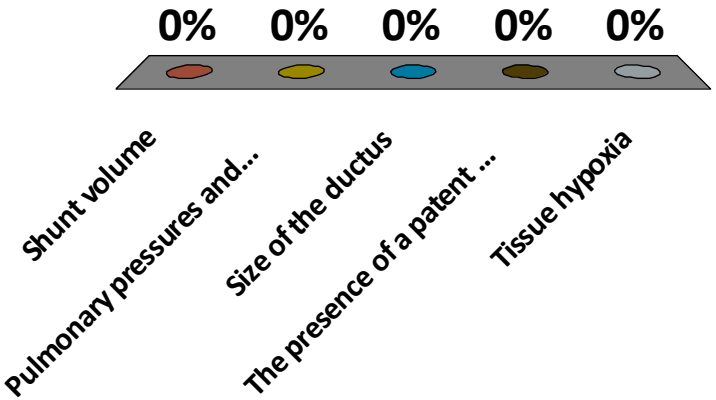
- Pressure: PA: 61/30, mean of 45, aortic: 97/46, mean of 67, pulmonary vein 3mm gradient
- Reactive to nitric oxide

Pulmonary vascular resistance calculated at 7.5Wood units

Post procedure echo RV pressures ~1/2 systemic with good biventricular function, pulmonary vein gradient ~5mmHg

What determines directionality of a patent ductus arteriosus?

A. Shunt volume
B. Pulmonary pressures and vascular resistance
C. Size of the ductus
D. The presence of a patent foramen ovale
E. Tissue hypoxia



What determines directionality of a patent ductus arteriosus?

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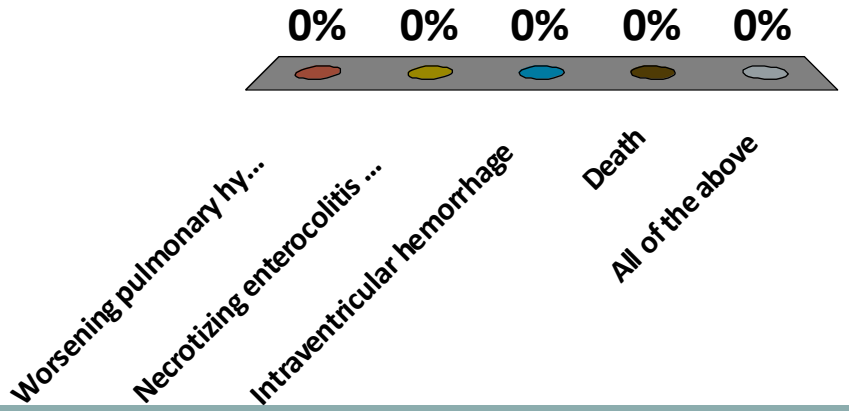
D. The presence of a patent foramen ovale

E. Tissue hypoxia

- Heuchan AM, Clyman RI. **Managing the patent ductus arteriosus: current treatment options.** Arch Dis Child Fetal Neonatal Ed. 2014 Jun 5.

What are the risks associated with closing a bidirectional patent ductus arteriosus?

A. Worsening pulmonary hypertension
B. Necrotizing enterocolitis (NEC)
C. Intraventricular hemorrhage
D. Death
E. All of the above

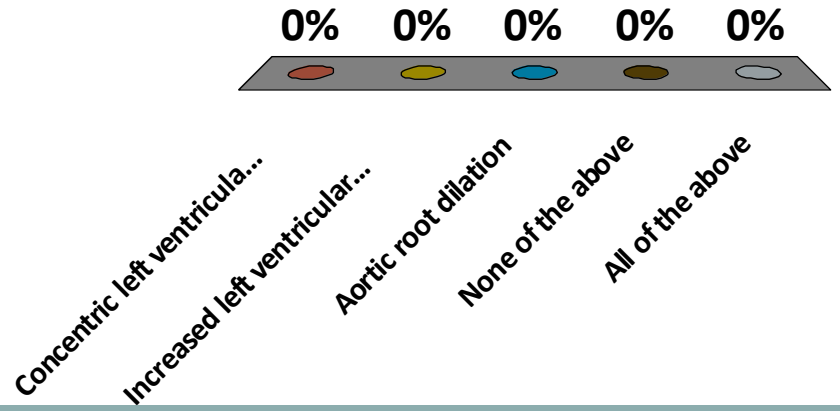


Complications from bidirectional PDAs

- Ethington PN, et al. **Treatment of patent ductus arteriosus with bidirectional flow in neonates**. Early Hum Dev. 2011 May;87(5):381-4.
- Smith SC, Rabah R. **Pulmonary venous stenosis in a premature infant with bronchopulmonary dysplasia: clinical and autopsy findings of these newly associated entities.** Pediatr Dev Pathol. 2012 Mar-Apr;15(2):160-4.
- D'Alto M, et al. **Patent ductus arteriosus stenting for palliation of severe pulmonary arterial hypertension in childhood.** Cardiol Young. 2014 Jul 7:1-5. [Epub ahead of print]
- Chock VY, et al. **Predictors of bronchopulmonary dysplasia or death in premature infantswith a patent ductus arteriosus.** Pediatr Res. 2014 Apr;75(4):570-5.
- del Cerro MJ, et al. **Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings,cardiovascular anomalies and outcomes.** Pediatr Pulmonol. 2014 Jan;49(1):49-59.

What are the associated cardiovascular findings from systemic hypertension?

A. Concentric left ventricular hypertrophy
B. Increased left ventricular mass
C. Aortic root dilation
D. None of the above
E. All of the above



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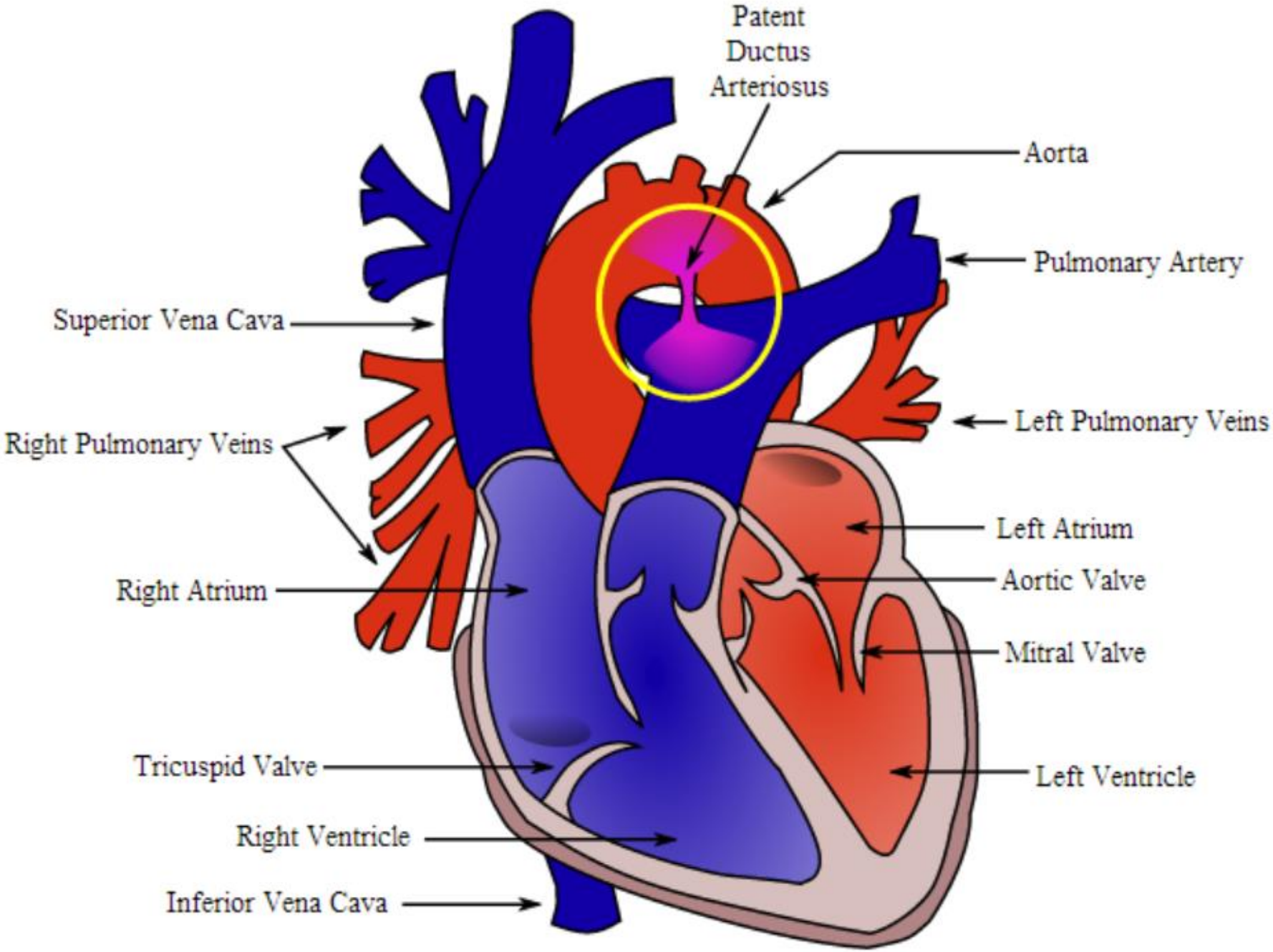
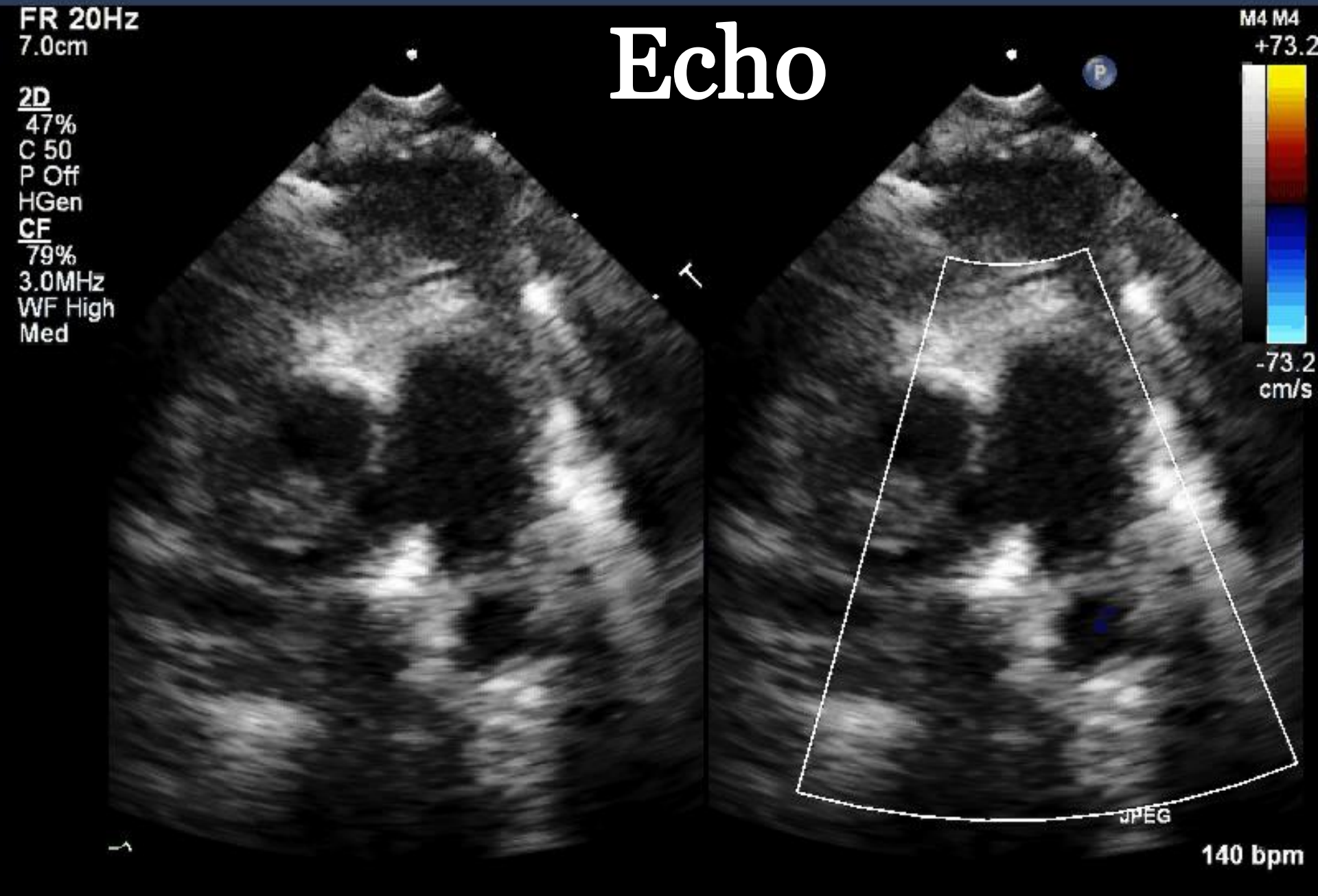
- Peterson AL, Frommelt PC, Mussatto K. **Presentation and echocardiographic markers of neonatal hypertensive cardiomyopathy.** Pediatrics. 2006 Sep;118(3):e782-5. Epub 2006 Jul 31.
- Monesha Gupta-Malhotra ; Archana Dave ; Brian Sturhan ; Ronald Portman. **Abstract 2998: Aortic Root Dilatation in Children with Systemic Hypertension.** Circulation. 2006;114:II_631. © 2006 American Heart Association, Inc.

Patent ductus arteriosus

- Patent ductus arteriosus (PDA) is a remnant of a fetal connection between the aorta (systemic circulation) and the pulmonary artery (pulmonary circulation)
- It functionally closes in most children by 24 hours of life and anatomically closes around 3 weeks of life
- It closes in response to oxygen and prostaglandin inhibitors
- It may remain open in some children, especially in the setting of
  - Prematurity
  - Genetic conditions such as Trisomy 21, Noonan's


Patent
Ductus
Arteriosus
Aorta
Pulmonary Artery
Superior Vena Cava
Left Pulmonary Veins
Right Pulmonary Veins
Left Atrium
Aortic Valve
Right Atrium
Mitral Valve
Tricuspid Valve
Left Ventricle
Right Ventricle
Inferior Vena Cava


FR 20Hz
7.0cm
2D
47%
C 50
P Off
HGen
CF
79%
3.0MHz
WF High
Med
M4 M4
+73.2
-73.2
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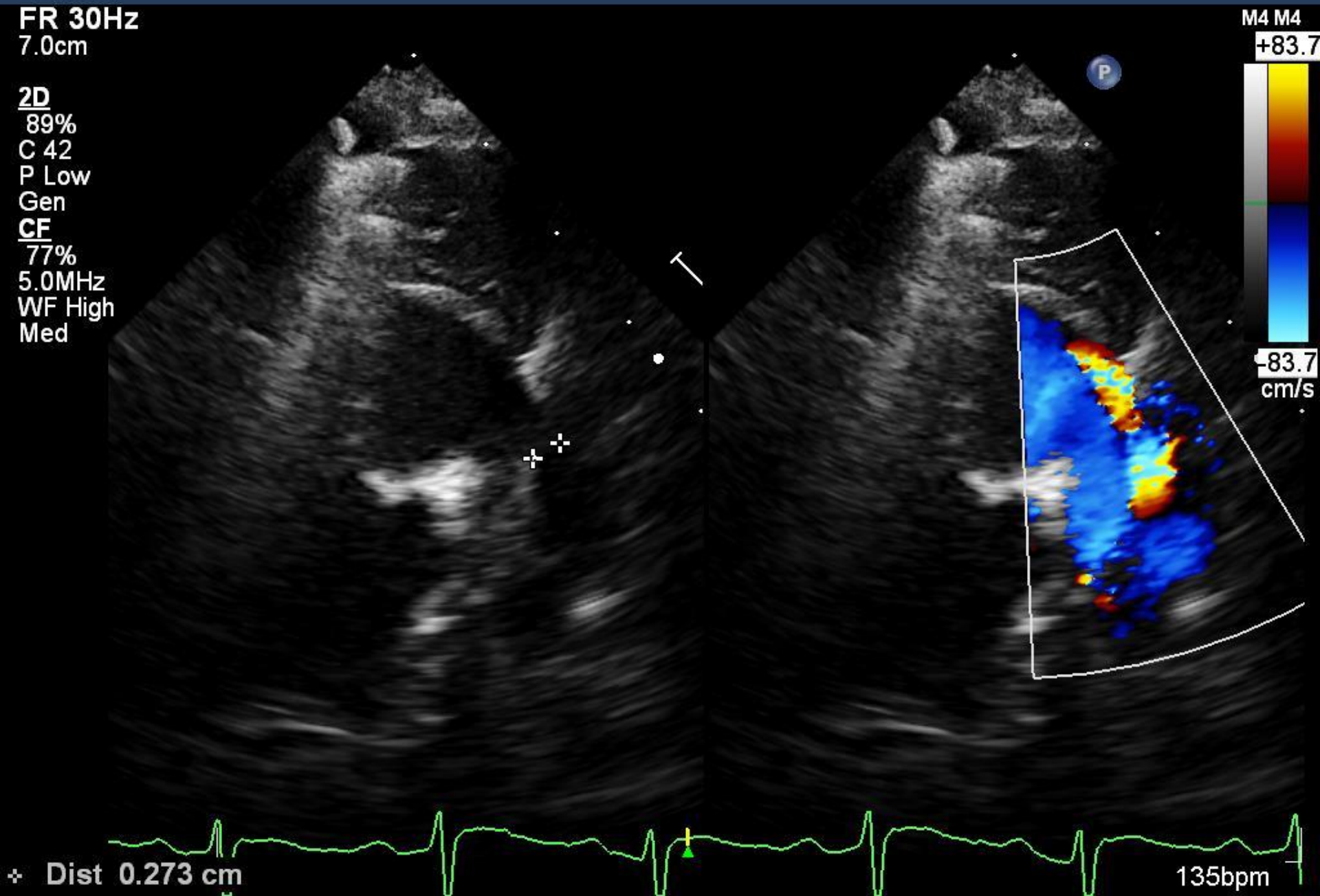
140 bpm

Echo


FR 30Hz
7.0cm
2D
89%
C 42
P Low
Gen
CF
77%
5.0MHz
WF High
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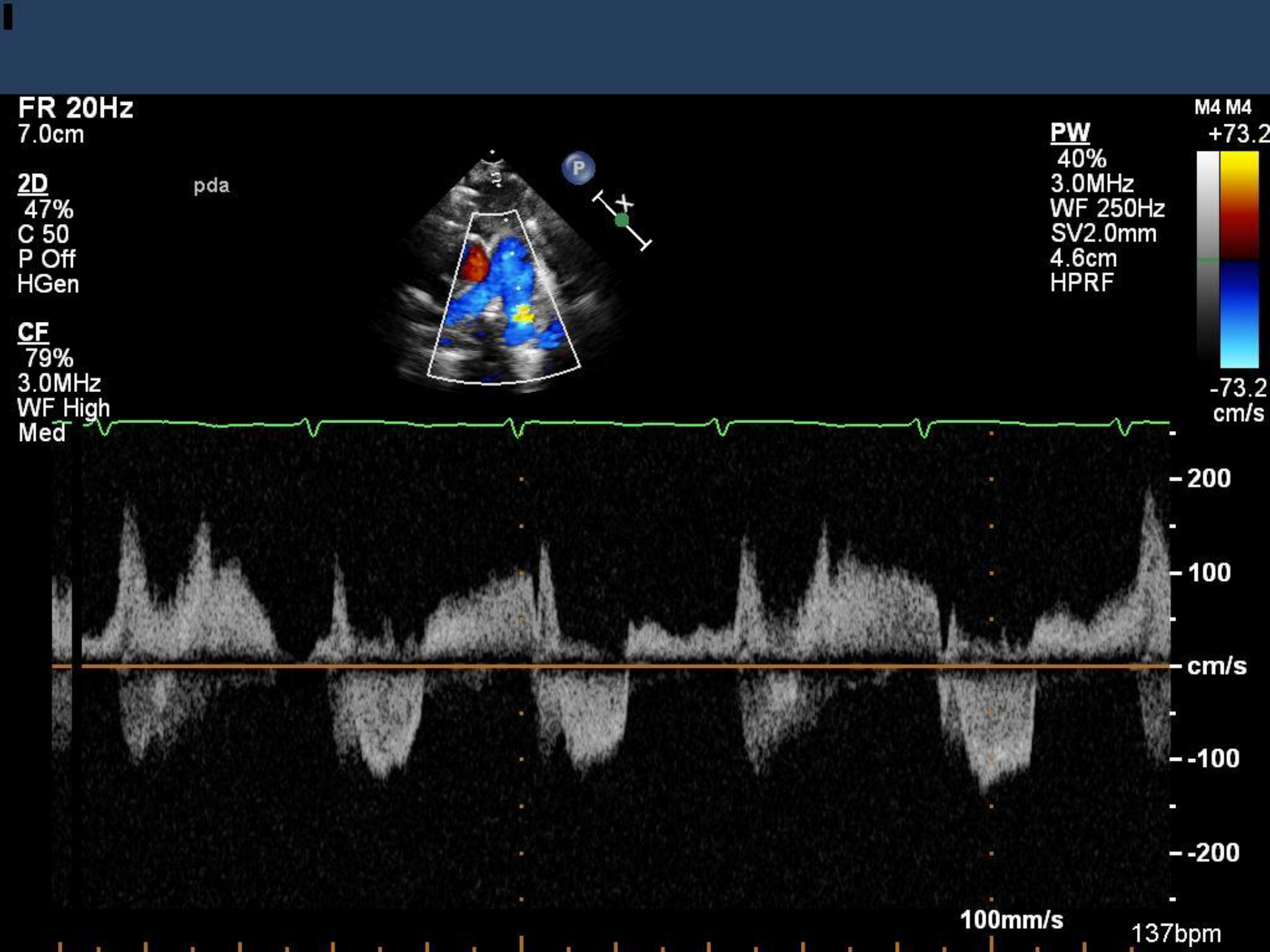
-83.7
cm/s
Dist 0.273 cm
135bpm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pda
PW
40%
3.0MHz
WF 250Hz
SV2.0mm
4.6cm
HPRF
M4 M4
+73.2
-73.2
cm/s
200
100
cm/s
-100
-200
100mm/s
137bpm

Patent ductus arteriosus

- The directionality of a PDA reflects physiologic conditions
- A PDA that shunts left to right reflects normalized pulmonary pressures/pulmonary vascular resistance and may cause volume overload as reflected by
  - Left ventricular dilation
  - Signs and symptoms of congestive heart failure
  - Bounding pulses

Patent ductus arteriosus

- A PDA that shunts right to left (or with bidirectional shunting) reflects increased pulmonary pressures/vascular resistance in the absence of congenital heart disease
- A bidirectional PDA provides much less volume load than in a pure left to right shunt and is more reflective of increased pulmonary artery pressures
  - The PDA shunts left to right in systole
  - However, when pulmonary pressures exceed systemic pressures in diastole, the PDA acts as a “pop off” and shunts right to left
  - Examples: lung infections such as RSV, pulmonary hypertension

Patent ductus arteriosus

- If a PDA with bidirectional shunting is closed, the lungs and other organs will see the effects of increased pulmonary vascular resistance/pressures
- Risks include:
  - Worsening pulmonary hypertension
  - Necrotizing enterocolitis (NEC)
  - Intraventricular hemorrhage
  - Pulmonary hemorrhage

Cardiac effects from systemic hypertension

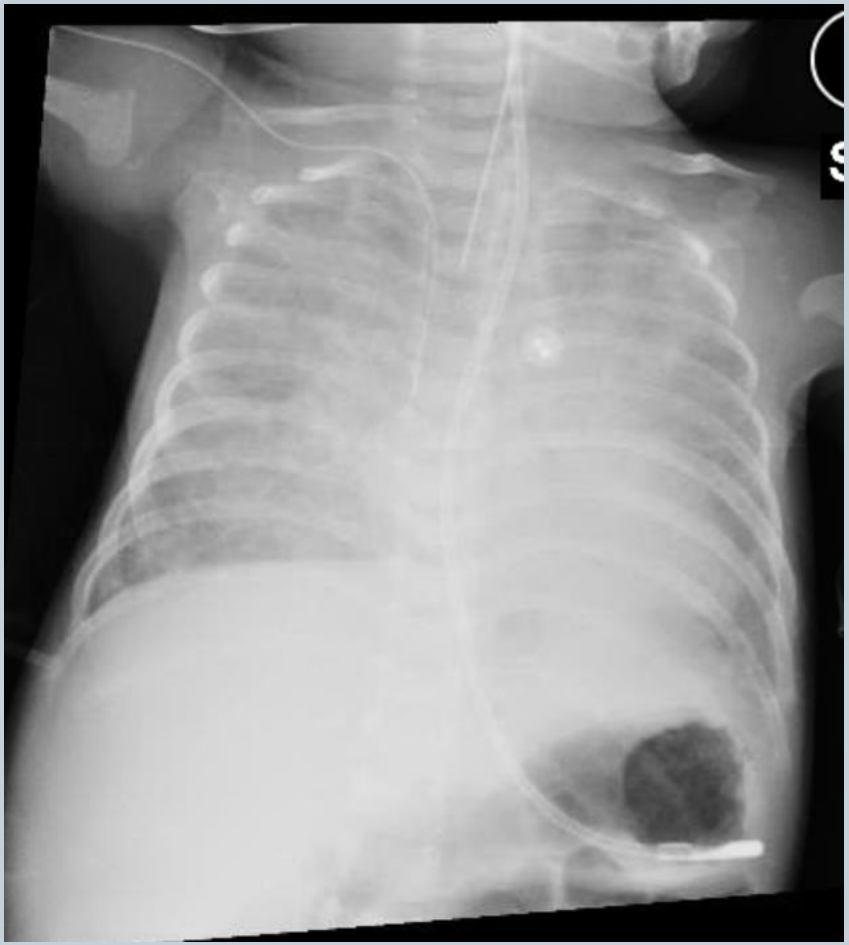
- Systemic hypertension has effects on many organs, including the heart
- Effects include:
  - Concentric left ventricular hypertrophy
  - Increased left ventricular mass
  - Aortic root dilation
- Standardized monitoring of left ventricular mass
  - For patients aged > 9 years, LVM/height(2.7). Values > 40 g/m(2.7) in girls and > 45 g/m(2.7) in boys can be considered abnormal (ie, > 95th percentile).
  - Patients < 9 years, the index varies with age. LVM/height(2.7) must be compared with percentile curves.

Cardiac effects from systemic hypertension

- Foster BJ, Mackie AS, Mitsnefes M, Ali H, Mamber S, Colan SD. **A novel method of expressing left ventricular mass relative to body size in children.** Circulation. 2008 May 27;117(21):2769-75.
- Malcolm DD, Burns TL, Mahoney LT, Lauer RM. **Factors affecting left ventricular mass in childhood: the Muscatine Study.** Pediatrics. 1993 Nov;92(5):703-9.
- Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. **Age-specific reference intervals for indexed left ventricular mass in children.** J Am Soc Echocardiogr. 2009 Jun;22(6):709-14.

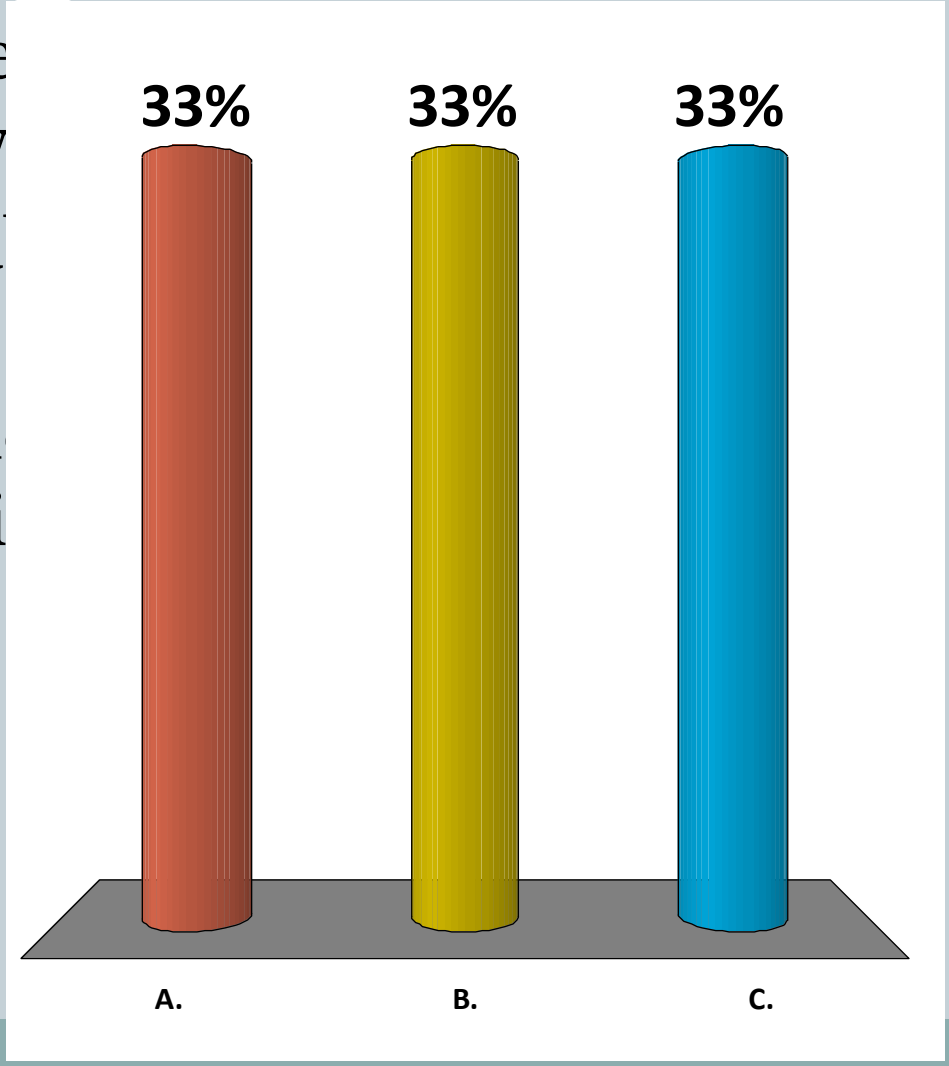
Transferred back to MCH after cardiac cath

- Follow-up ECHO:
  - At least moderate right ventricular hypertension based on septal motion
  - Trace tricuspid regurgitation, insufficient jet to estimate RV systolic pressure
  - Mildly increased gradient across RU pulm vein, significantly improved from prior study – mild RUPV stenosis
  - No PDA, normal biventricular systolic function
- Vent settings unable to be weaned after 3 wks of mechanical ventilation



Is the patient a candidate for tracheostomy?

A. Yes, because she has be
ventilation for over 3 w
B. Yes, because she is una
ventilator
C. No, because she does n
diagnosis causing respi

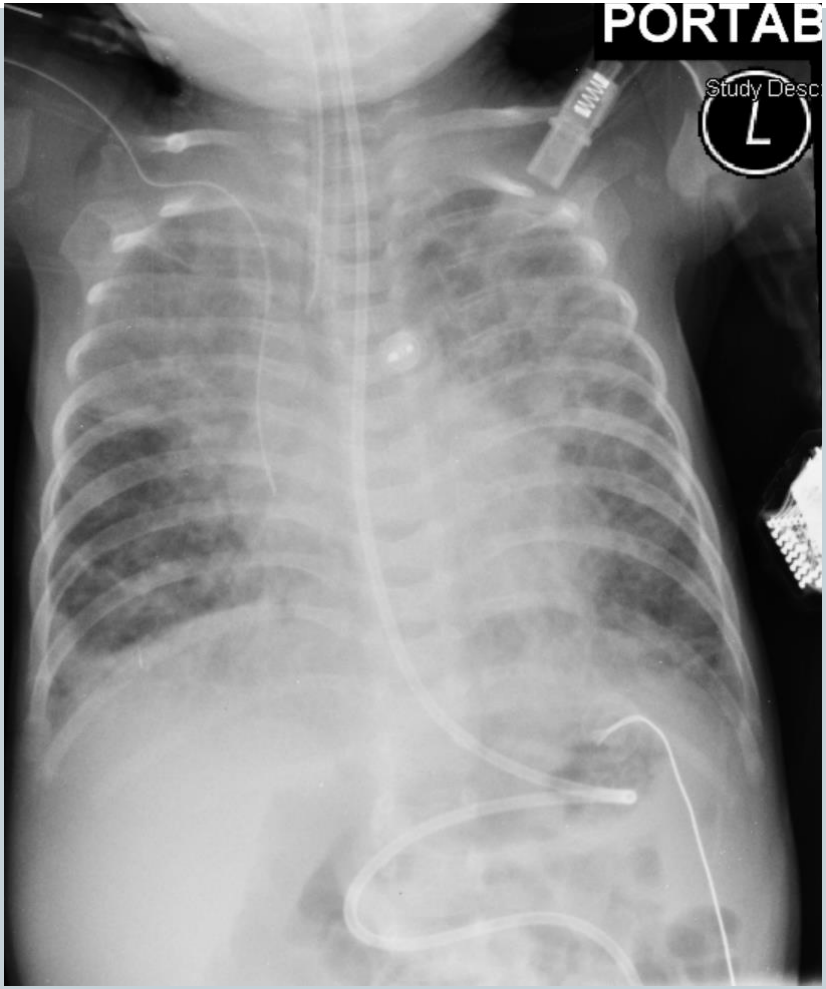


Chronic Respiratory Failure

- A condition for which mechanical ventilation is required for at least 4 hours/day x 1 month or longer
- Cannot be weaned after at least 1 month of consistent attempts while medically stable
- Patient has irreversible diagnosis causing respiratory failure

EM bronchial wash + lamellar bodies

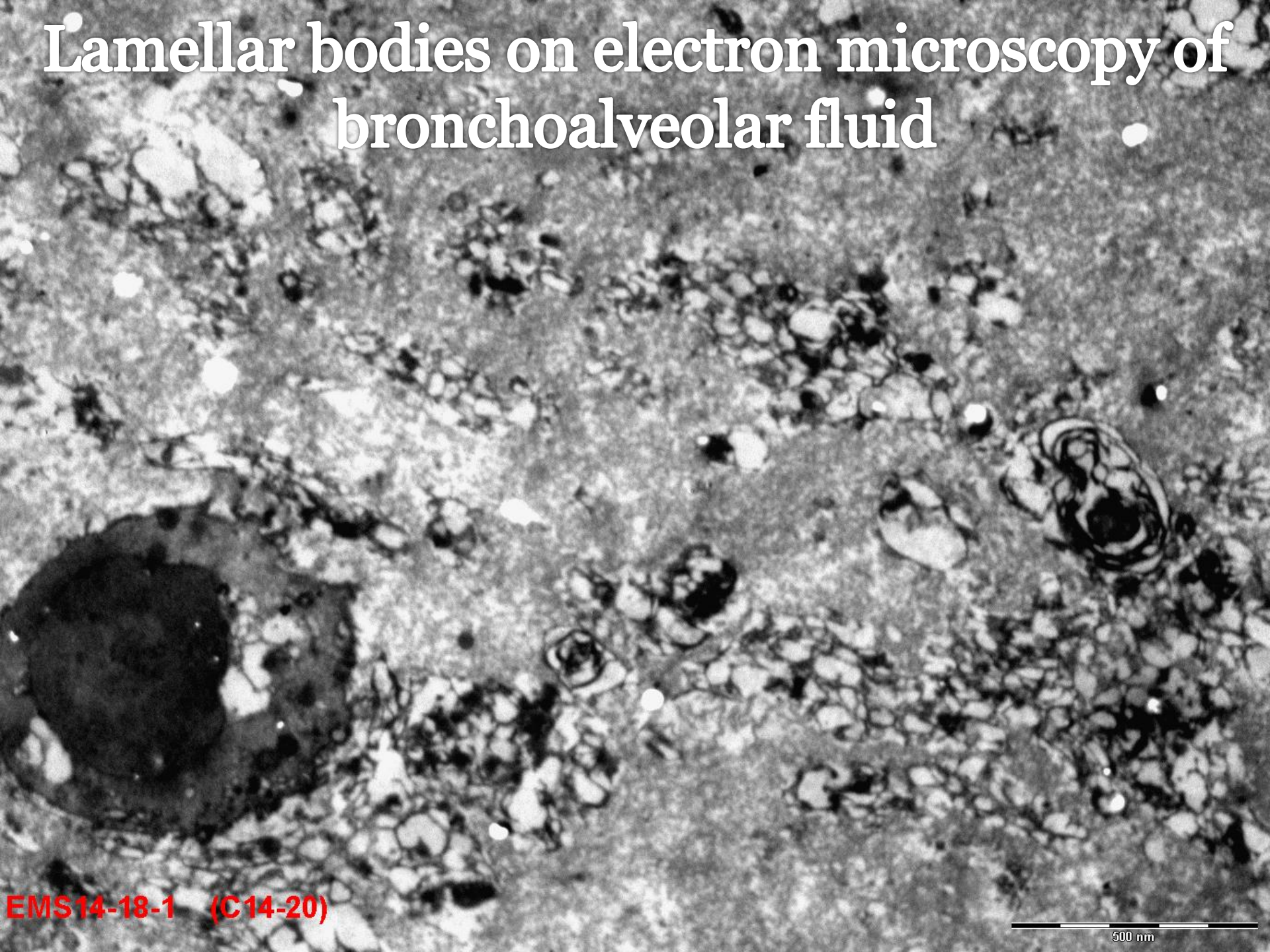
- Question of pulmonary alveolar proteinosis (PAP)
- Genetic analysis negative for surfactant deficiencies
- Solumedrol empirically started for PAP
- Anti-GM-CSF antibodies sent to Cincinnati
- Underwent LUL lung biopsy



Pathology (Part 1)

LISA SHANE, MD
PEDIATRIC PATHOLOGY

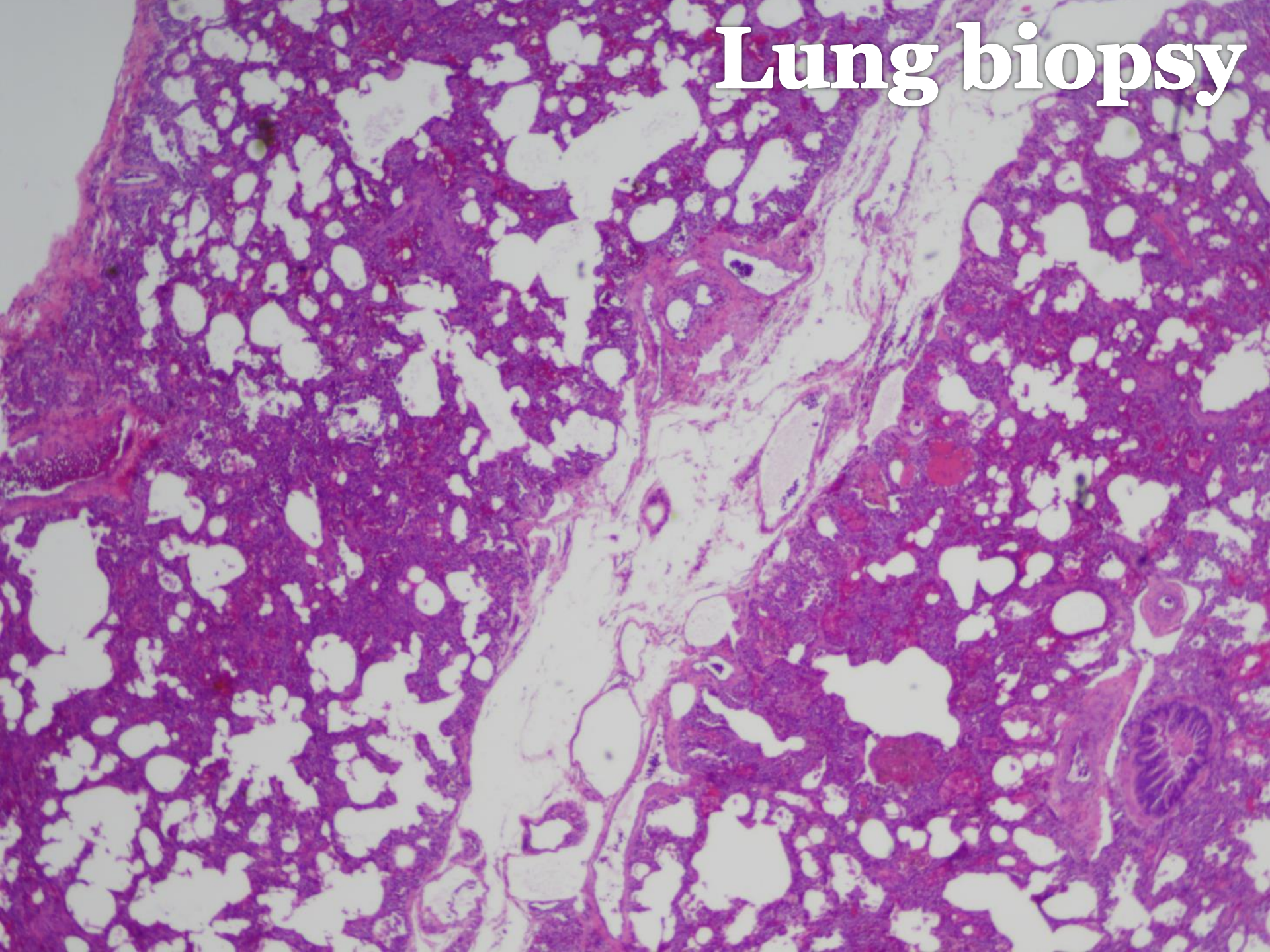
Lamellar bodies on electron microscopy of bronchoalveolar fluid

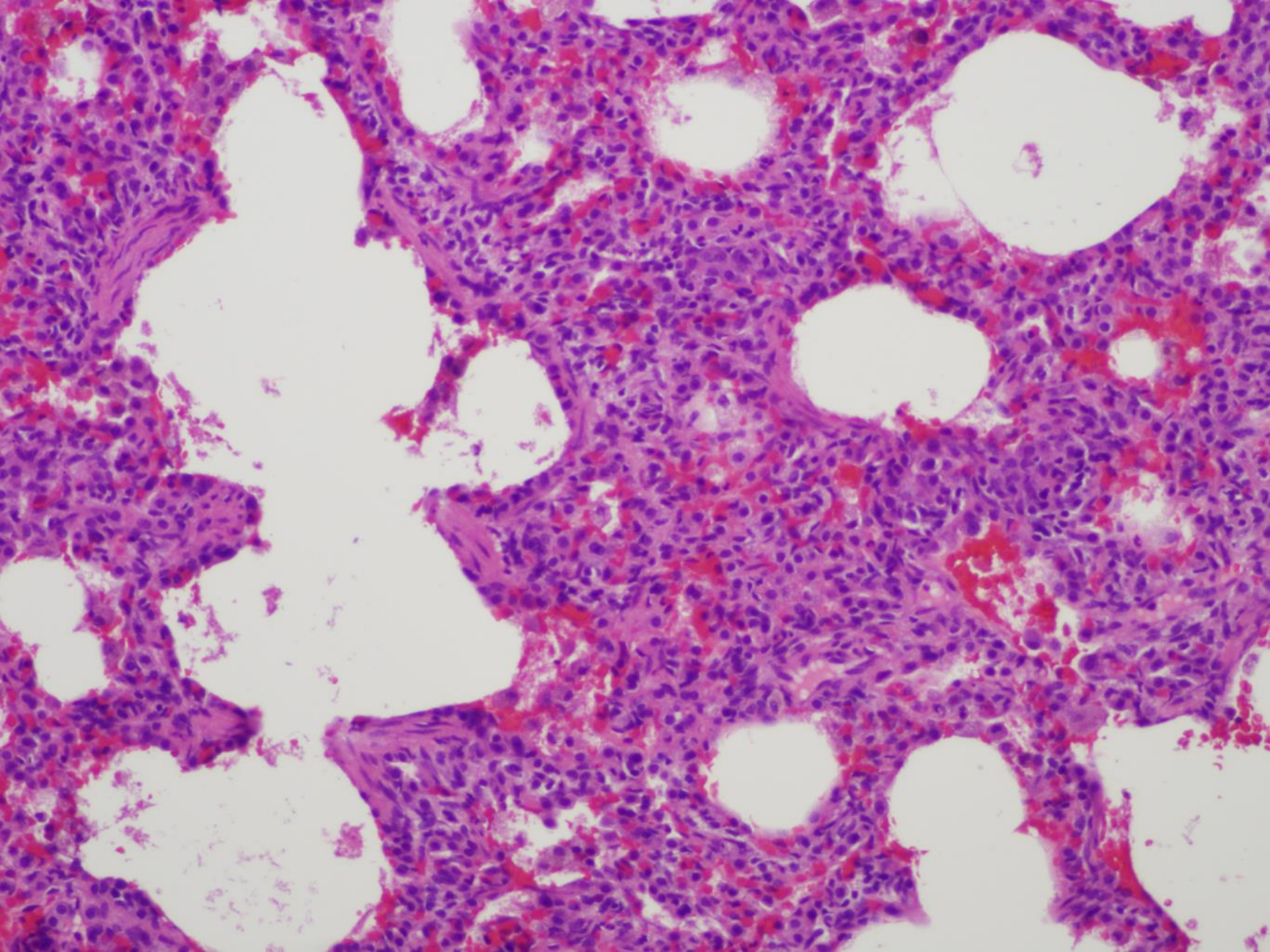


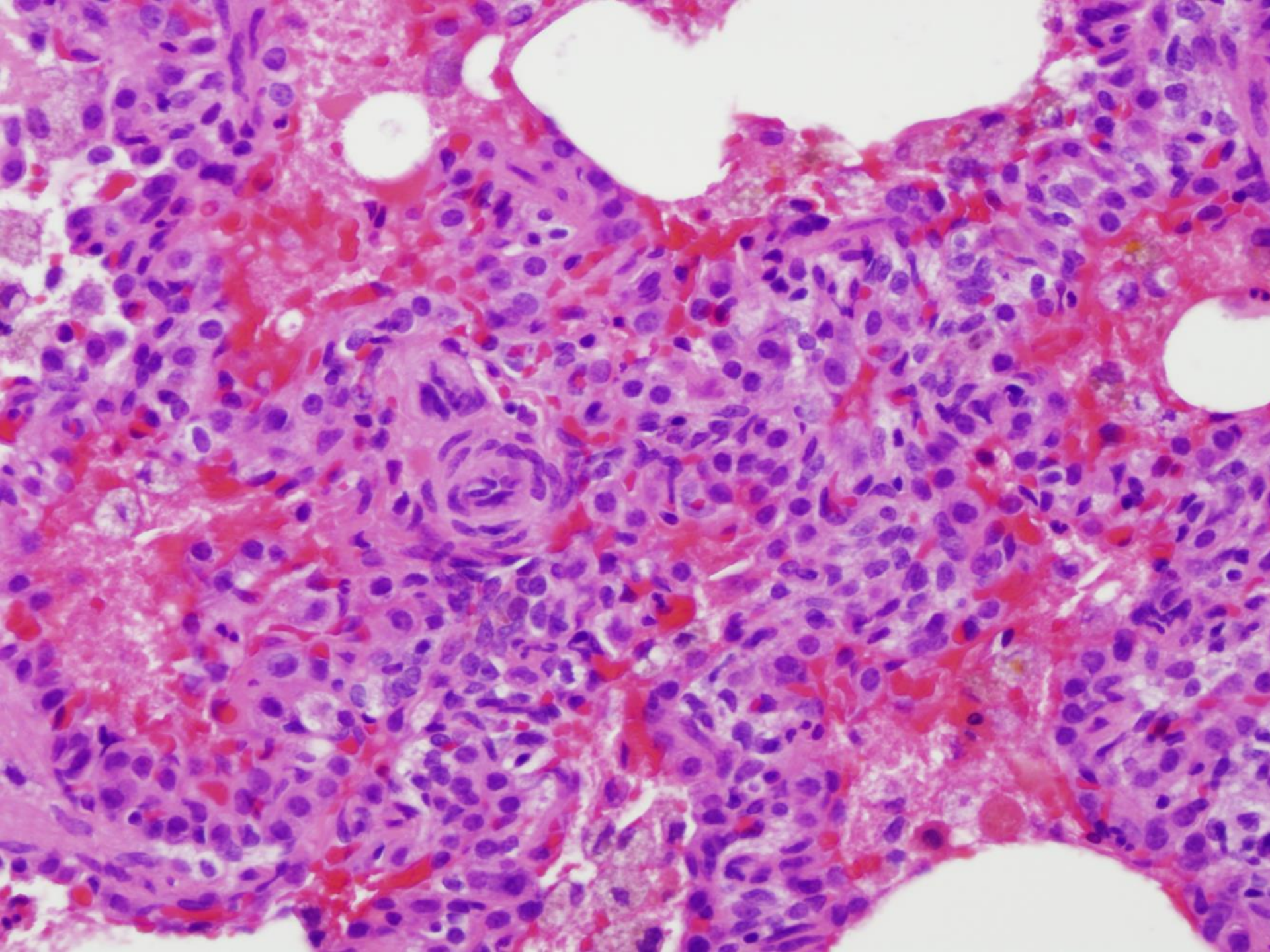
Lamellar bodies

- Lipid storage and secretory organelles
- Are the storage form of the lung surfactant
- May be seen in
  - Congenital mutations in GM-CSF receptor
  - Autoimmune disease
  - Infection
  - Idiopathic

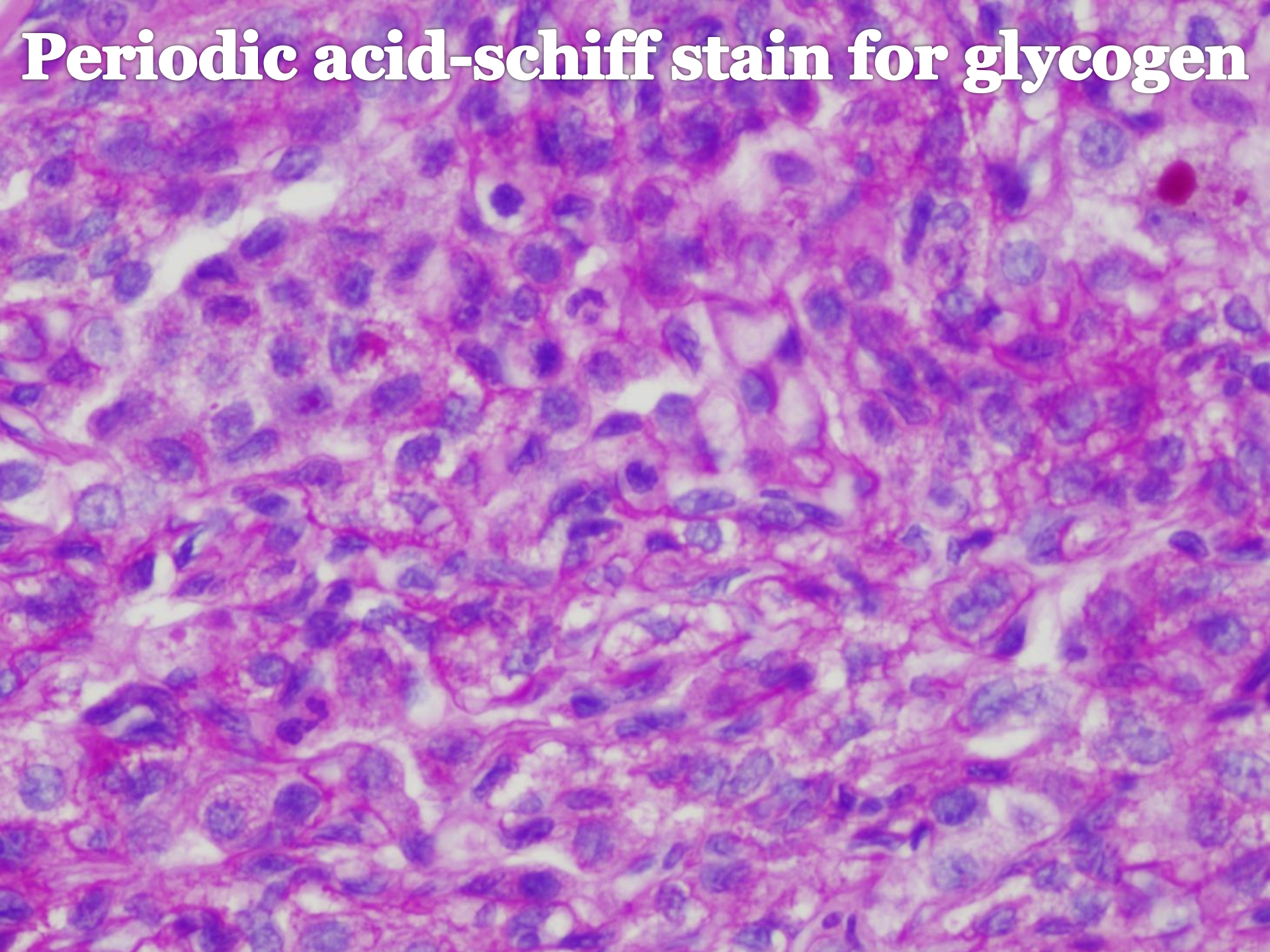
Lung biopsy



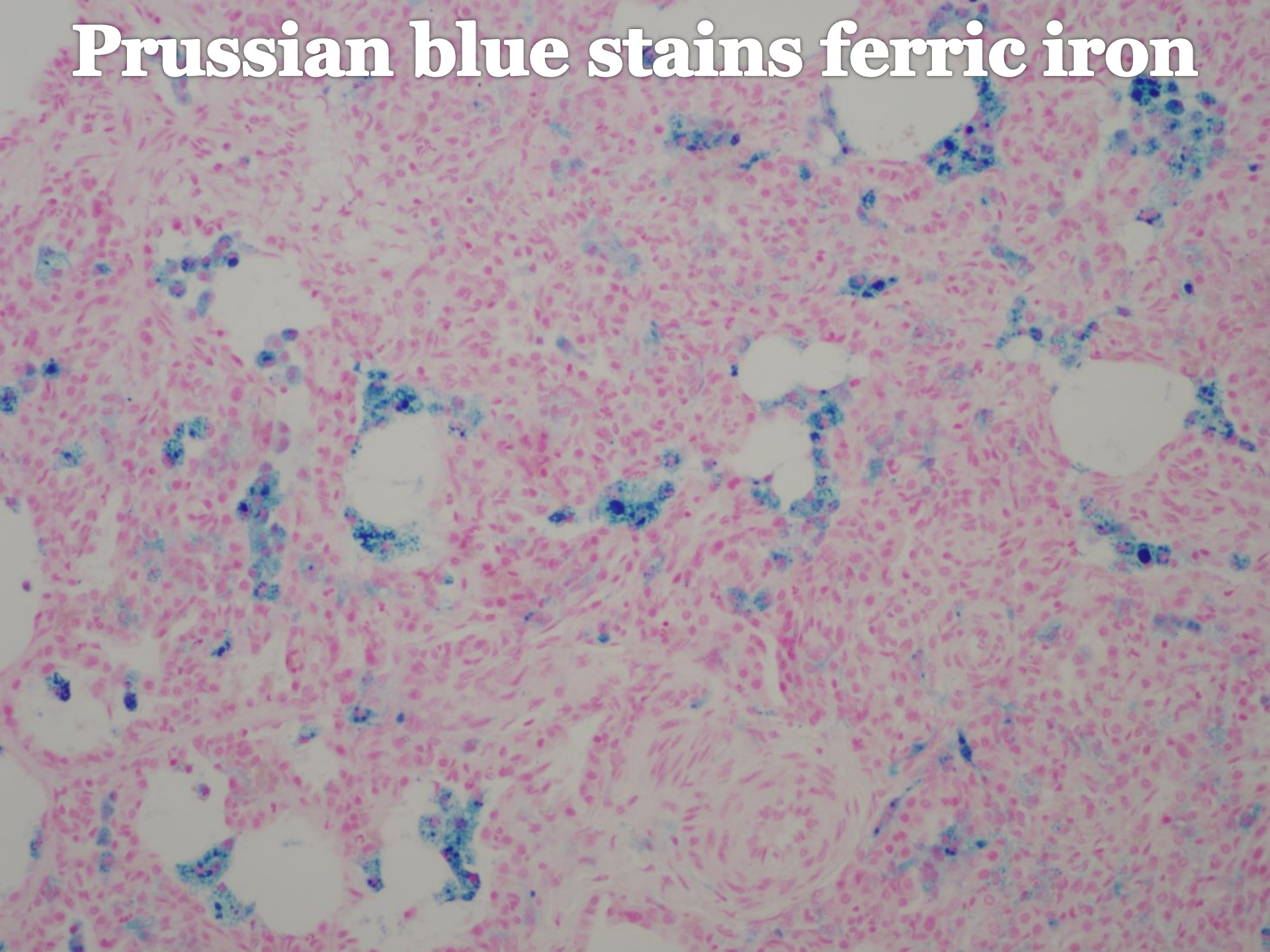




Periodic acid-schiff stain for glycogen



Prussian blue stains ferric iron

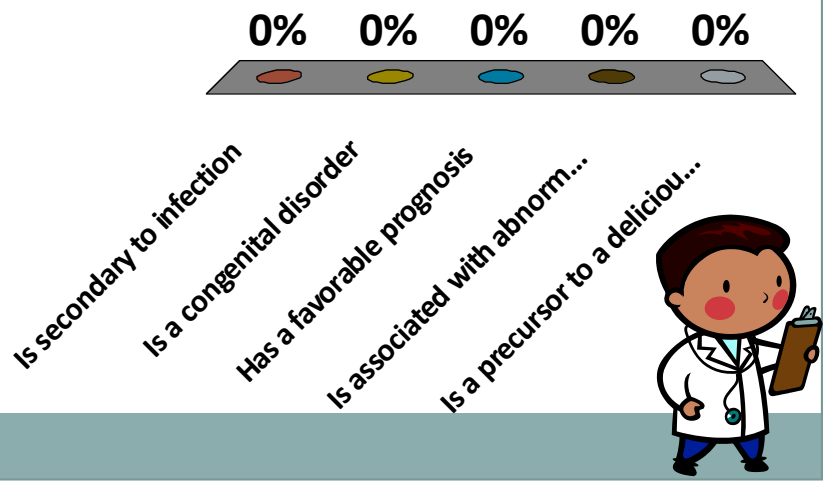


Diagnosis - Pulmonary interstitial glycogenosis

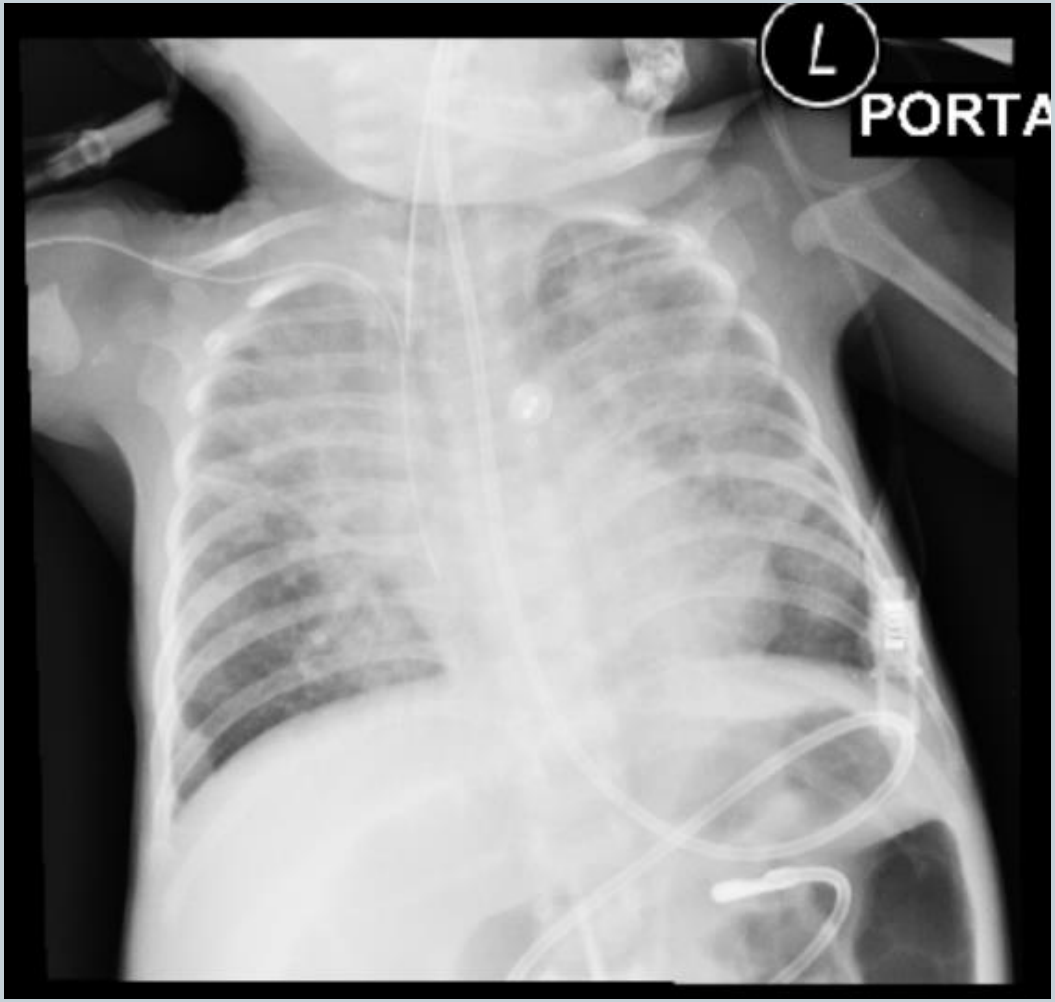
- Other findings:
  - Prominent alveolar space distension focally consistent with mechanical ventilation
  - Alveoli contain small to moderate number of CD68+ macrophages, often containing iron
  - Mildly prominent muscular walls of arteries suggestive of mild pulmonary hypertension
- Negative findings:
  - No significant iron deposition in the interstitium
  - No evidence of acute or granulomatous inflammation
  - No significant T- or B-cells or macrophages
  - No significant hyperplasia of alveoli, no evidence of hyaline membranes, cholesterol deposition or features of alveolar proteinosis
  - No findings of advanced pulmonary hypertension appreciated

PIG – which is the best answer

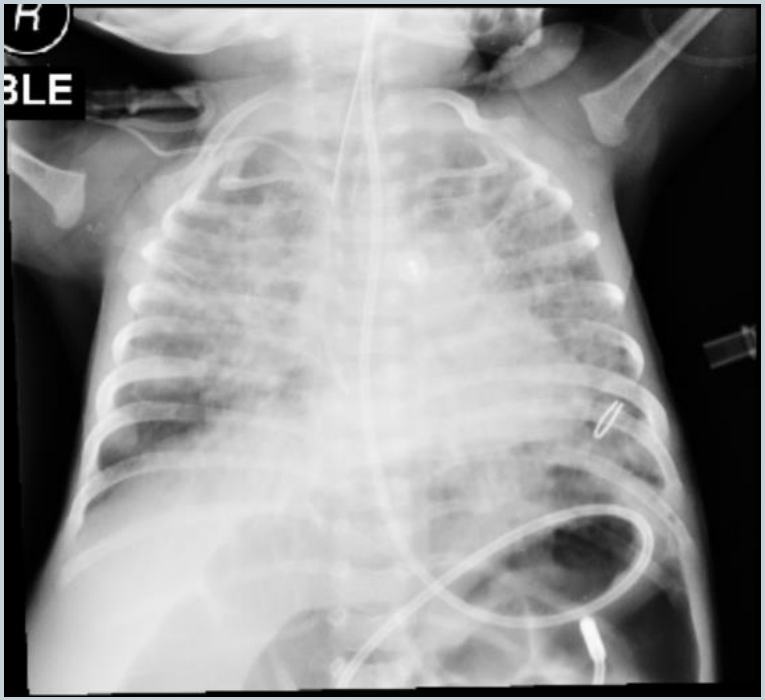
A. Is secondary to infection
B. Is a congenital disorder
C. Has a favorable prognosis
D. Is associated with abnormalities of surfactant
E. Is a precursor to a delicious breakfast food

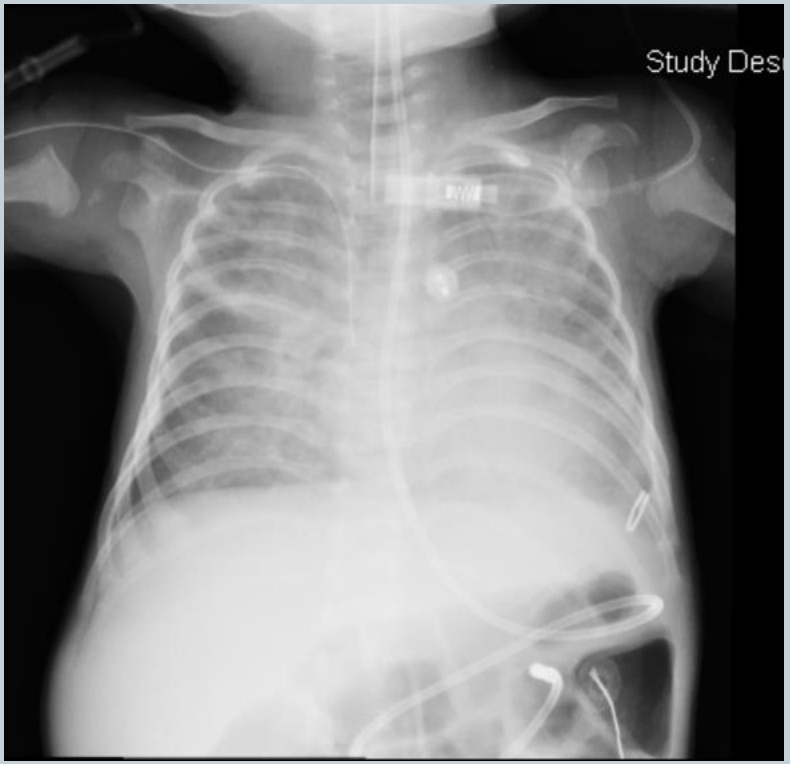


Solumedrol 10 mg/kg/day daily x 3 days



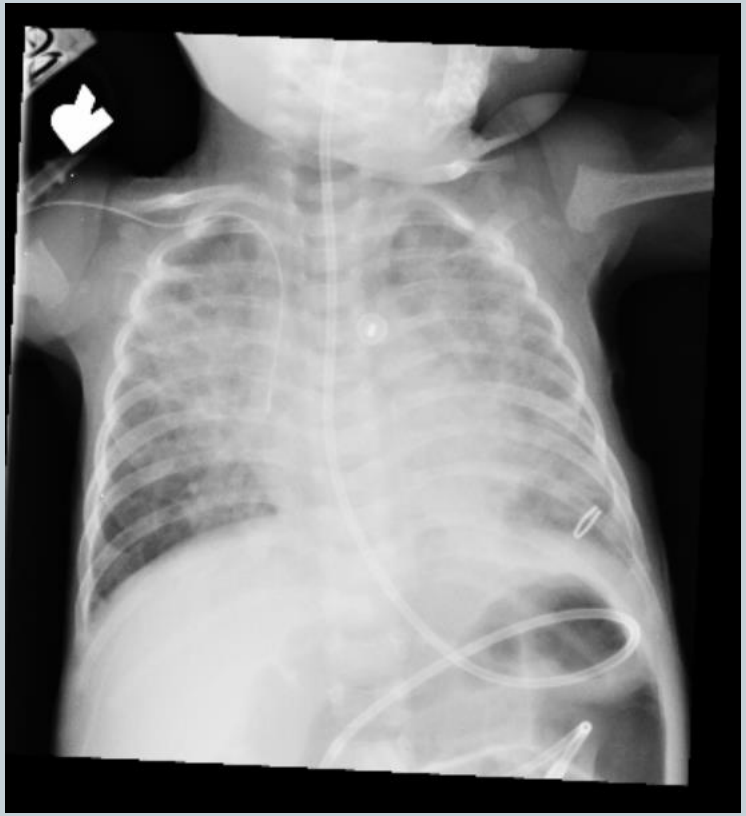
After 1 day of pulse steroids





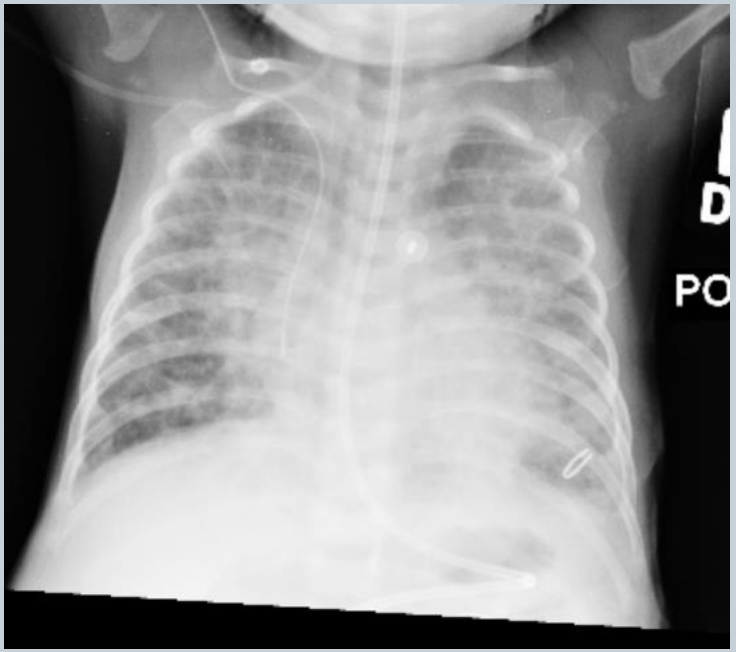
Successfully weaned toward extubation

- Within 1 day of starting pulse steroids, she was able to tolerate weaning of vent settings
- Within 3 days, she was extubated and placed on BiPAP
- After 1 wk, she was weaned to low flow NC



Reintubated 1 week later

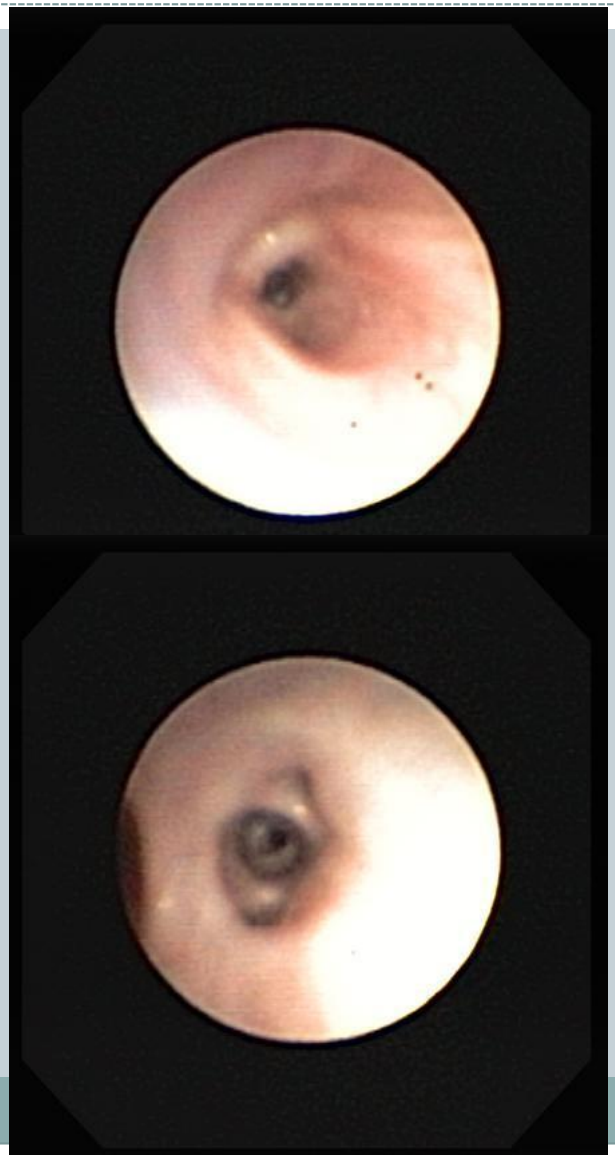
- Placed back to BiPAP and then intubated for increased work of breathing
- CBG pH 7.14 | pCO2 82 | pO2 26 | BE -1 | HCO3 28
- Vent settings: TV 12 cc/kg | FiO2 0.70
- Solumedrol restarted as well as cytotoxic agents

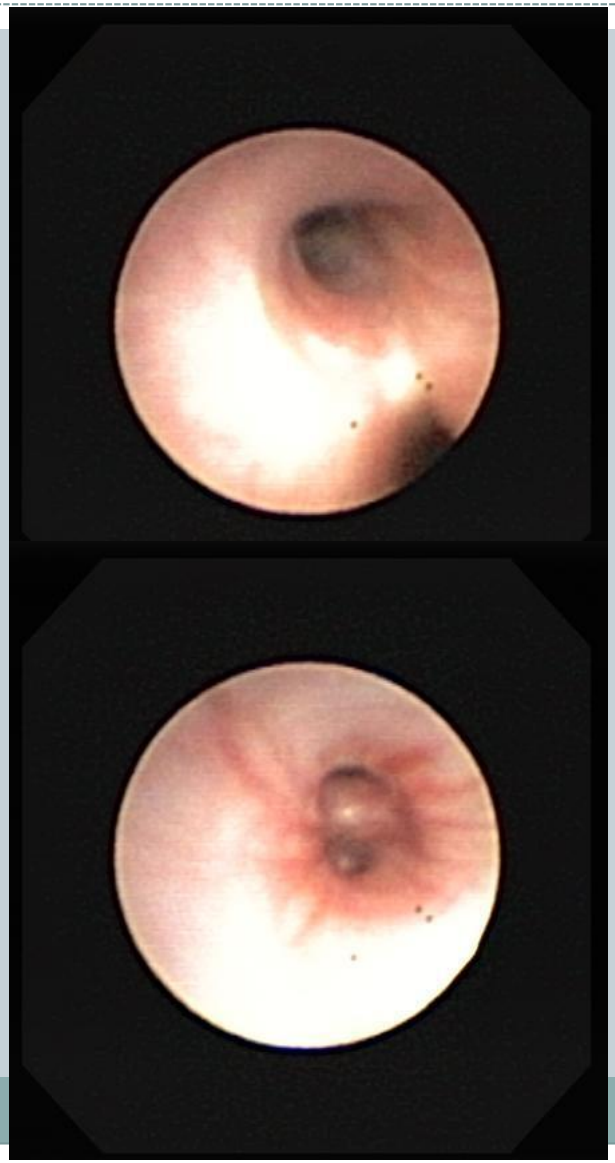


Underwent tracheostomy placement

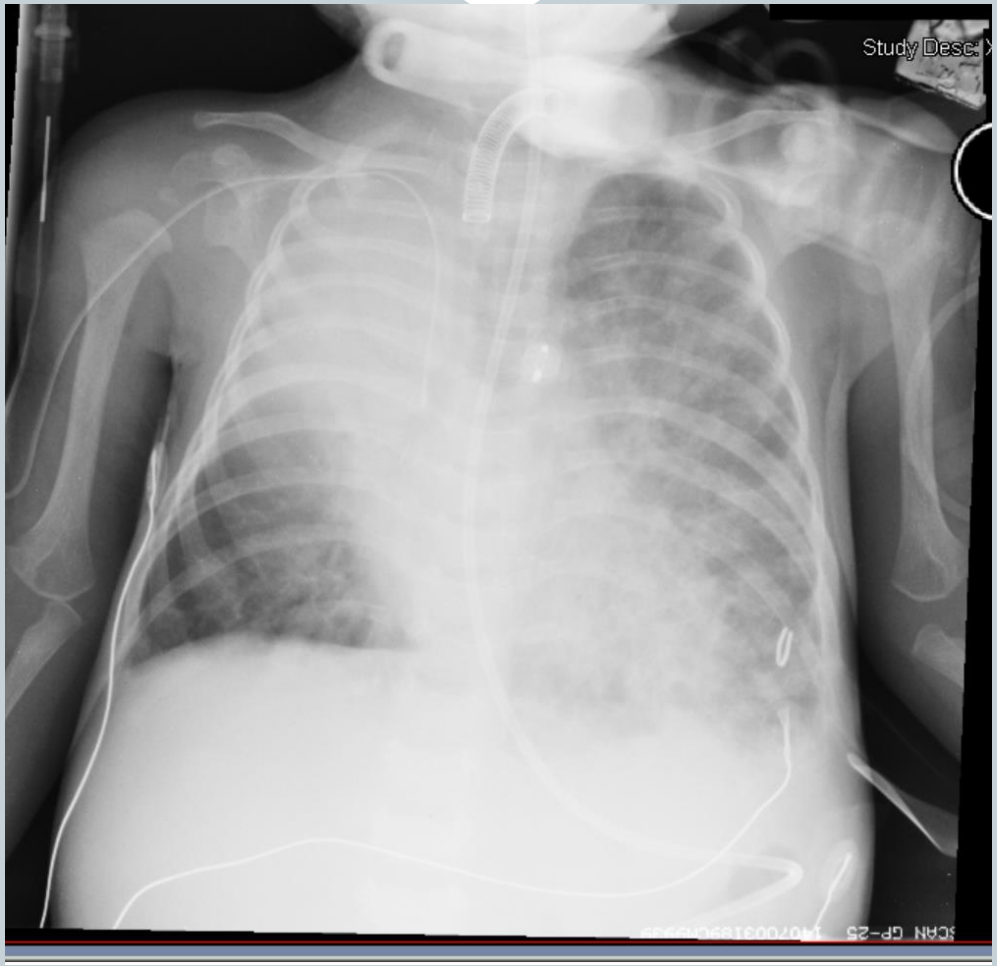
- Continued to require high vent settings: TV 15 cc/kg | FiO2 0.70
- iNO restarted
- Deteriorated after tracheostomy placement
- Serial bedside bronchoscopies were done
  - Evaluation of chronic pulmonary hemorrhage
  - RLL and RML collapse
  - Right lung atelectasis - severe mucoid impaction of airways and blood clots found

Bronchoscopy #2





RUL Atelectasis



Bronchoscopies Cell Counts

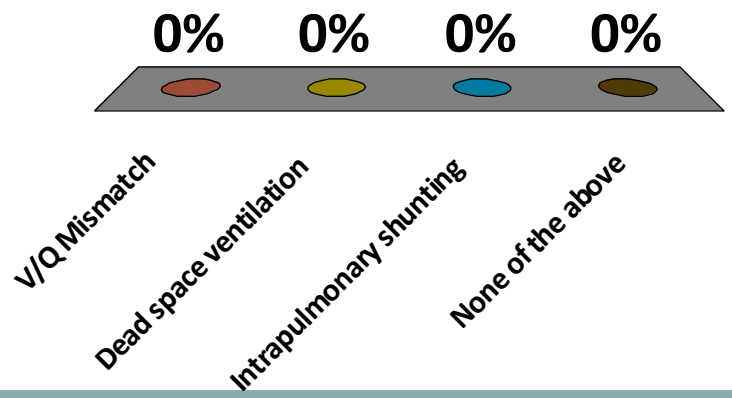
	Bronch #1	Bronch #4
Volume	8 mL	10 mL
Blood	Absent	**Present**
Fibrin	Absent	Present
WBC	**567**	7
Segs	**79%**	**37%**
Lymphs	11%	34%
Monos	9%	29%
Eos	1%	
Mesos		Present
Macrophages	Present	Present
Total cells counted	100	100

Pediatric Intensive Care Perspective

CHRISTOPHER BABBITT, MD
PEDIATRIC INTENSIVIST

Hypoxia that occurs with respiratory failure and is unresponsive to oxygen is referred to as:

A. V/Q Mismatch
B. Dead space ventilation
C. Intrapulmonary shunting
D. None of the above

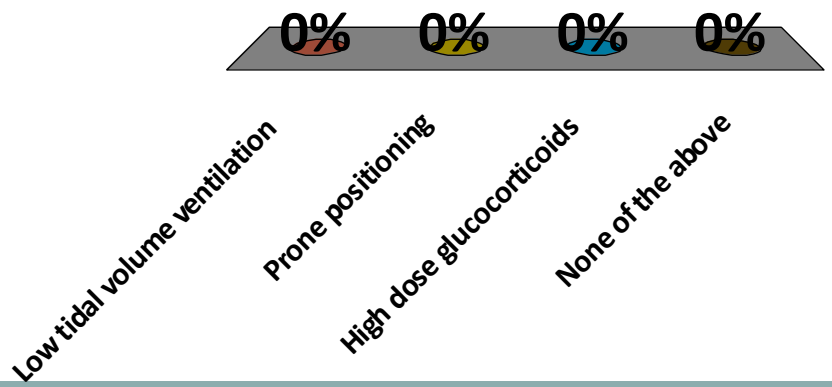


ARDS and Hypoxemia

- Intrapulmonary shunt is the predominant cause of venous admixture (blood returns to left heart with reduced P_{O2})
- There are areas of low V/Q ratio that can initially be overcome with oxygen
- Hypercarbia is rare in early ARDS, but after days/weeks there is fibrosis and pulmonary capillary obliteration, dead space ventilation or elevated V/Q ratio

Which therapy has not been shown to improve acute hypoxemic respiratory failure?

A. Low tidal volume ventilation
B. Prone positioning
C. High dose glucocorticoids
D. All of the above



Treatments for ARDS

- Guérin, Reignier, Richard, et al. **Prone Positioning in Severe Acute Respiratory Distress Syndrome**. *N Engl J Med 2013*; 368:2159-2168
  - RCT multicenter, 466 adults with ARDS
  - 28 day mortality 16 vs. 32%
  - 90 day mortality 24 vs. 41%

- ARMA Trial: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network.** *N Engl J Med. 2000 May 4;342(18):1301-8.*
  - 861 adults RCT for ARDS
  - Conventional (10-15 cc/kg) vs. Low TV (6cc/kg)
  - Improved survival (31 vs 39%)
  - Decreased LOV

Continued to require maximal ventilatory and medical support

VBG: pH 7.03 | pCO2 127 | pO2 21 | BE 2 | HCO3 33

- Had frequent desaturations requiring bagging
- Suctioning yielded large thick amounts of bloody secretions with plugs
- During an episode of desaturation, she became bradycardic with HR < 45 bpm and hypotensive to 60's and CPR was started
- The decision was made to not resuscitate with the next arrest, and patient eventually expired