Paediatric Lung Transplantation

Cross Canada Rounds

Dr. Lucy Perrem

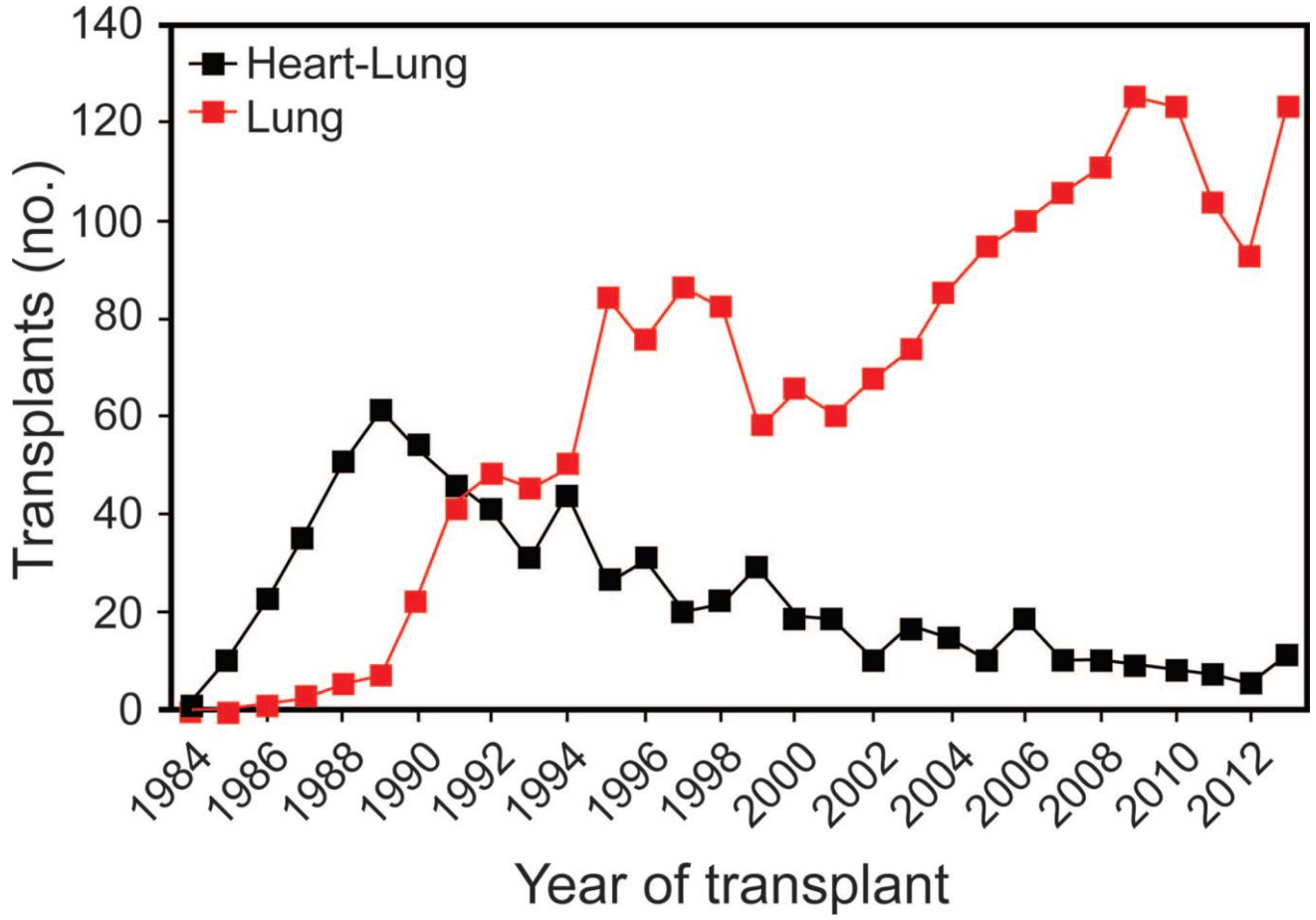
Respiratory Medicine Fellow

Dec 21st 2017

Objectives

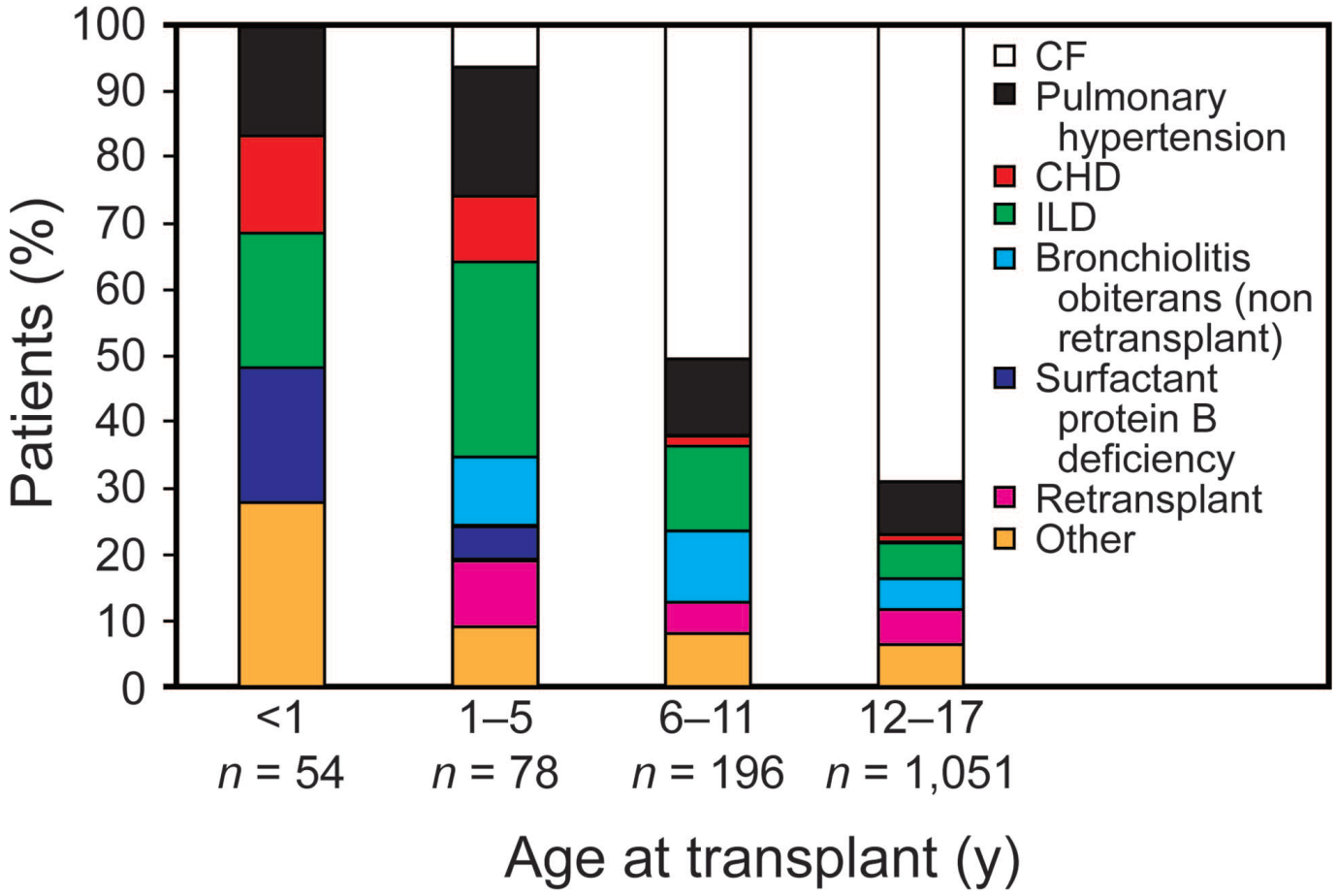
1. Overview of paediatric lung transplantation
2. Discuss acute management and complications in context of recent cases in HSC

Incidence



Goldfarb S et al, J Heart Lung Transplant, 2015; Sweet S, Resp Care 2017

Indications – ISHLT registry data



Sweet S , Respiratory Care, 2017

Contraindications

Absolute
Active malignancy within 2 y*
Sepsis
Active tuberculosis
Severe neuromuscular disease
Documented, refractory non-adherence
Multiple-organ dysfunction†
Acquired immunodeficiency syndrome
Hepatitis C with histologic liver disease
Significant psychiatric illness in patient or primary caregiver

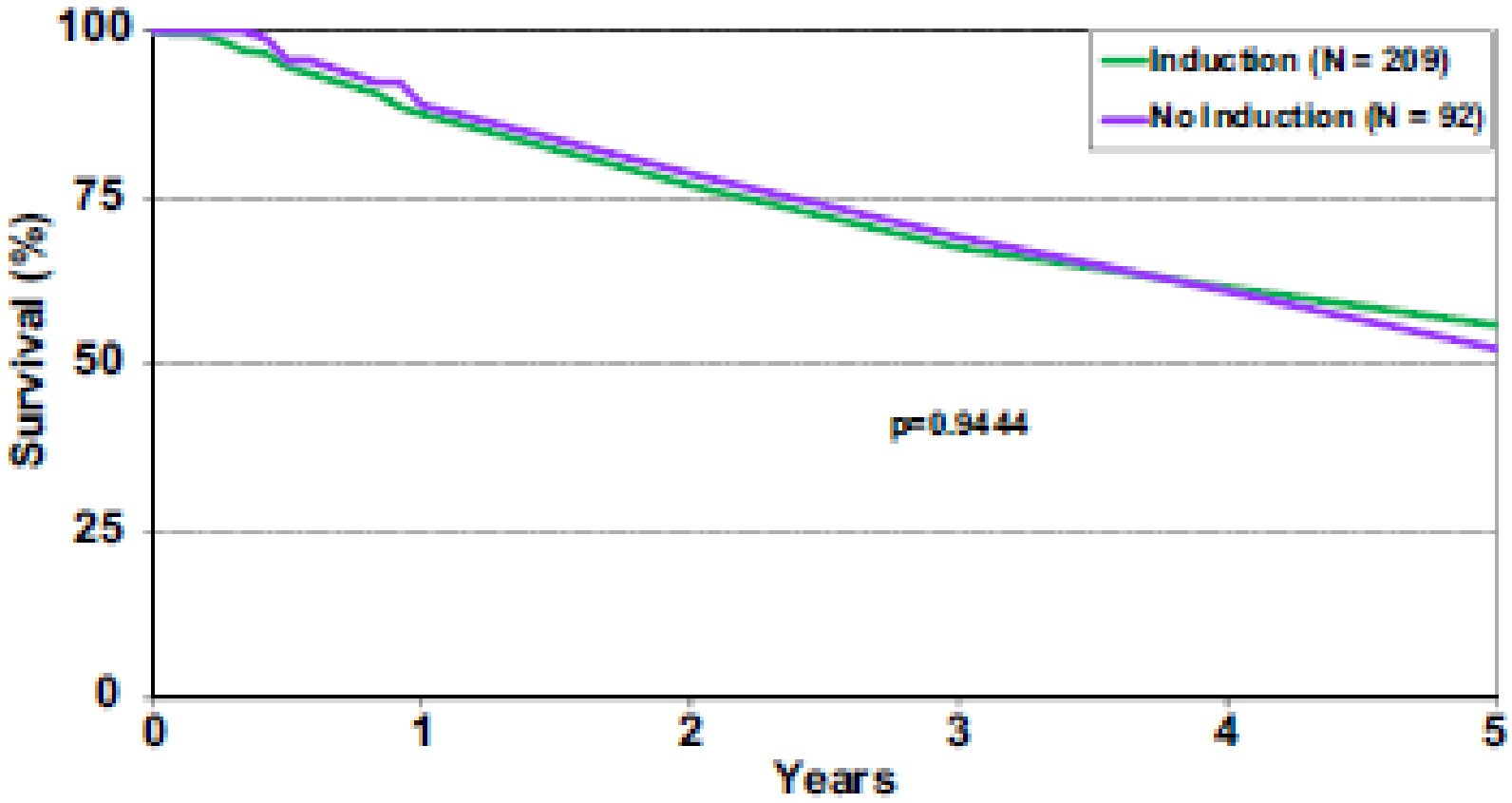
Faro et al, Am J Transplant 2007; Sweet S, Resp Care 2017

Contraindications

Absolute	Relative
Active malignancy within 2 y*	Pleurodesis
Sepsis	Renal insufficiency
Active tuberculosis	Markedly abnormal body mass index
Severe neuromuscular disease	Mechanical ventilation or ECMO‡
Documented, refractory non-adherence	Scoliosis
Multiple-organ dysfunction†	Poorly controlled diabetes mellitus
Acquired immunodeficiency syndrome	Osteoporosis
Hepatitis C with histologic liver disease	Chronic airway infection with multiply resistant organisms§
Significant psychiatric illness in patient or primary caregiver	Fungal infection/colonization
	Atypical mycobacteria infection/colonization (particularly smear-positive)
	Hepatitis B surface antigen-positive

Faro et al, Am J Transplant 2007; Sweet S, Resp Care 2017

Survival

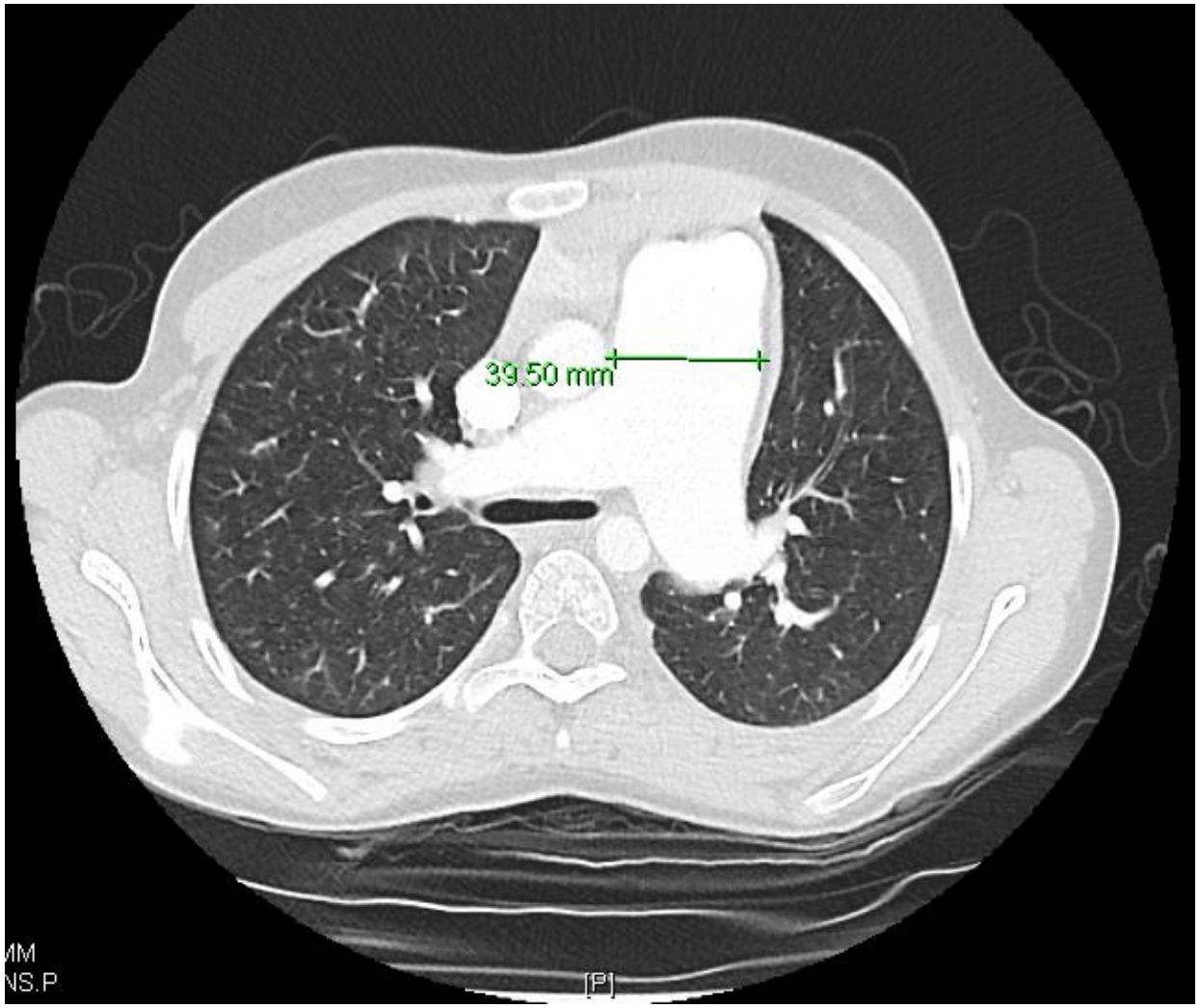


Goldfarb S et al, J Heart Lung Transplant, 2015

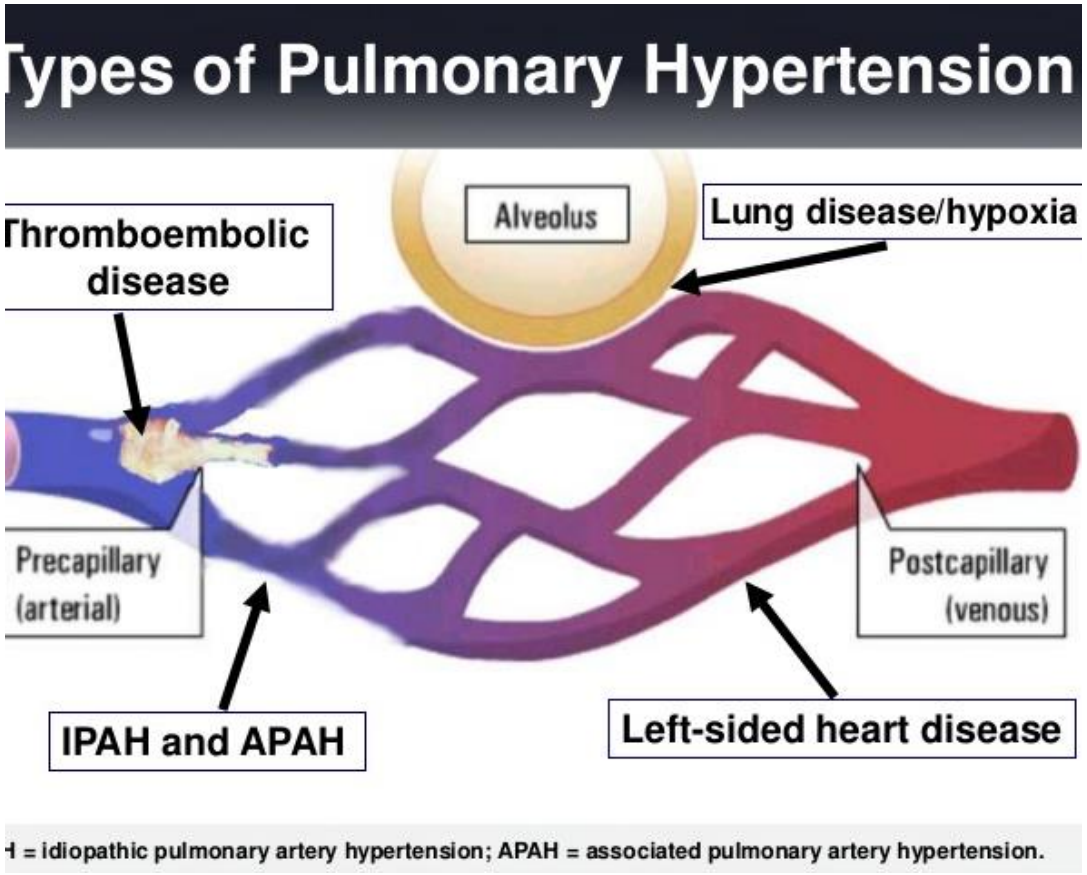
Case 1

NS – 12 year old ♀

- Idiopathic pulmonary arterial hypertension (dx age 6)



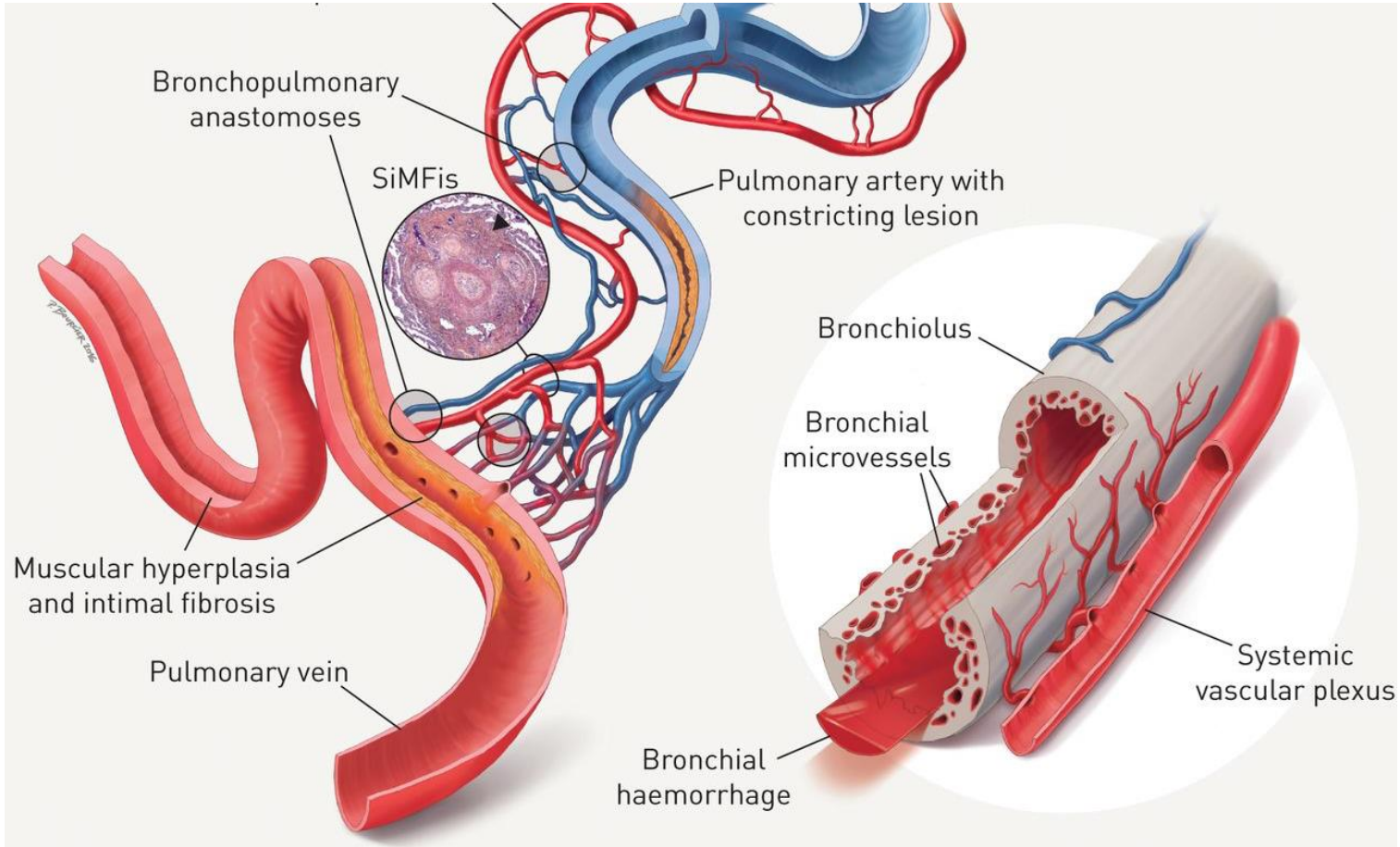
Pulmonary Hypertension



mean pulmonary artery pressure ≥25 mmHg at rest (WHO)

- Group 1 – Pulmonary arterial hypertension (PAH)
- Group 2 – PH due to left heart disease
- Group 3 – PH due to chronic lung disease and/or hypoxemia
- Group 4 – Chronic thromboembolic pulmonary hypertension (CTEPH)
- Group 5 – PH due to unclear multifactorial mechanisms

$$\text{Vascular resistance} = \frac{\text{input pressure} - \text{output pressure}}{\text{blood flow}}$$



1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin, SMAD9, CAV1, KCNK3
1.2.3. Unknown
1.3. Drug- and toxin-induced

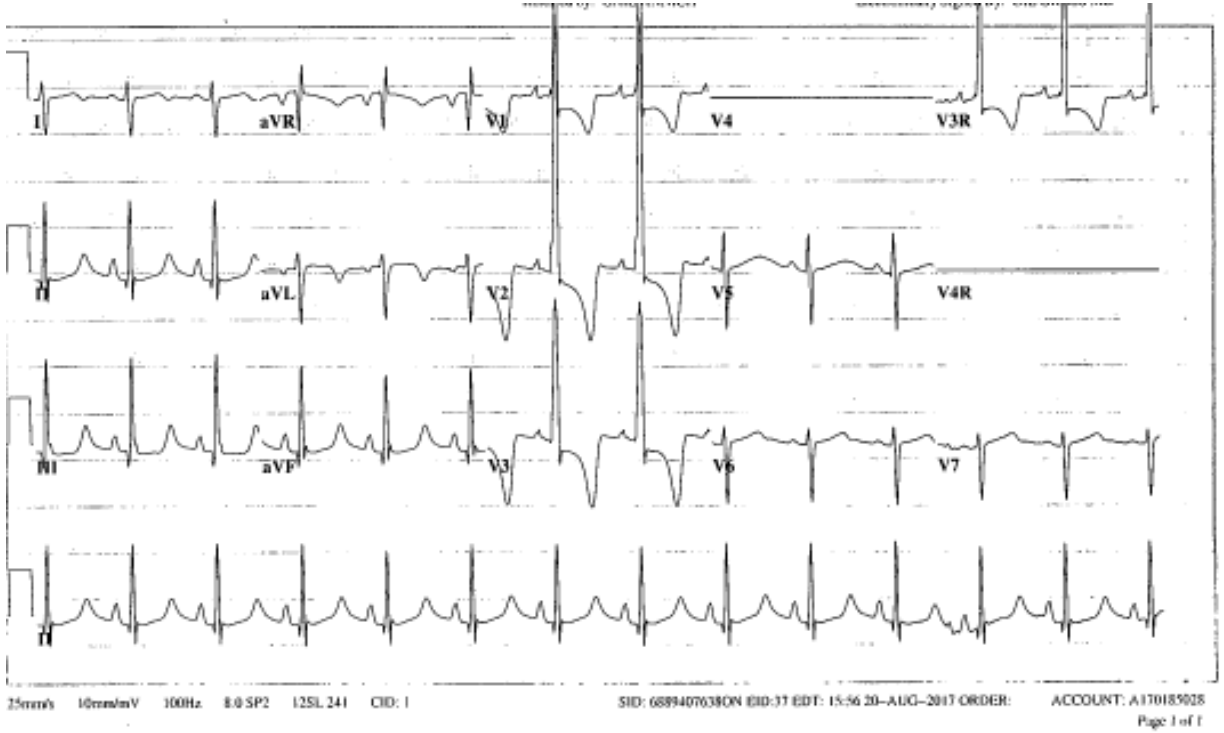
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
1′′. Persistent pulmonary hypertension of the newborn (PPHN)

NS – 12 year old ♀

- Idiopathic pulmonary arterial hypertension
- Rx:
  - Treprostinil (Remodulin®) s/c continuous infusion
  - Tadalafil (Adcirca®) 40mg daily
  - Macitentan (Opsumit®) 10mg PO daily
  - Oxygen 1.5L/min (nocturnal + with exercise)
- Listed Feb 2016

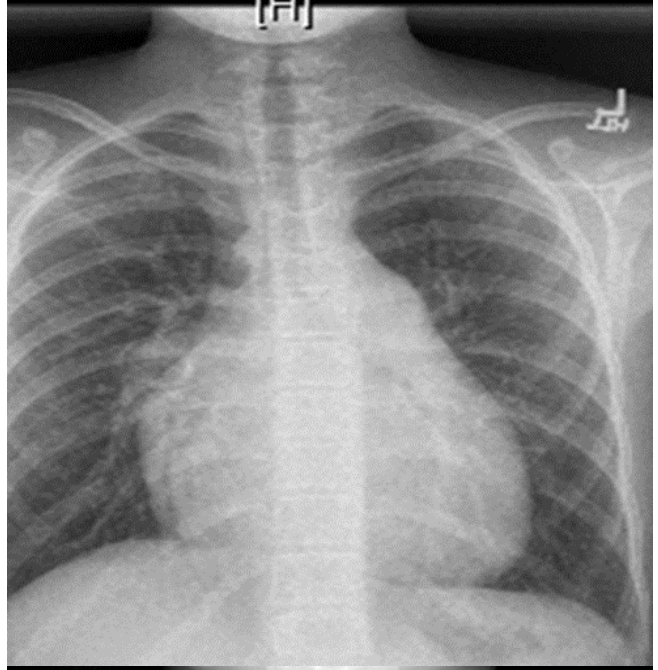
NS – 12 year old ♀

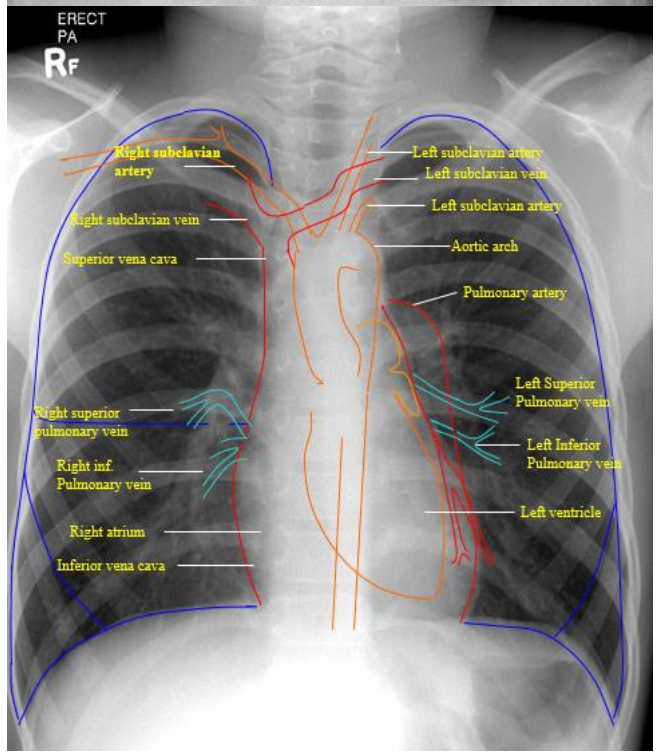
- Symptoms++
- Echo: Severely dilated and severely reduced RV systolic fxn. RVSp > 2/3rd systemic pressure (78mmHg)
- ECG: 2017-06-27: Biatrial enlargement. right ventricular hypertrophy.



NS – 12 year old ♀

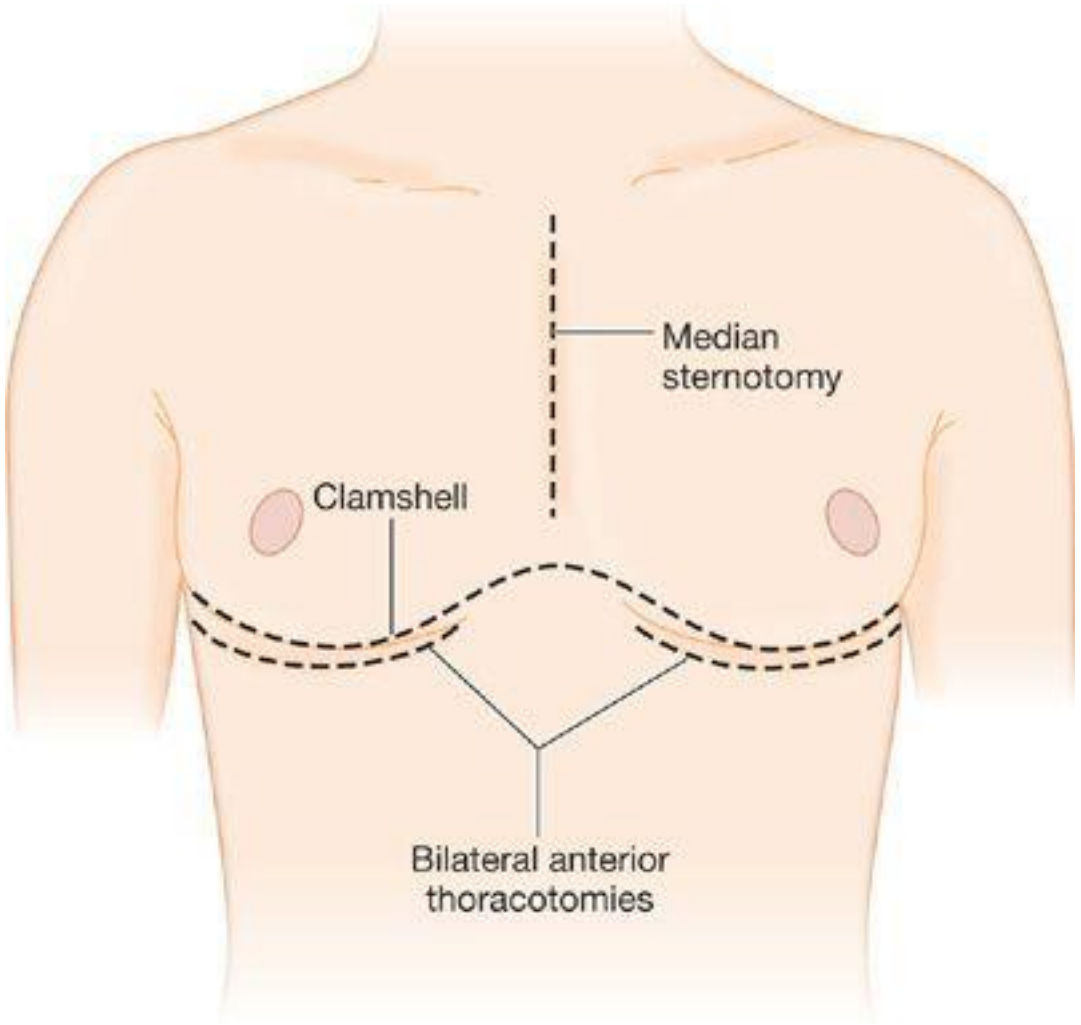
- Transplanted Aug 2017
- Pre-op exam:
  - HR108 RR18 BP96/57 SpO2 96%
  - CVS: Increased JVP, Loud P2. Normal pulses, CRT<2sec, no peripheral edema
  - Resp: equal a/e bilat, no adventitious sounds
  - GIT: SNT, no HSM





Double Lung Transplant

- Bilateral sequential lung transplant with end-to-end bronchial to bronchial anastomosis - on ECMO



Double Lung Transplant

- Bilateral sequential lung transplant with end-to-end bronchial to bronchial anastomosis - on ECMO
- Virtual crossmatch positive, high PRAs

Preventing hyperacute rejection

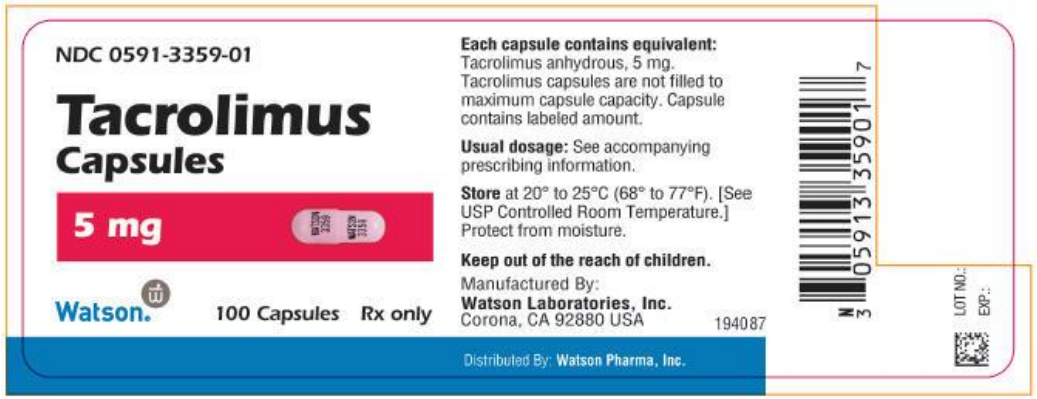
- Step 1 - “Virtual crossmatch” – screening for the presence of recipient pre-formed anti-HLA antibodies to the prospective donor HLA type.
- →decision to proceed with transplant
- Step 2 - An “actual crossmatch” with donor cells and recipient serum (flow cytometry)
  - Usually resulted AFTER transplant

Double Lung Transplant

- Bilateral sequential lung transplant with end-to-end bronchial to bronchial anastomosis - on ECMO
- Virtual crossmatch positive, high PRAs
  - Receives plasmapheresis in OR
  - Receives plasmapheresis in ICU
  - Then actual crossmatch negative. No DSAs detected

Double Lung Transplant

- Triple immunosuppression:
- IS: Prednisone, tacrolimus, MMF

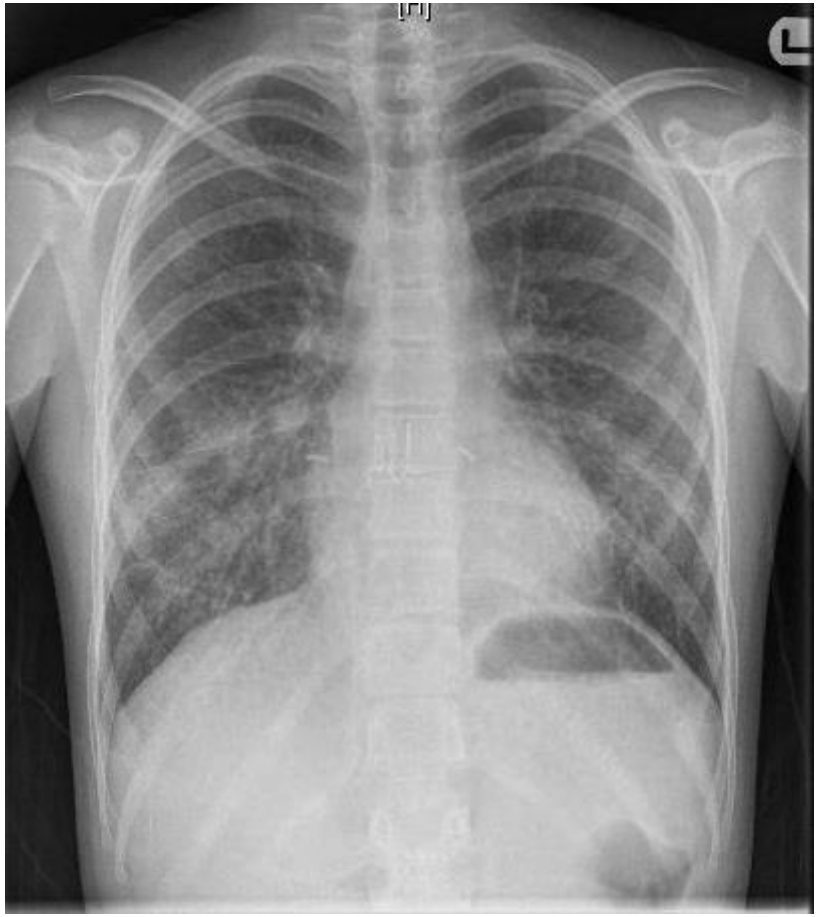


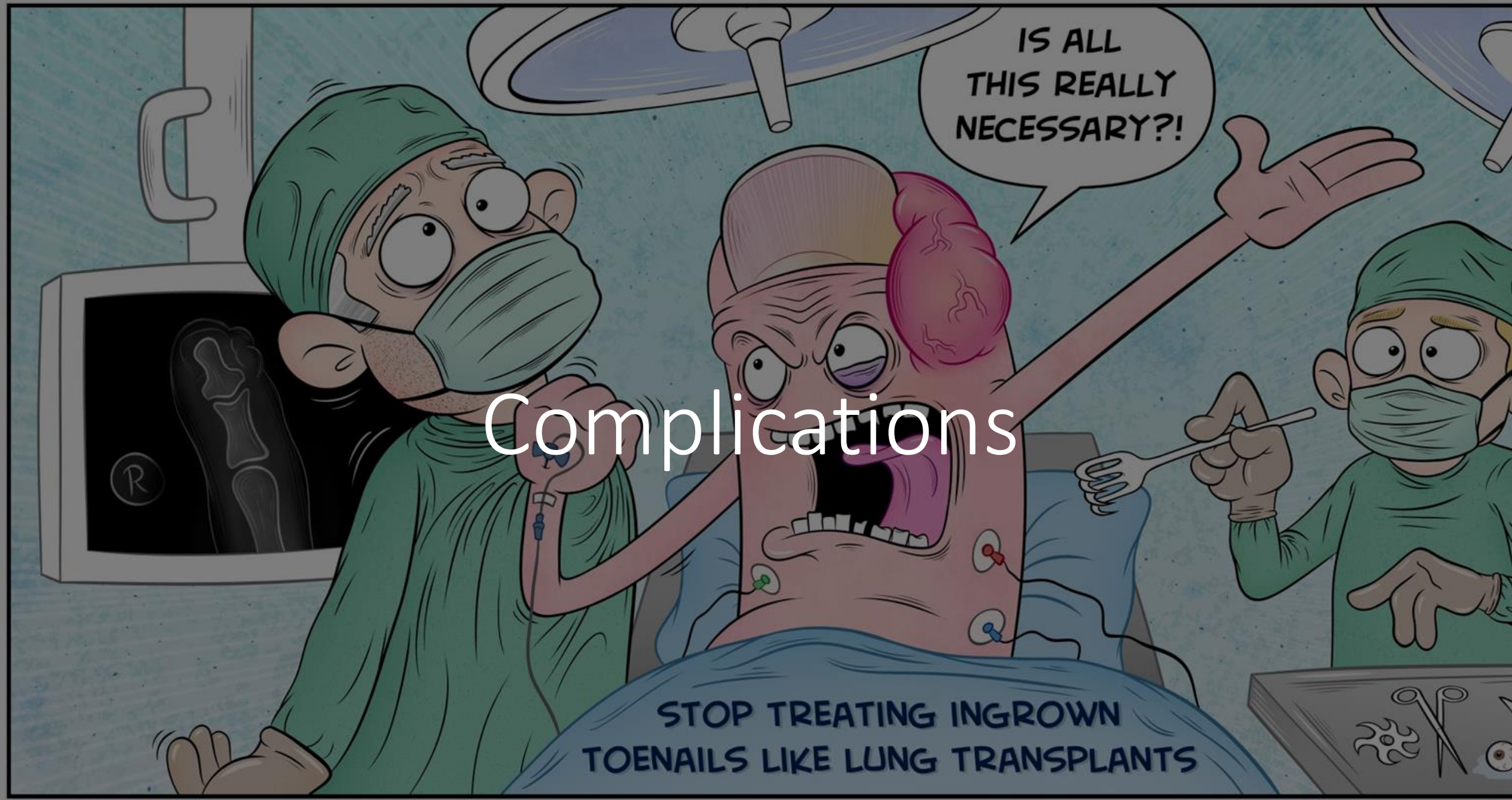
Double Lung Transplant

- Treated with pip-tazobactam for donor +ve staph aureus and E. Coli
  - RLL consolidation - donor consolidation
- EBV: D+/R+ and CMV: D-/R-
- Candida prophylaxis

Double Lung Transplant

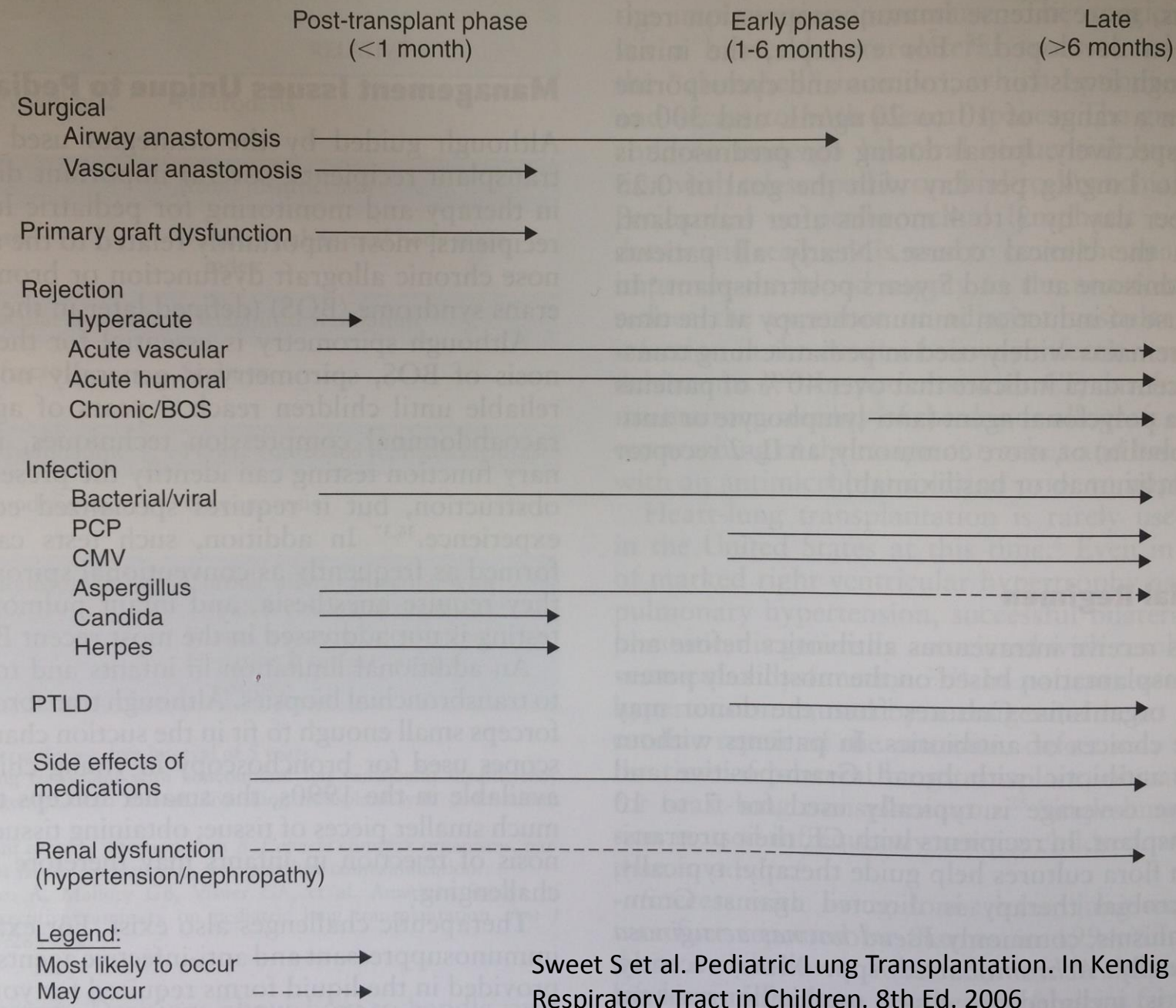
- Leaves hospital on day 14.





Complications

TABLE 64-2 TIMING OF COMPLICATIONS AFTER LUNG TRANSPLANTATION



Sweet S et al. Pediatric Lung Transplantation. In Kendig and Chernick's Disorders of the Respiratory Tract in Children. 8th Ed. 2006

Post-transplant phase

1) Surgical
   - Bleeding
   - anastomotic and non-anastomotic airway stenosis
   - anastomotic dehiscence
   - lobar torsion
   - Pneumothorax
   - Nerve injury
     - Phrenic nerve
     - Recurrent laryngeal nerve
     - Vagus nerve

Tejwani V, et al.. Chest. 2016
Grasemann H, et al. Springer International. 2017 (in press)

Immediate/Early Complications

1) Surgical
   - Bleeding
   - anastomotic and non-anastomotic airway stenosis
   - anastomotic dehiscence
   - lobar torsion
   - pneumothorax
   - Phrenic nerve injury
   - Vagus nerve injury

2) Primary Graft Dysfunction

   w/i 72h

   ischemia-reperfusion injury

   dx exclusion

Tejwani V, et al.. Chest. 2016
Grasemann H, et al. Springer International. 2017 (in press)

Immediate/Early Complications

3) Immunological complications

- Hyperacute rejection
- Acute cellular rejection
- Antibody mediated rejection

Tejwani V, et al.. Chest. 2016
Grasemann H, et al. Early Postoperative Management, Springer International. 2017 (in press)

Immediate/Early Complications

3) Immunological complications
- Hyperacute rejection
- Acute cellular rejection
- Antibody mediated rejection

4) Infectious complications
- Bacterial/
- Viral
  - CMV
  - EBV
  - Herpes
- Fungal
  - Aspergillus
  - Candida
  - PCP

Tejwani V, et al.. Chest. 2016
Grasemann H, et al. Early Postoperative Management, Springer International. 2017 (in press)
Sweet C, Resp Care. 2017

Immediate/Early Complications

5) Iatrogenic

- Transfusion related acute lung injury
- Medication SE
  - Diabetes
  - Renal impairment
  - Neurological complications
  - Leukopenia

De Perrot et al, Am J Crit Care Med. 2003

Immediate/Early Complications

5) Iatrogenic

- Transfusion related acute lung injury
- Medication SE

6) Other

- Pulmonary edema
- pulmonary arterial or venous thrombus
- Donor lung injury
- Pulmonary aspiration
- Gastroparesis/GIT dysmotility
- SVT

De Perrot et al, Am J Crit Care Med. 2003

Sept 5

Returns to clinic 5 days post discharge:

c/o SOB, cough, chest pain, asking for oxygen

O/E:

Hypoxemia 78% room air (SpO2 90% in 100% O2)

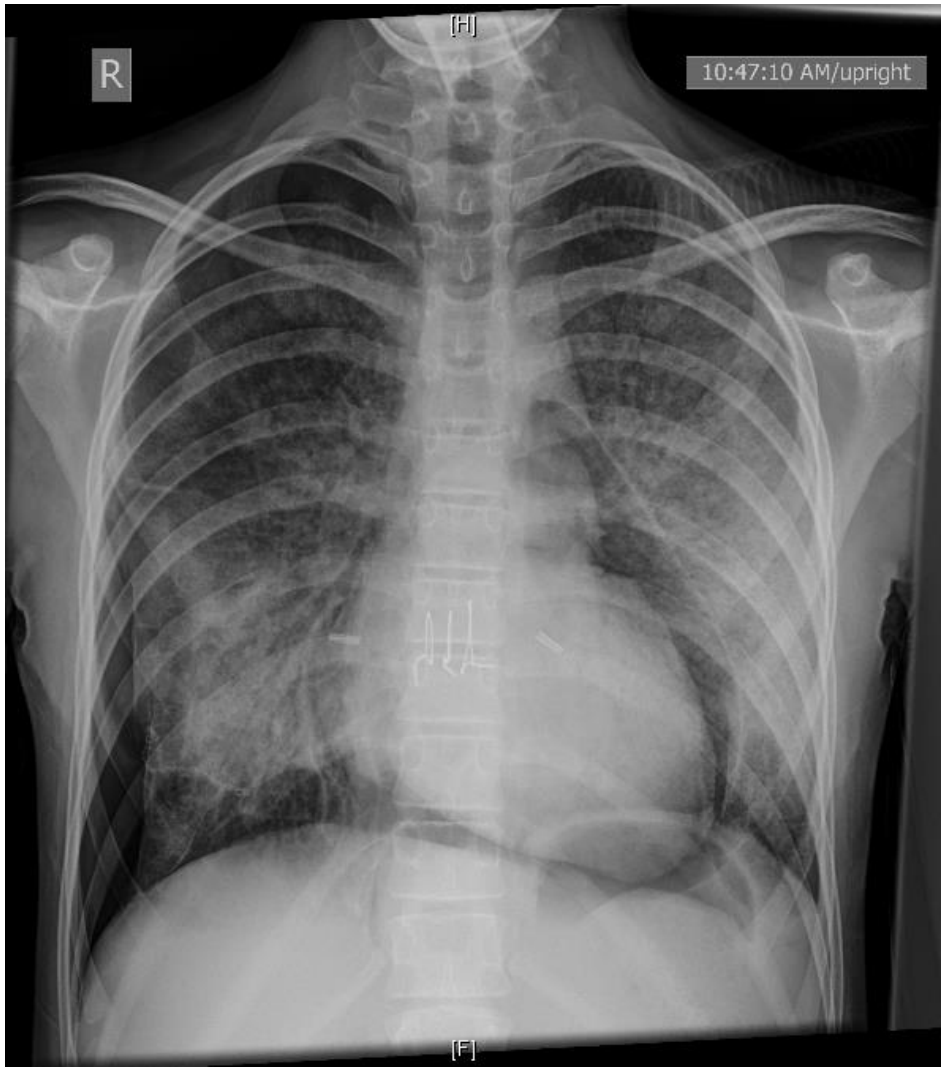
Respiratory distress

Reduce air entry on the right

WCC 46 x 10^9/L

CRP 32 mg/L

Rx: Pip/taz & Vancomycin



Sept 5

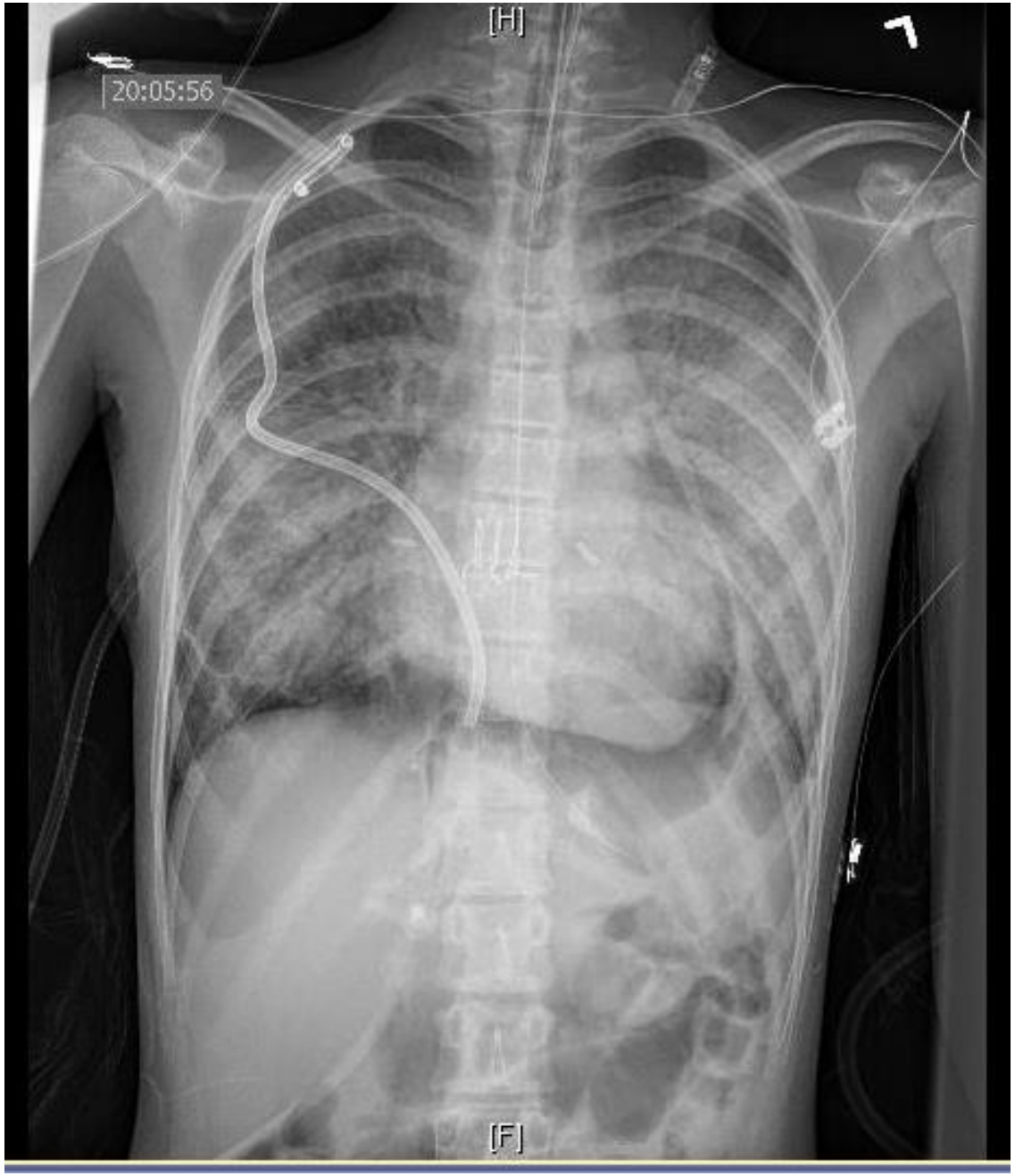
Chest tube placed

Bronchoscopy:

Yellow secretions in right main stem bronchus

Anastomosis in tact

BAL sent (x1 dose abx before BAL)



Sept 6

Intubated in the ICU – FiO2 100%

BAL from Sept 5 still negative for infection

Question:
Next steps?

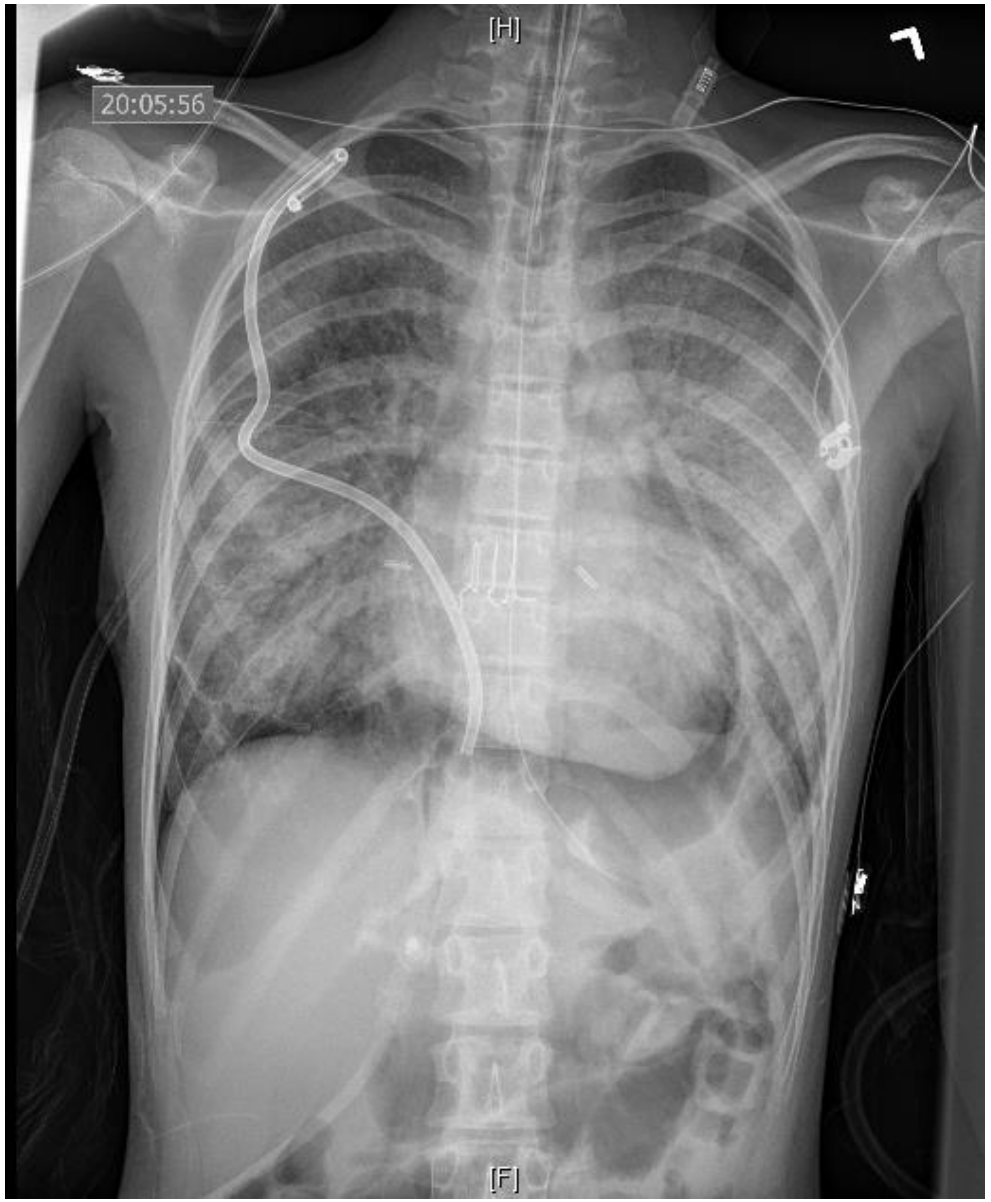
- A) Empirical treatment with Pulse IV Methylprednisolone
- B) Trans-bronchial biopsies and then Pulse IV MP for ACR
- C) Plasmapheresis
- D) Continue current management while awaiting complete BAL cultures

Question:
Next step?

- A) Empirical treatment with IV Methylprednisolone
- B) Transbronchial biopsies and then IV Methylprednisolone for ACR
- C) Plasmapheresis
- D) Continue current management while awaiting complete BAL cultures

Sept 6

- Once stabilized:
- Insertion of surgical chest-tube
- Vancomycin stopped, Pip/taz continued



Sept 7- 8

- Initial response to treatment with decreased FiO2 from 100% to 60%
- Extubated but requiring BIPAP and increasing FIO2 requirement
- Preliminary tbbx report suggestive of infection with ++neutrophils in airways…EBV/CMV/fungal/adeno stains negative
- Antibiotics coverage broadened – vancomycin, meropenam, azithromycin

Sept 9 - 10

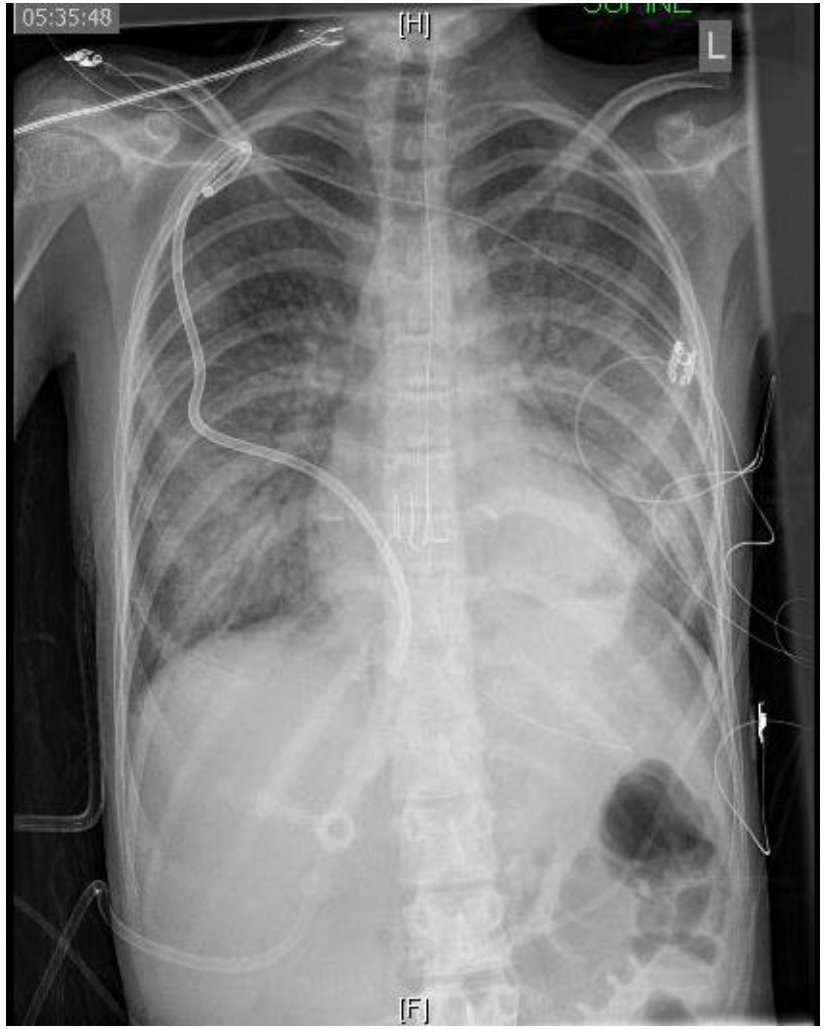
Clinical deterioration

PRAs sent urgently

Received Plasmapheresis while waiting results

Clinical response

FiO2 90%, decreased to 60%



- +DSAs A1 and A24 ‘saturated’ (had historic weak A24)

Path report

- Diffuse and organizing alveolar damage. Multiple distinct foci of dense perivascular mononuclear infiltrates, no capillaritis.
  →indicative of grade A4 acute cellular rejection.
- Mucopururlent exudate in large airways and large airway inflammation suspicious for co-existing infection
- In the presence of DSAs the biopsy findings could be consistent with antibody-mediated rejection. (despite negative C4d staining)

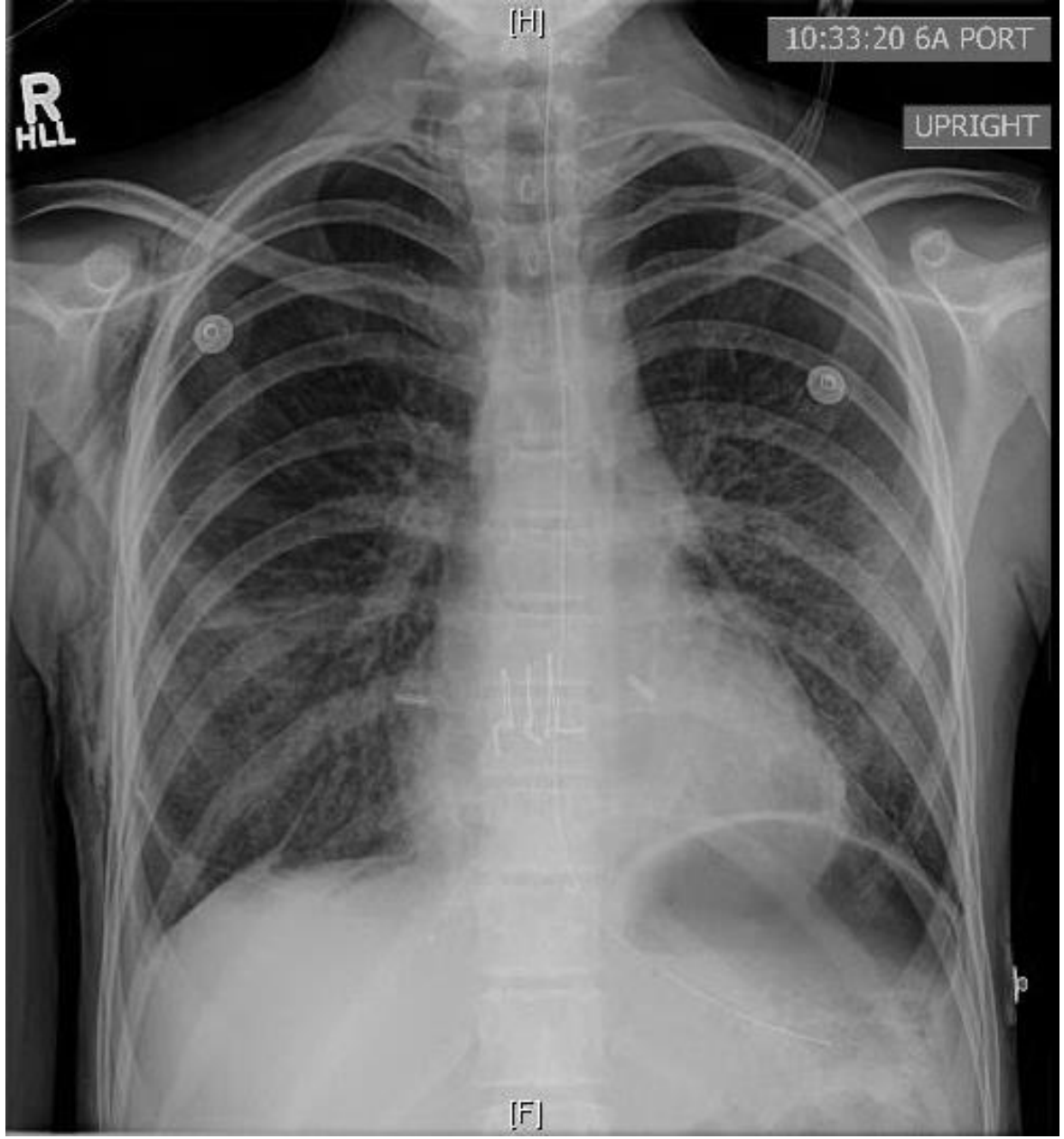
5 day course of plasmapheresis with IVIG at end

Increased dose of MMF

Improving bilateral airspace opacification

Monthly IVIg and rituximab

Ongoing close monitoring of PRAs




That looks foreign..
a funny looking MHC. Are you from this part of town?
Yeah.. That's nothing.. Umm.. Busy day eh officer?
Oh no.. I am being detected. What am I even doing here?
T
CD8 + T cytotoxic
MHC
Transplanted cell

REJECTION

Hyperacute rejection

- Hyperacute rejection – within hours
  - Rare, potentially catastrophic
  - Circulating pre-formed recipient antibodies that bind to donor human leukocyte antigen (HLA) molecules on vascular endothelium,

  →leading to vascular damage, obstruction and severe graft ischemia.
  - Pre-op screening with virtual cross-match

Sweet S and Noyes B 2006. Paediatric Lung Transplantation. In Kendig and Cherneck's Disorders of the Respiratory Tract in Children. 8th Ed.

Acute Cellular Rejection

- ACR occurs when recipient lymphocytes react with donor antigens
- Majority of lung transplant recipients, most common in first 3m
- Low early mortality but most significant RF for CLAD
- Non-specific clinical presentation – hypoxia, fever, cough, new infiltrates, obstructive pattern on PFTs
- Can occur as early as one week and up to 2-3 years post
- Surveillance bronchs for subclinical rejection – controversial
- Grade A2 and above → Rx: Pulse Methylprednisolone x3 days

Husain AN et al. Archives of pathology & laboratory medicine. 2016

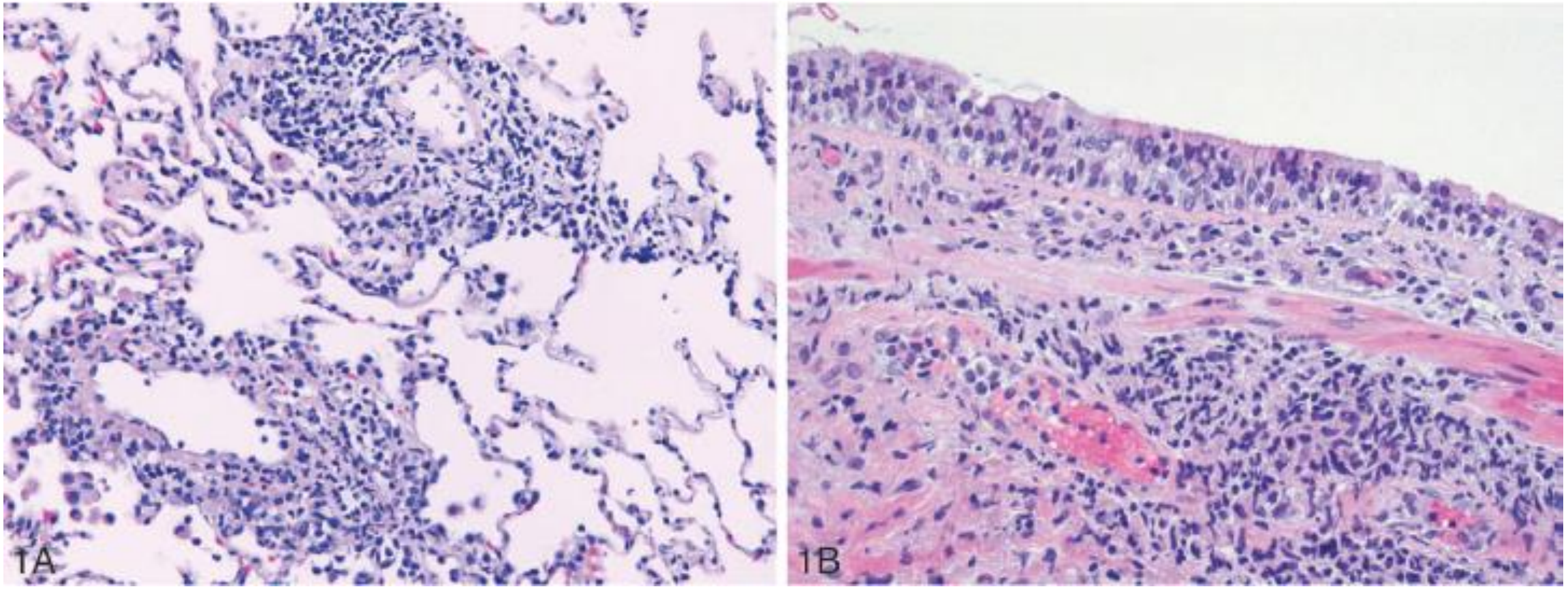


Figure 1. *Acute rejection is characterized by perivascular (A) and airway (B) inflammatory infiltrates (hematoxylin-eosin, original magnification ×200 [A and B]).*

Histologically – perivascular lymphocytic infiltrates with or without airway inflammation
→ standardized scoring none (A0) to severe (A4)

Husain AN et al. Archives of pathology & laboratory medicine. 2016

Antibody Mediated Rejection

- Development of DSA's can lead to AMR
- AMR vs. ACR vs infection ??
- → multidisciplinary approach to diagnosis:
  - Clinical allograft dysfunction (can be subclinical)
  - Circulating DSA's
  - Pathological findings (TBBx)
  - +/- complement 4d within the graft (C4d staining)
- AMR = driver of both acute and chronic lung allograft dysfunction (CLAD).
- No consensus on treatment strategies

Case 2

Consent 👍

EE – 3 year old boy

B/G

1. Ex 37/40 , MAS and NAIT in neonatal period
2. Group A Sepsis (age 2)
3. Recurrent RTI
4. Asthma
5. Mild Developmental delay

EE – Aug 2016

Presented to ED with “haematemesis”

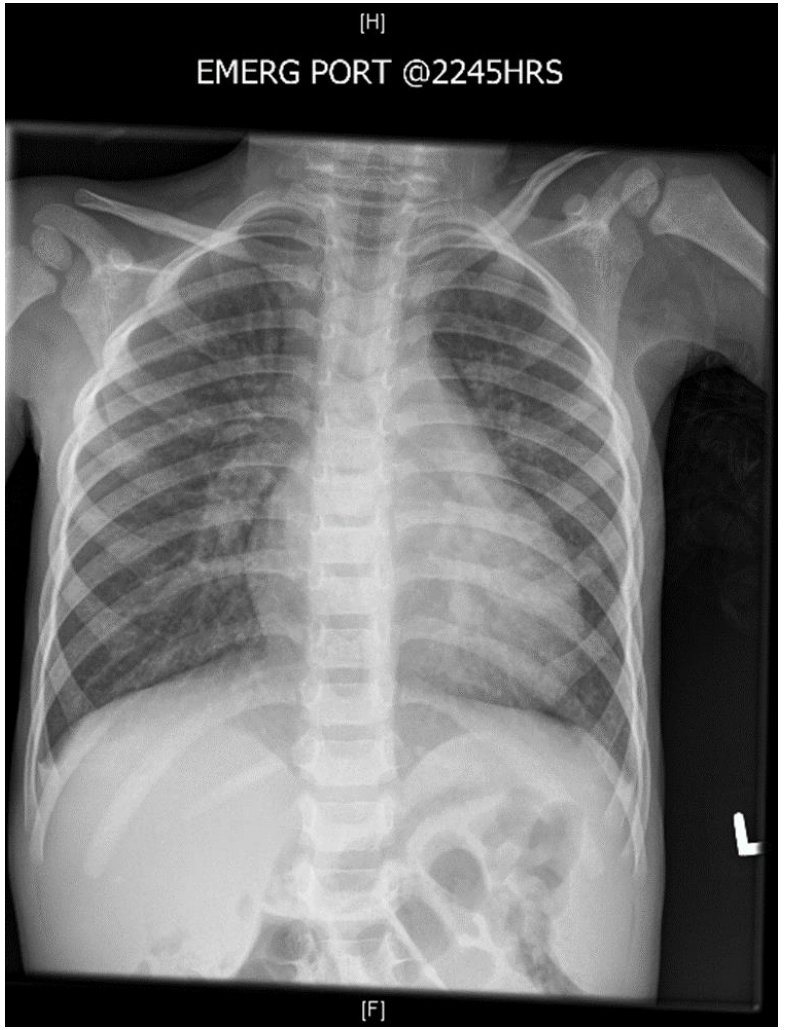
GI scope

→

In PACU frank blood in ETT

Transferred to PICU I+V

Bronchoscopy confirmed blood in airways



EE – 3 year old boy

CT Chest –

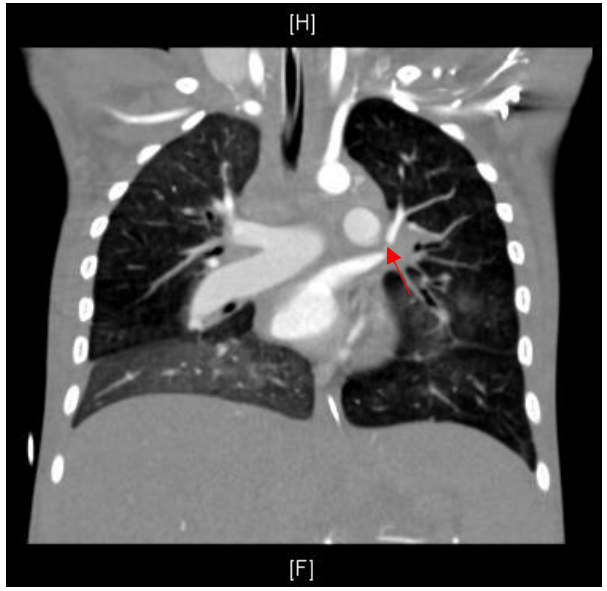
severe PVS, dilated pulmonary arteries and right ventricular hypertrophy.

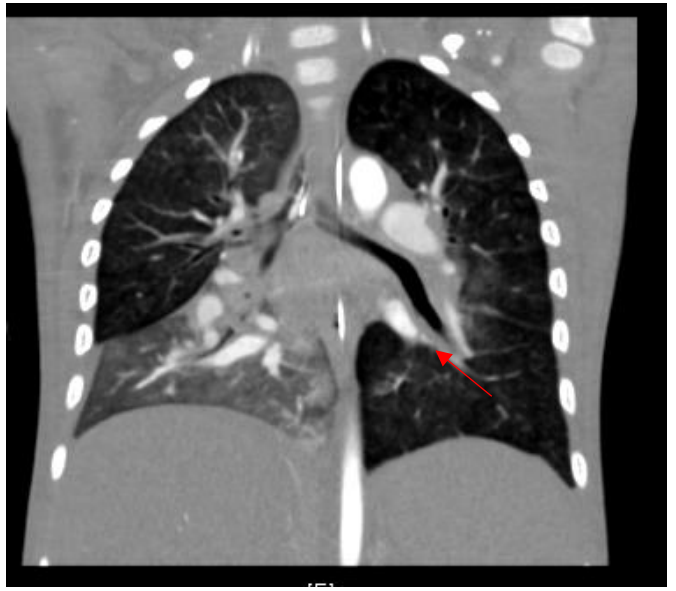
Ground glass opacities in RLL

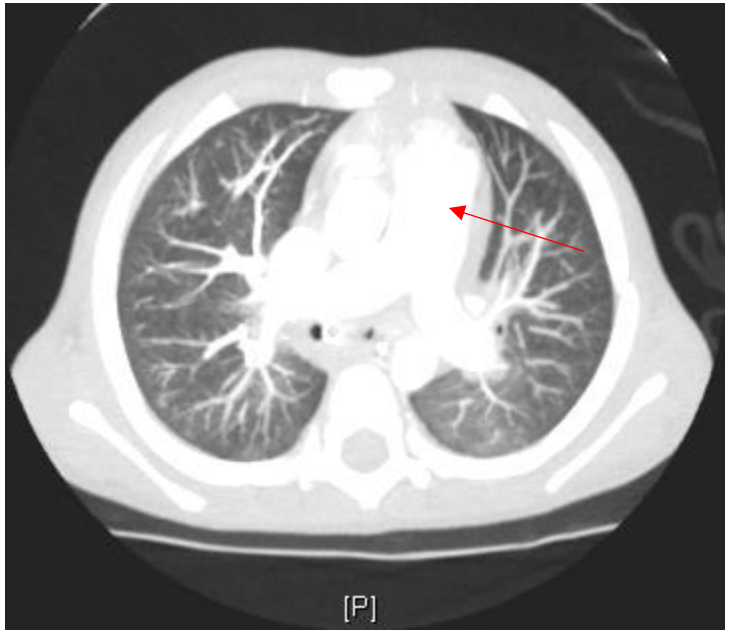
?fibrosing mediastinitis

?Primary or secondary PVS

Echo: Pulmonary HTN, mildly dilated RV, RVH
Good BV function (no PHTn on echo in 2015)







EE – 3 year old boy

Rx:

- multiple catheter interventions with balloon dilations,
- ASD creation
- Listed for Lung transplant Jan 2017

→

- Sutureless repair of the R pulmonary veins (2017-02).

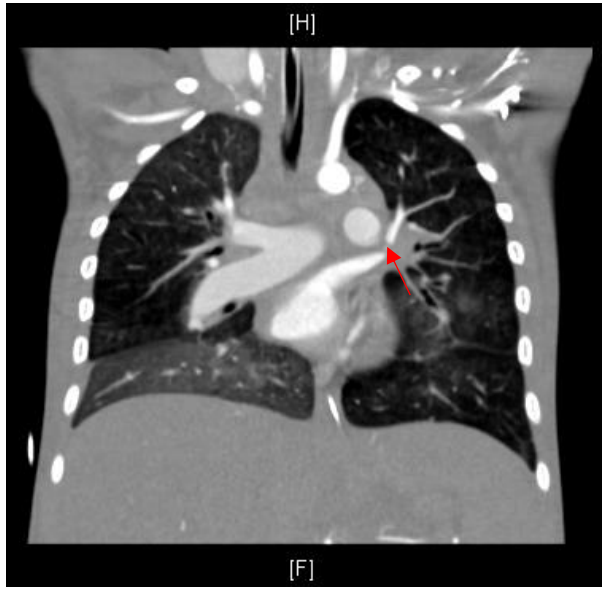
→

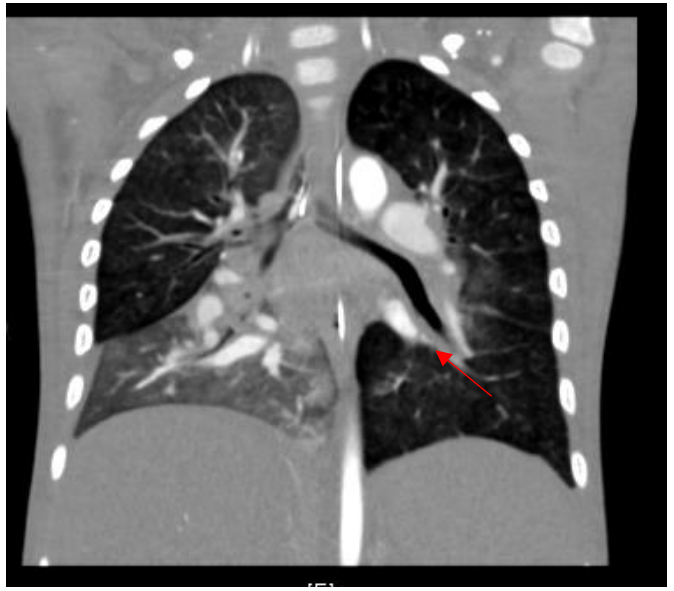
Residual pulmonary vein stenosis post repair on CT (2017-05) – limited response to procedures

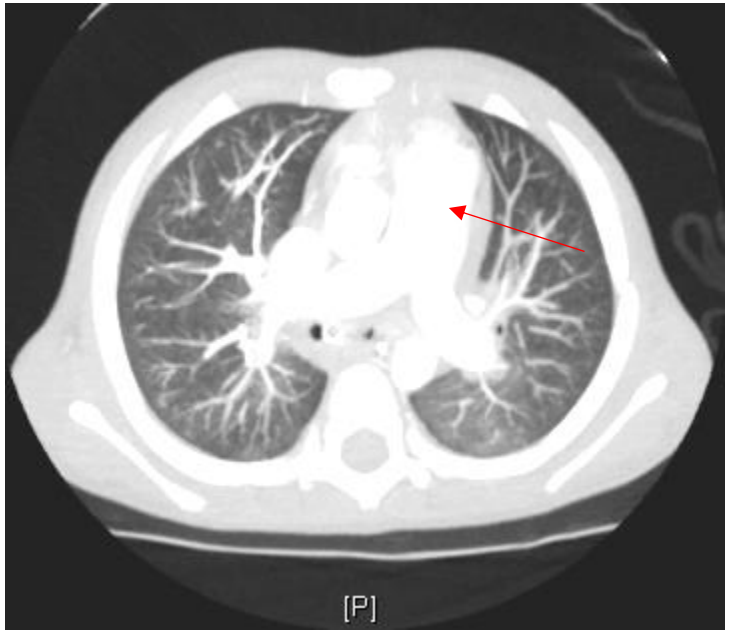
Relisted for lung transplant

Treated with daily corticosteroids for unknown but potentially inflammatory aetiology

July 2017 - RVSp 61% systemic measured







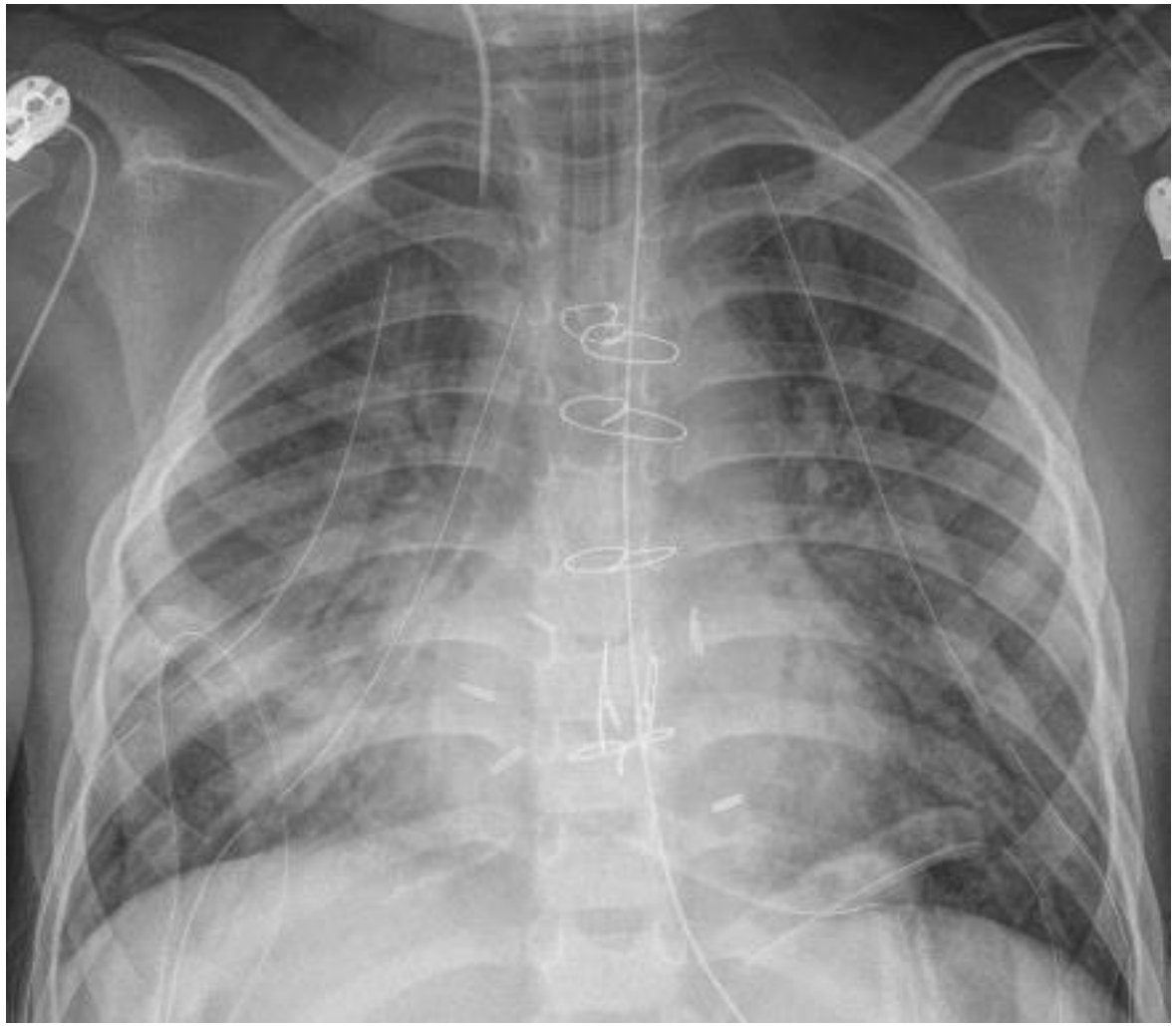
EE – Day 0

Donor:

- RLL consolidation
- Donor lungs underwent EVLP for borderline status
- CMV neg, EBV neg

Transplant

- Uneventful
- ECMO - 3h
- Stable vascular and bronchial anastomosis on intra-op bronchoscopy
- Chest tubes x6



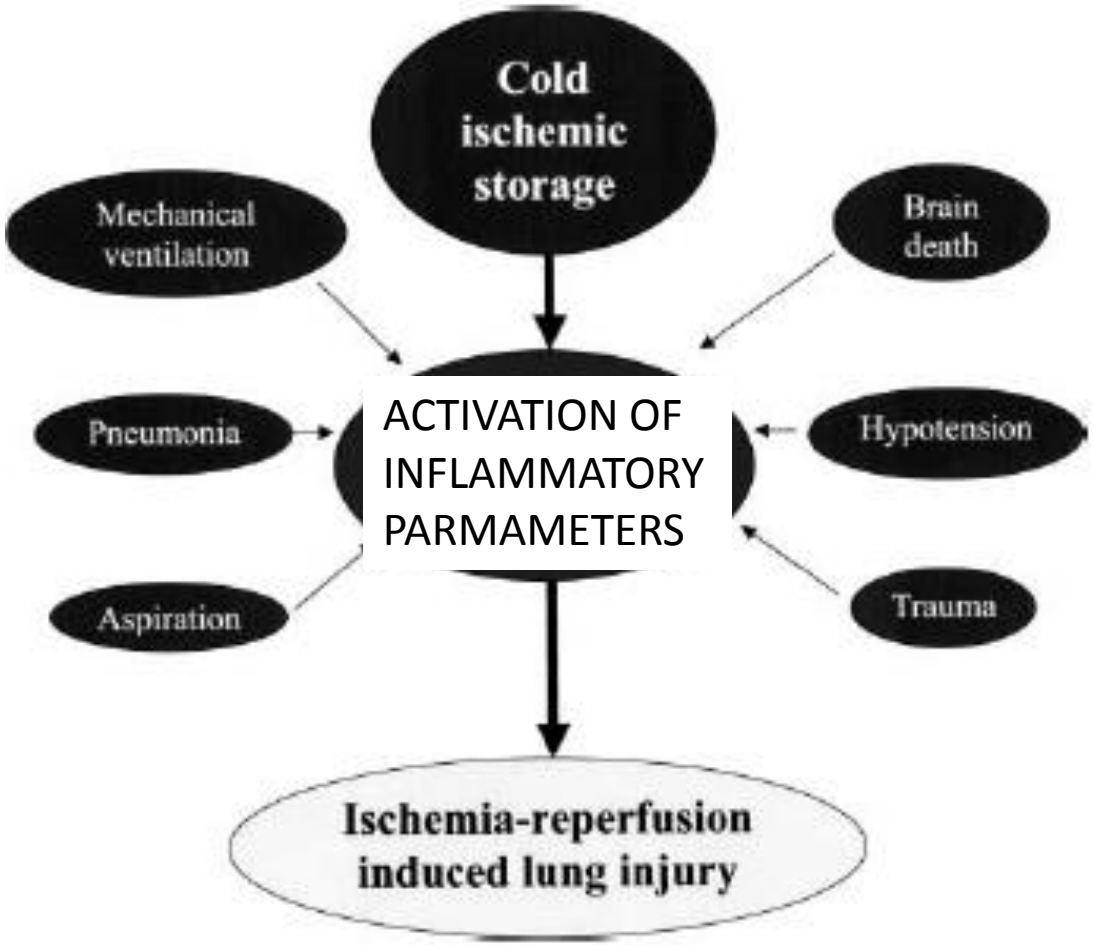


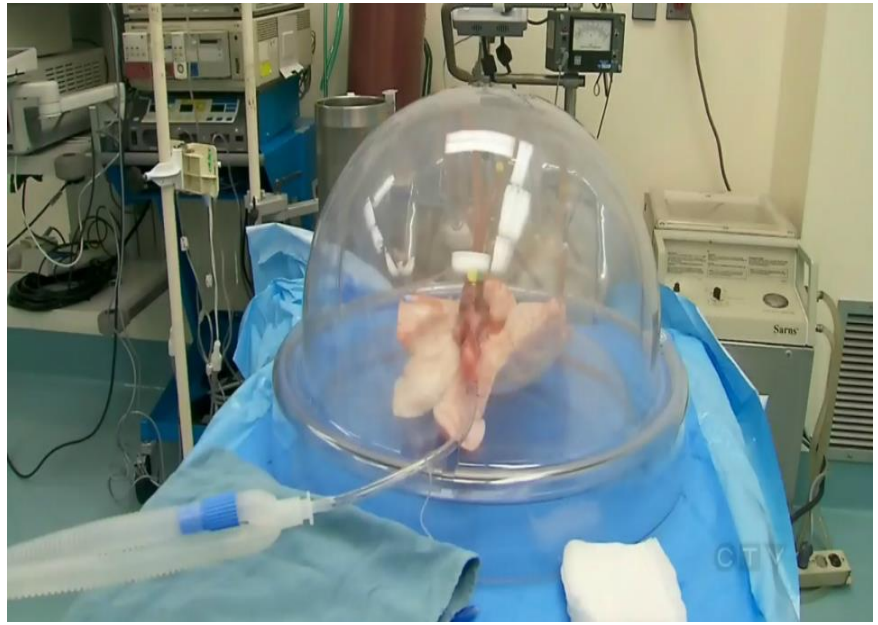
Figure 1. Ischemia–reperfusion–induced lung injury may be aggravated by a number of events occurring in the donor before lung retrieval.

De Perrot et al. Am J Crit Care Med. 2003

ORIGINAL ARTICLE

Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.



- Lungs perfused and ventilated ex-vivo at body temperature to mimic physiological conditions for 4hours
- If PaO2:FIO2 ratio >=350mmHg lungs considered suitable for transplant
- The incidence of Grade 2 or 3 PGD at 72h was 15% (n=20) compared to 30% (n=116) in the control group (p=0.11)
- Transplantation of high-risk donor lungs that were physiologically stable during 4 hours of ex vivo perfusion led to results similar to those obtained with conventionally selected lungs.

Cypel M et al. NEJM, 2011

EE – Day 1

Hemodynamic instability – inotropes

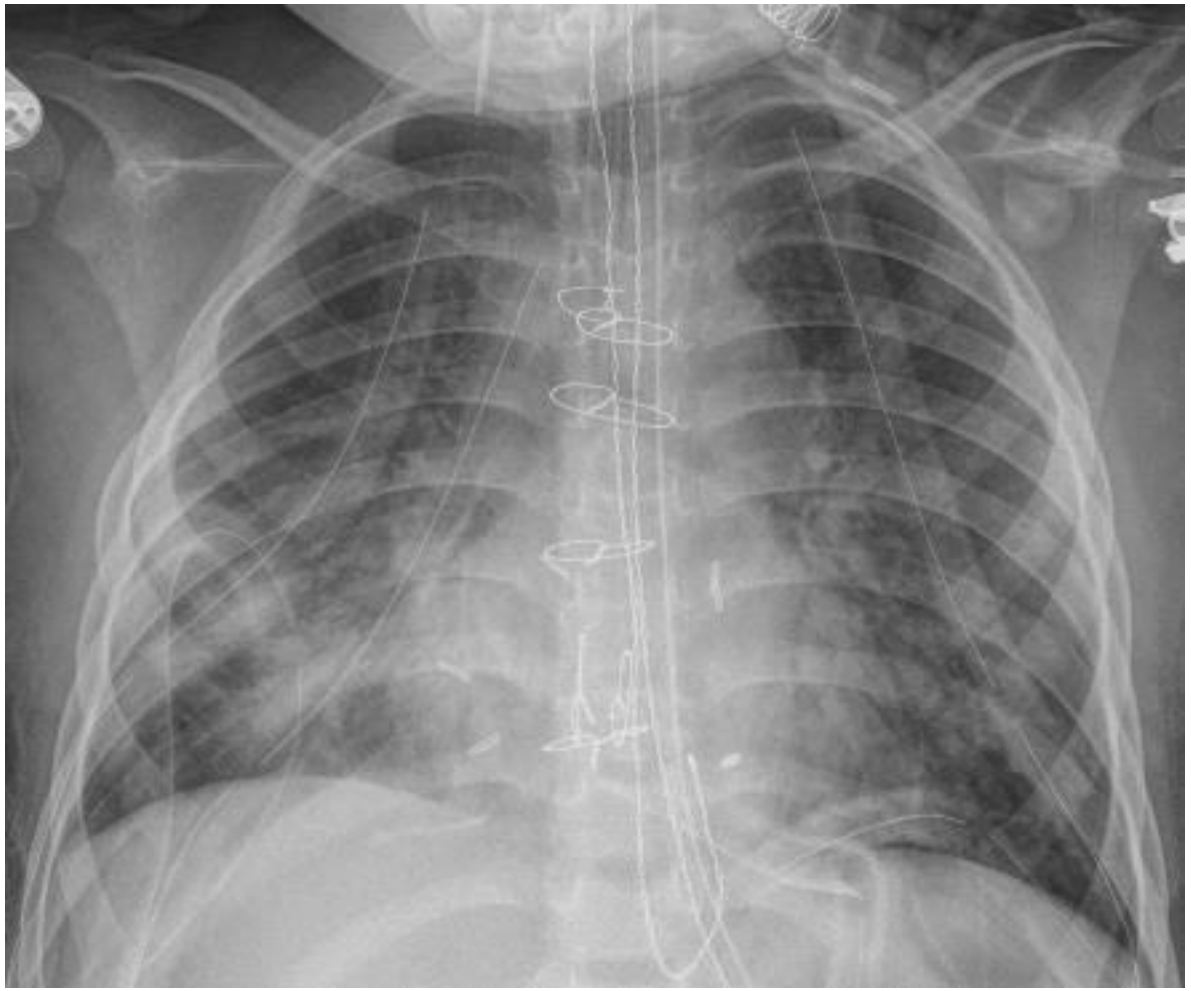
Hypoxia –

PS18 PEEP 10cmH20 50% –

iNO

Donor BAL growing Staph Aureus (Rx Pip/taz & Vanco)

Immunosuppression with IV Methylprednisolone, tacrolimus and MMF



Worsening pulmonary infiltrates

Day 2

Day 3

Aetiology of pulmonary infiltrates?

- A) Pulmonary edema
- B) Infection
- C) Donor lung injury
- D) Right ventricular dysfunction
- E) Hyperacute cellular rejection

EE – Day 4

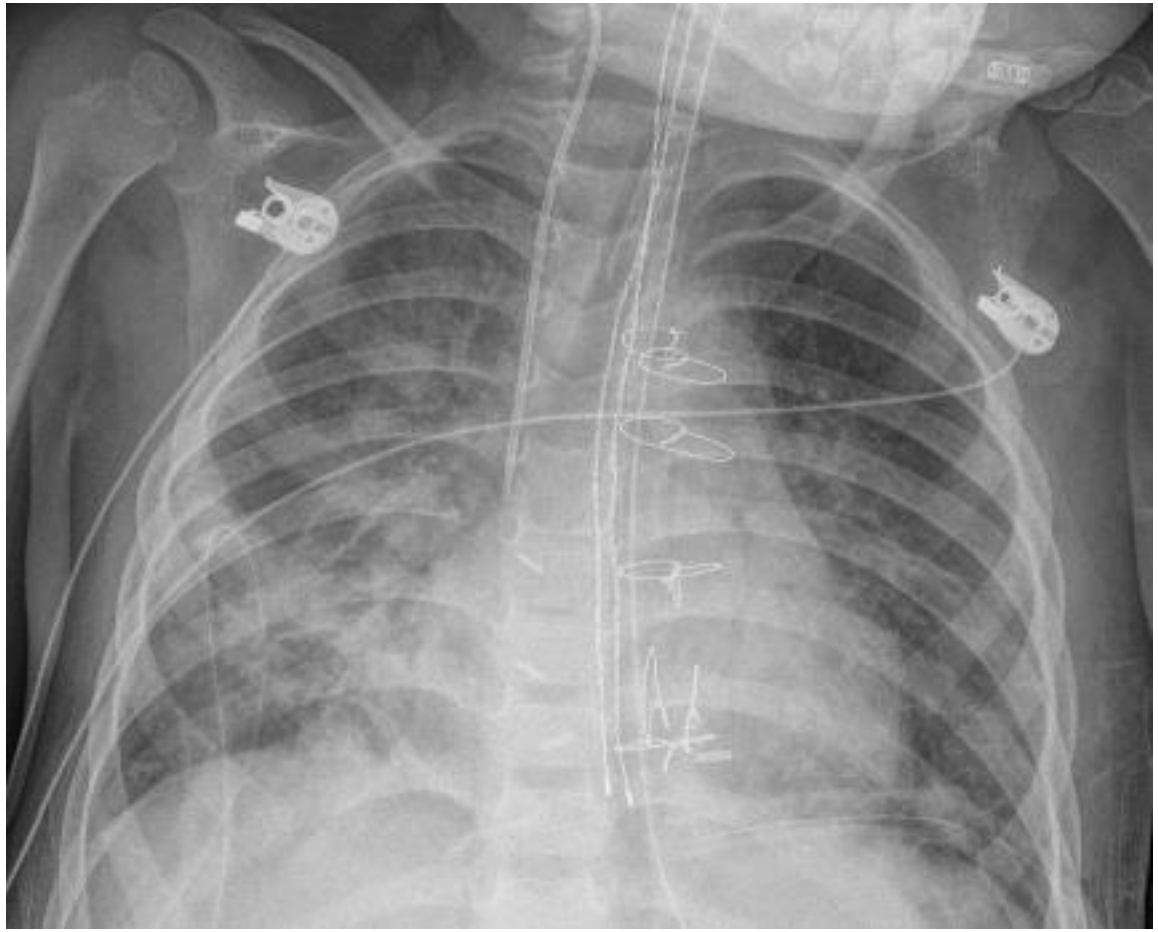
Aggressive diuresis and fluid restriction

Echo - RVSp 18mmHg + CVP 15cmH20

Inotropes stopped

iNO weaned and discontinued

Vancomycin stopped (MSSA)



Aetiology of pulmonary infiltrates?

- A) Pulmonary edema
- B) Infection
- C) Donor lung injury
- D) Primary graft dysfunction
- E) Acute cellular rejection

Pulmonary edema

- Pulmonary edema common occurrence due to increased vascular permeability and severed lymphatics
- Management
  - Minimize pulmonary capillary wedge pressure and central venous pressure
    - Fluid restriction, diuresis, iNO, milrinone
  - Balanced with need to maintain systemic pressure
    - inotropes

Yeung JC et al. Cold Spring Harbor perspectives in medicine. 2014; 4:a015628

Primary Graft Dysfunction

- The expression of all the injury in the donor through to the time of reperfusion.

- Manifests as hypoxemia in the presence of radiographic infiltrates
  - Typically airspace consolidation or interstitial opacities in the perihilar or basilar regions

- Clinically defined - ISHLT
  - Syndrome occurring within 72 hours post lung transplant,
  - characterized clinically by pulmonary edema and
  - pathologically by non-specific diffuse alveolar damage

Christie JD et al. The Journal of heart and lung transplantation. 2005; 24:1454-9
De Perrot M et al. Am Jour Cri Care Med.. 2003;

Mimics

- Diagnosis of exclusion
  - Cardiac dysfunction
  - Pulmonary aspiration
  - Infection
  - Fluid overload
  - Pulmonary venous outflow obstruction obstruction
  - Antibody mediated rejection

PGD

- Overall incidence approximately 10%

- Grading system
  - Graded 0-3 by the presence of
    - radiographic infiltrates consistent with pulmonary edema and
    - reduced oxygenation index (Pa)2/fraction of inspired O2) <300 or <200 depending on severity

Christie JD et al. The Journal of heart and lung transplantation. 2005; 24:1454-9

PGD

- Treatment is supportive
  - Intensified mechanical ventilation
  - Inhaled Nitric Oxide
    - Improves V/Q mismatch as NO delivered to ventilated alveoli
    - Anti-inflammatory properties
  - Extra-corporeal life support (ECLS) / interventional lung assist (iLA) – bridge to recovery

Yeung JC, et al. Cold Spring Harbor perspectives in medicine. 2014; 4:a015628

PGD - Prognosis

- Significance
  - Decreased 30 day mortality - 42% versus 6% for patients without PGD
  - PGD contributes to nearly half of the short-term mortality after lung transplantation.
  - Survivors of primary graft dysfunction have increased risk of death extending beyond the first post-transplant year.
  - Increased risk of chronic allograft dysfunction

Samano M, et al. Elsevier; 2012
Yeung JC, et al Cold Spring Harbor perspectives in medicine. 2014
Christie JD, et al. American journal of respiratory and critical care medicine. 2005

EE – multiple pulmonary complications

- Donor Lung injury (RLL consolidation)
- Infection (donor BAL +)
- Pulmonary edema
- Presumed acute cellular rejection
- Pulmonary aspiration
- Phrenic nerve injury

Summary

- Viable option for treatment of end-stage lung disease despite multiple complications – many of which can occur in the same patient
- The donor pool is a limiting factor but can be improved by EVLP