

Pediatric Lung transplantation

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Welcome to



ATS 2020 | VIRTUAL IWV #shgv

Disclosures

- No financial disclosures relevant to this presentation



Pediatric lung transplant - Overview

Indications and Contraindications

Outcomes and Complications

Challenges and Opportunities



Lung Transplant Indications

- Untreatable end-stage pulmonary parenchymal or vascular disease
- Low probability of recurrence
- No other significant medical diseases
- Limitation of daily activity
- Pulmonary rehabilitation potential
- Satisfactory psychosocial support system

Absolute Contraindications

- Second major organ failure
- Burkholderia Cenocepacia colonization
- HIV Infection*
- Hepatitis B or Hepatitis C* Infection
- Active malignancy within past two years
- Progressive Neuromuscular Disorder

*Becoming debatable

Relative Contraindications

Invasive Ventilation

- Risk Factor in Adults
- Less in in infants

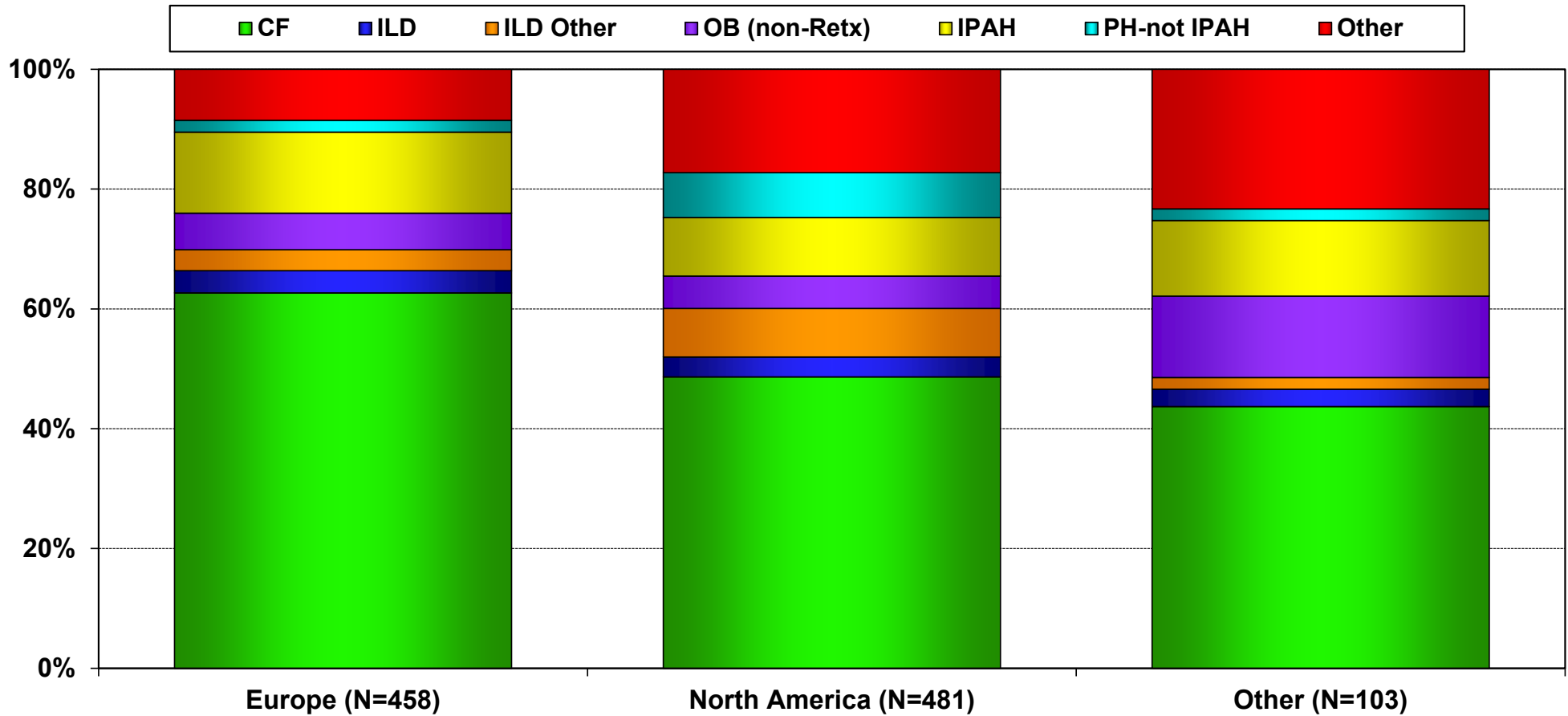
Fungal and ATM Colonization

- PreTx Eradication vs. PostTx Prophylaxis
- Problematic with Single LT

Psychosocial Issues

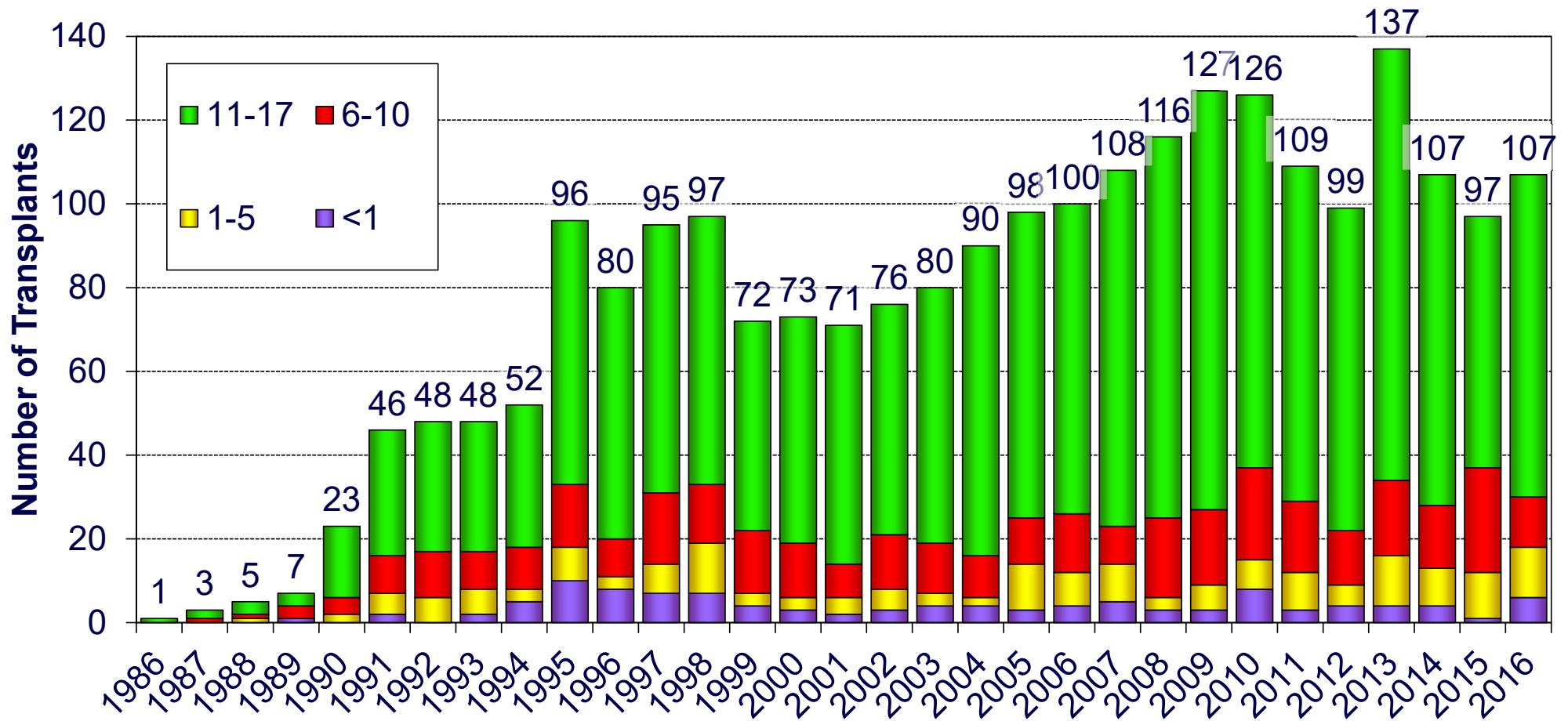
- Major Psychoaffective Disorders
- Refractory Nonadherence

Pediatric Lung Transplants: Diagnosis Distribution by Location



(Transplants: January 2008 – June 2017)

Pediatric Lung Transplants: Recipient Age Distribution by Year of Transplant



Lung Transplant Diagnoses: Infancy

Parenchymal Disease

- ChILD
 - SPB, SPC, ABCA3, NKX2.1
- Filamin A
- Rarely BPD

Pulmonary Vascular Disease

- PH related to CHD
- ACD / MPV
- Pulmonary Vein Stenosis

Mixed

- CDH with pulmonary hypoplasia and PH

Lung Transplant in Infants & Toddlers

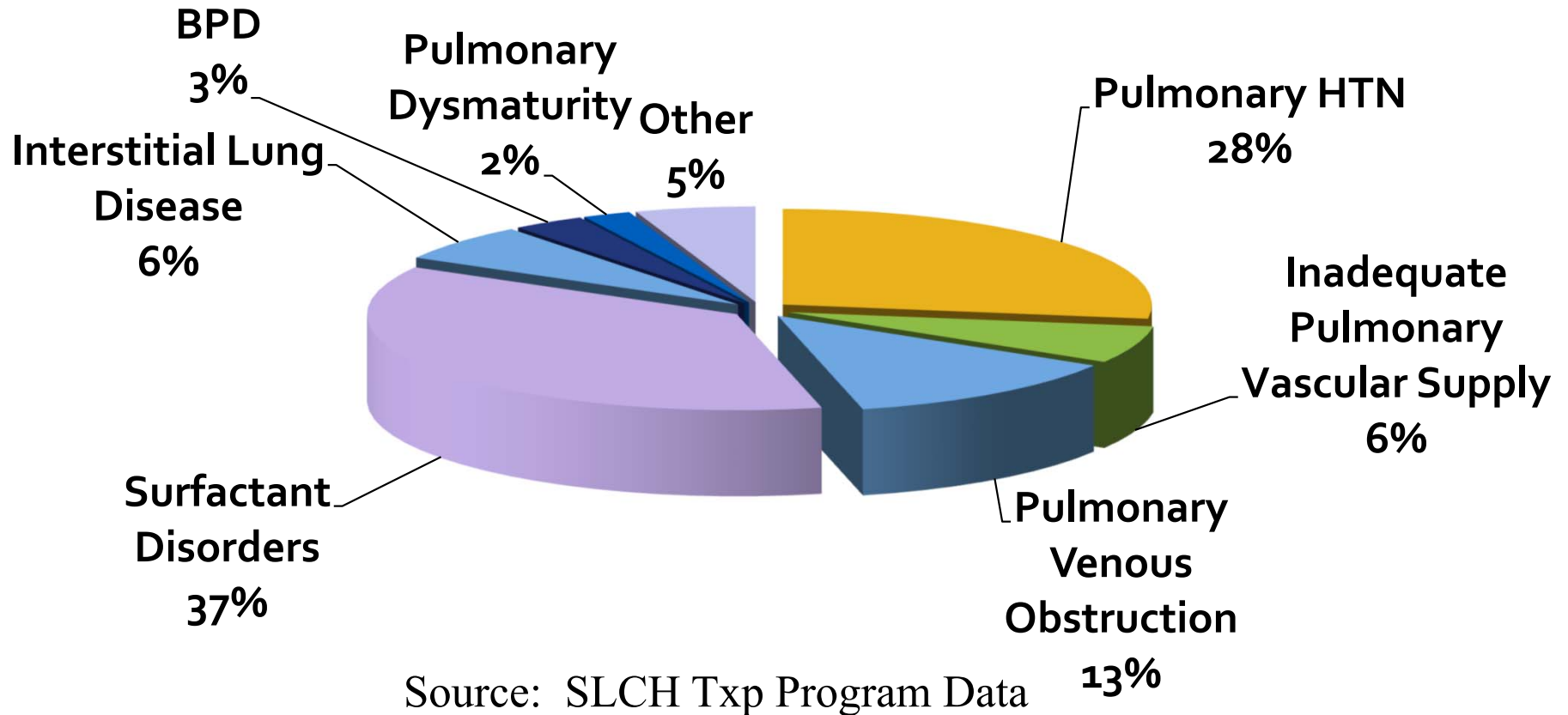
Added Challenges

- Lung Function Assessment
- Bronchoscopy / Biopsy
- Lung Growth

Specific Infant Requirements

- Weight > 3.5 kg
- EGA > 26-28 weeks
- No other organs involved
- Stable for Transport

Infant and Toddler Diagnoses



Timing of Referral

- Early! – No downside
- Cystic Fibrosis & Bronchiectasis
 - $FEV_1 < 40\text{-}50\%$ predicted for children (Ramos et al. JCF 2019 18(3):321-333)
- Pulmonary Hypertension
 - Progressive disease despite therapy
 - $CI < 2.0$ L/min/m², RA pressure > 15 mm Hg, Mean PA pressure > 55 mm Hg
 - Hemoptysis, syncopal episodes
 - Consider Pott's Shunt (Aggarwal et al Circulation:cardiovascular imaging 2018 11(12))
- Infants with congenital respiratory failure (SBP, ABCA3, NKX2.1), PVS - soon
- Other Diseases Less Clear

Lung Transplant Evaluation

Pulmonary Function Testing

- Spirometry
- Lung Volumes
- DLCO
- Blood Gases

Studies

- CXR
- Chest CT
- Echo / Cath?
- Consider VQ
- 6 MWT

Laboratory

- Comprehensive Metabolic Panel
- Viral Serologies
- Sputum Culture
- HLA Antibodies

Psychosocial Evaluation

- Social Work
- Psychology
- Child Life
- Financial

Pre-Transplant Case #1

- Full term infant with Respiratory Distress Syndrome
 - 3.9 kg infant born at 40 weeks.
 - Respiratory distress at birth
 - Intubated in the Delivery Room.
 - CXR with ground glass infiltrates.
 - Minimal response to surfactant administration.
 - Now 2 weeks old with slowly increasing respiratory support.
 - Open lung biopsy with alveolar proteinosis.

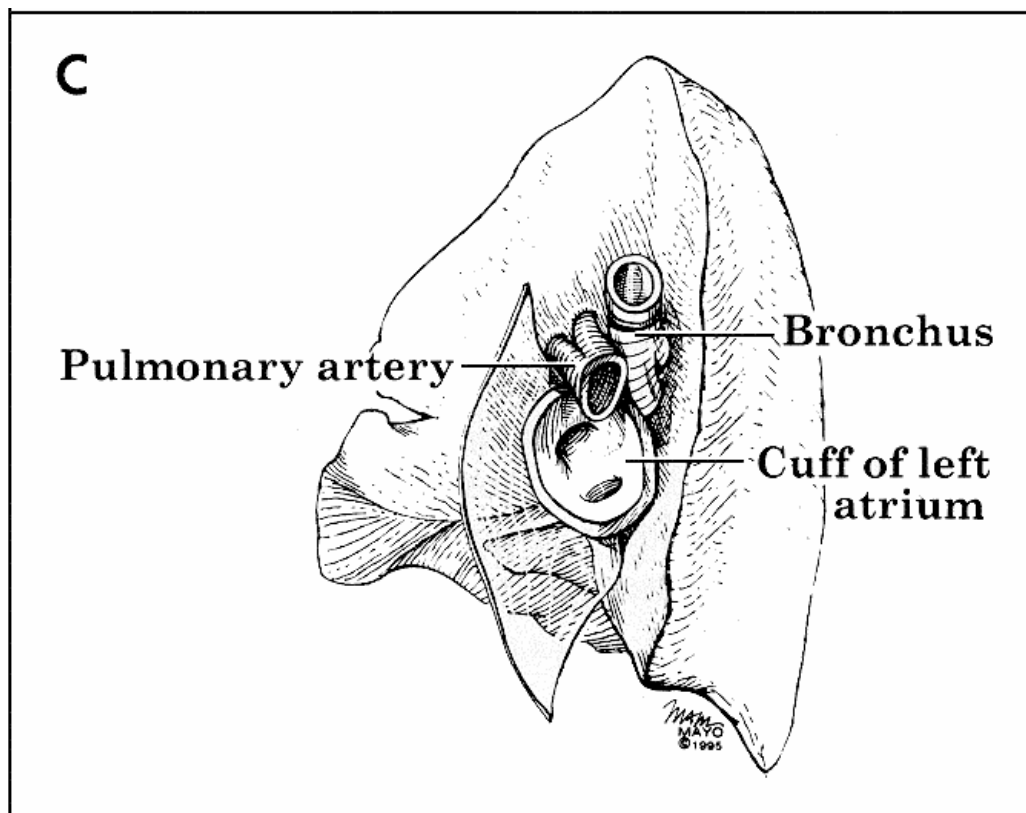
Pre-Transplant Case #1

- For this term infant with RDS, what is the least likely diagnosis?
 - a) ABCA3 Transporter Deficiency
 - b) Surfactant Protein B Deficiency
 - c) NKX2.1 Mutation
 - d) Surfactant Protein C Deficiency

Pre-Transplant Case #1

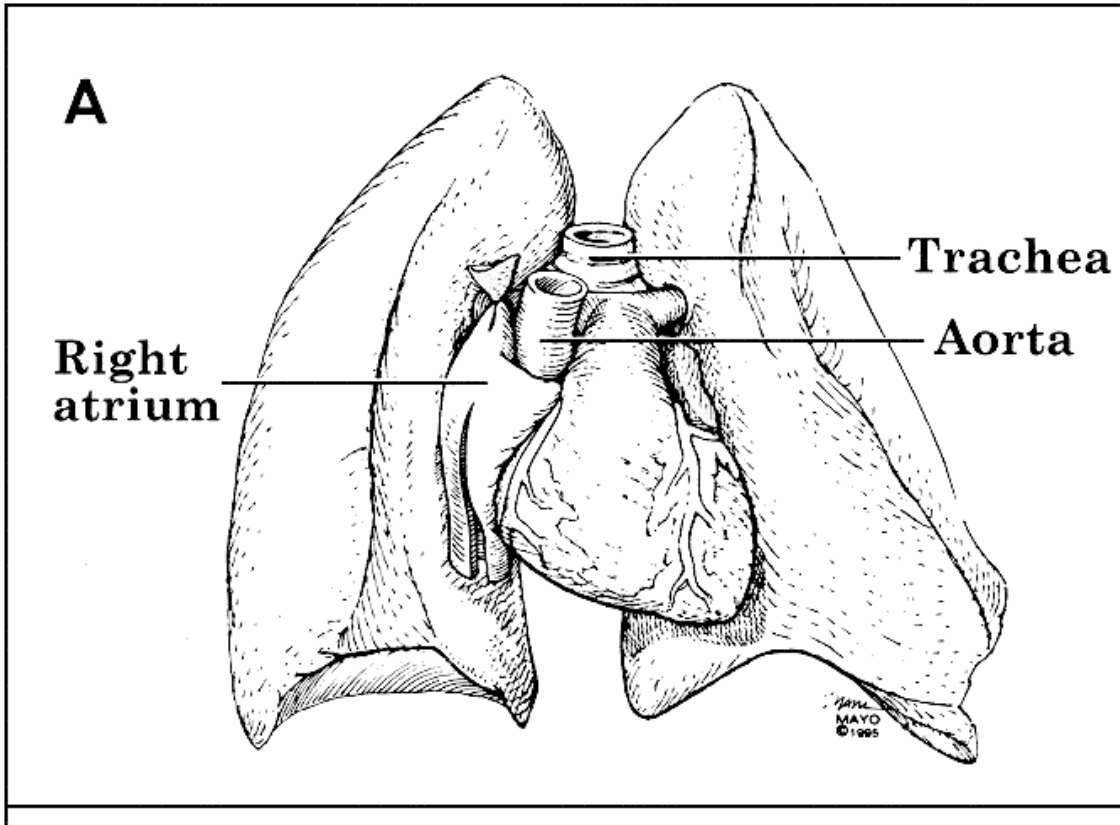
- For this term infant with RDS, what is the least likely diagnosis?
 - a) ABCA3 Transporter Deficiency
 - b) Surfactant Protein B Deficiency
 - c) NKX2.1 Mutation
 - d) **Surfactant Protein C Deficiency**

Lung Transplant Operation



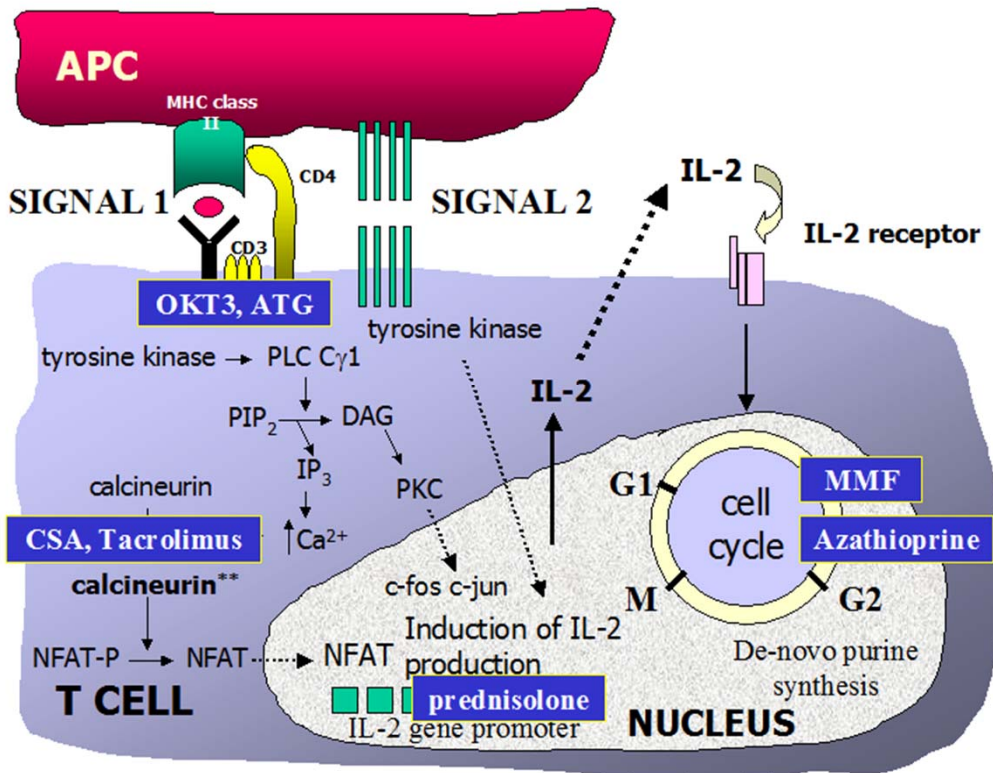
- Bilateral Sequential
 - Most Common in Pediatrics
 - Clamshell incision
 - CPB or ECMO
- En bloc
 - Median sternotomy
 - Tracheal anastomosis
- Single Lung Transplant
 - Rare

Lung Transplant Operation



- Heart Lung Transplant
 - LV failure
 - Irreparable congenital cardiac abnormality
 - Waiting times longer
 - Outcomes track with lung transplant

Initial Post-transplant Therapies



- Empiric Antibiotics
 - Cover pre-transplant organisms
 - Cover any organisms in donor
- Prophylactic Antibiotics
 - Antifungals (i.e. posaconazole)
 - CMV/HSV (Valgan / Valacyclovir)
 - PJP (TMP/SMX)
 - Candida (Nystatin)

Pediatric lung transplant - Overview

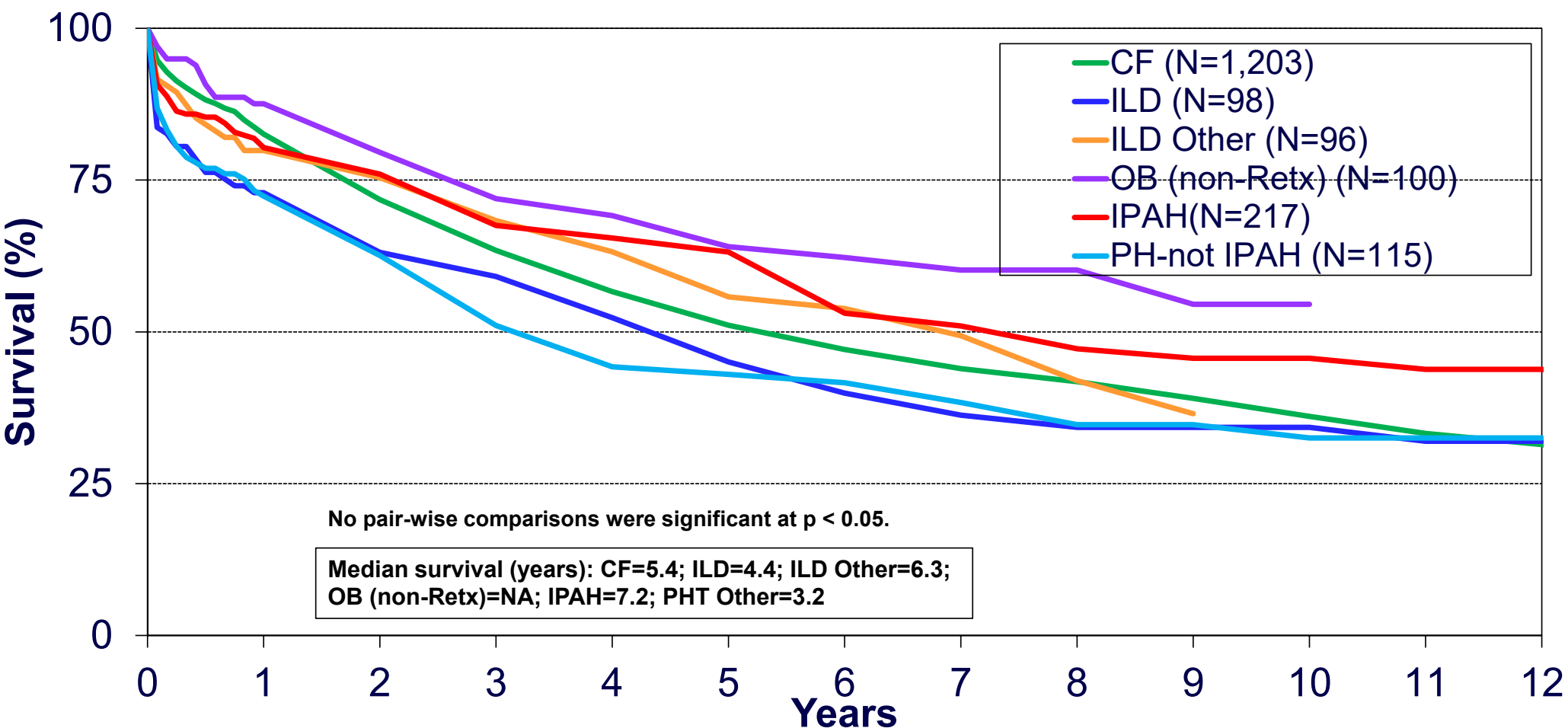
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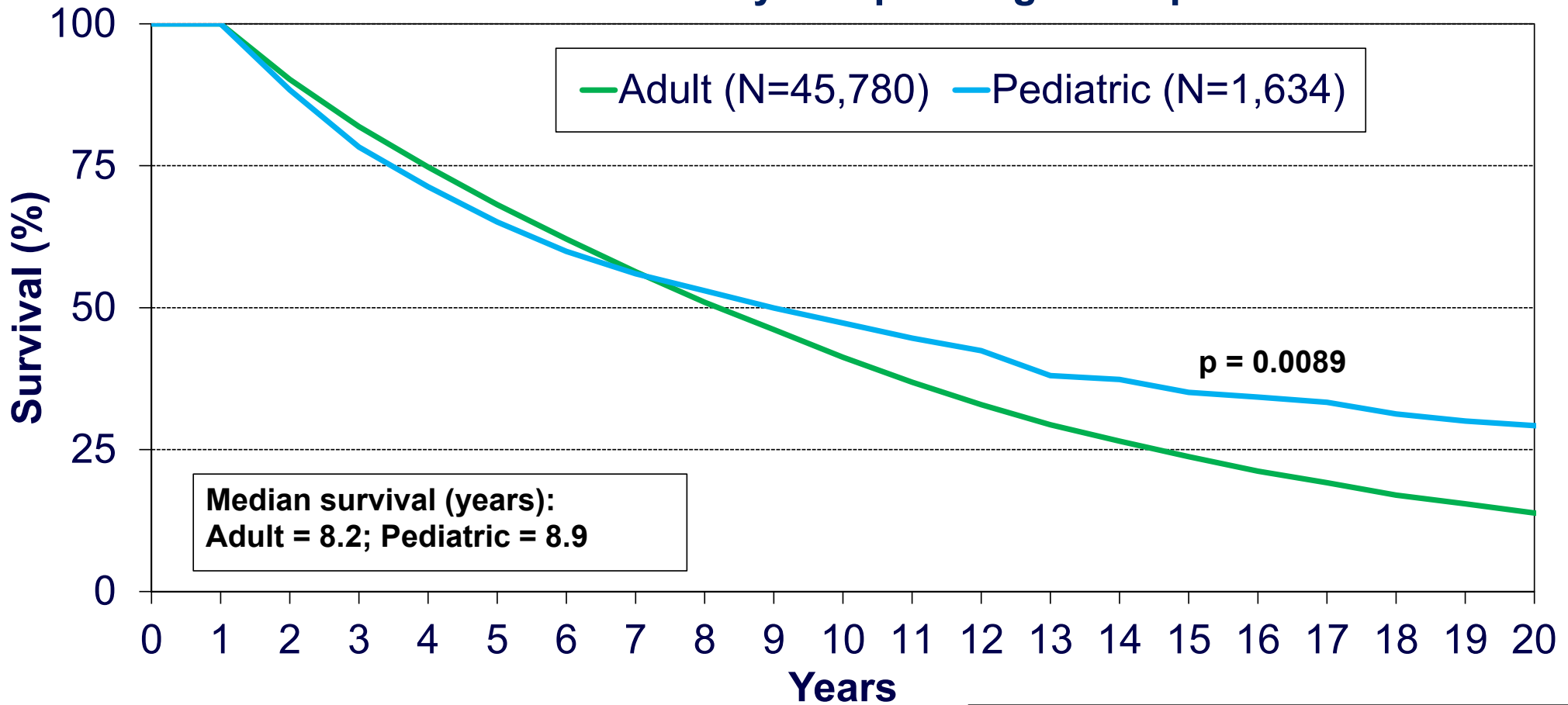


Pediatric Lung Transplants: Kaplan-Meier Survival by Diagnosis



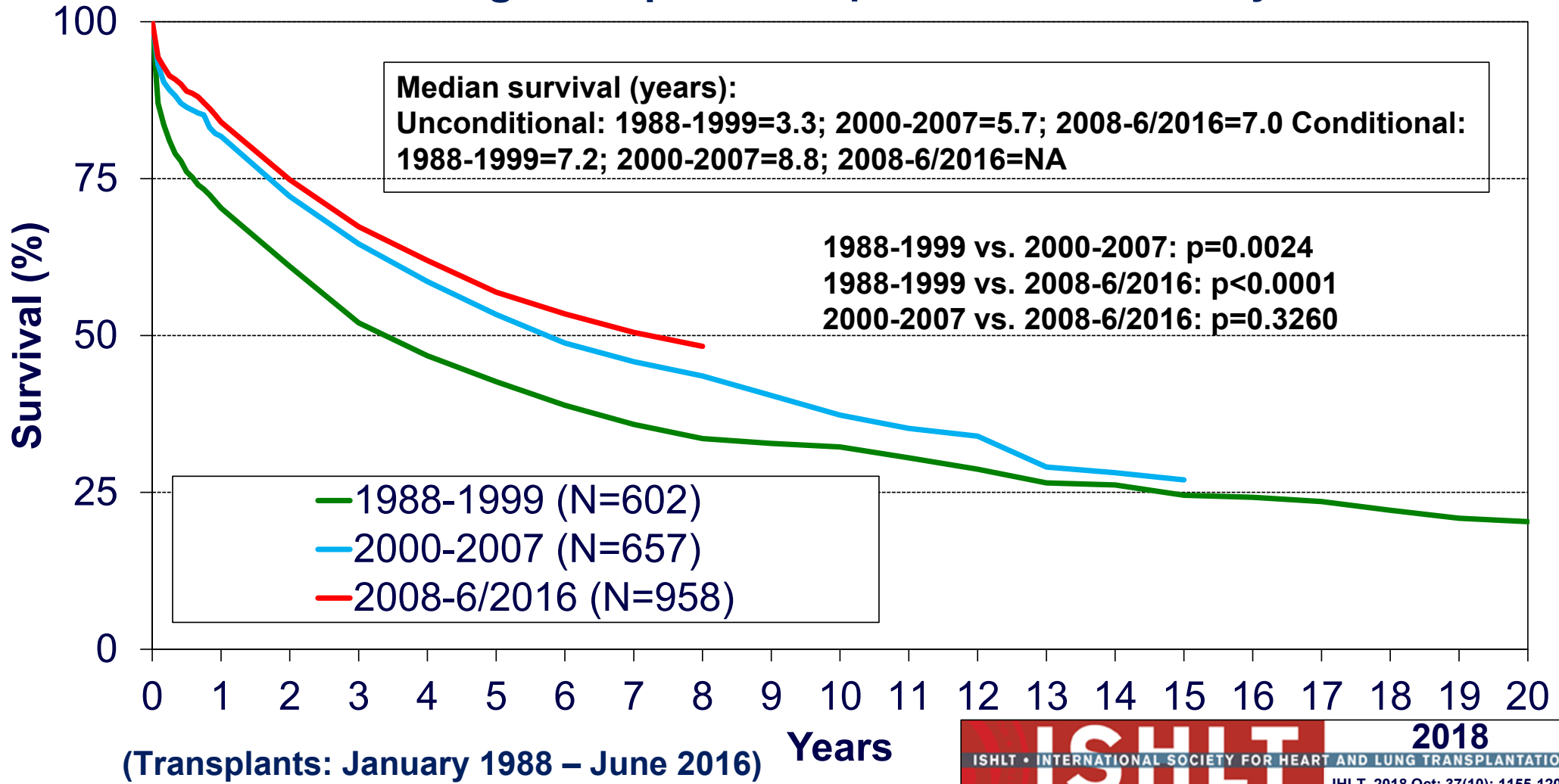
(Transplants: January 1990 – June 2016)

Lung Transplants: Kaplan-Meier Survival Conditional on Survival to 1 Year by Recipient Age Group

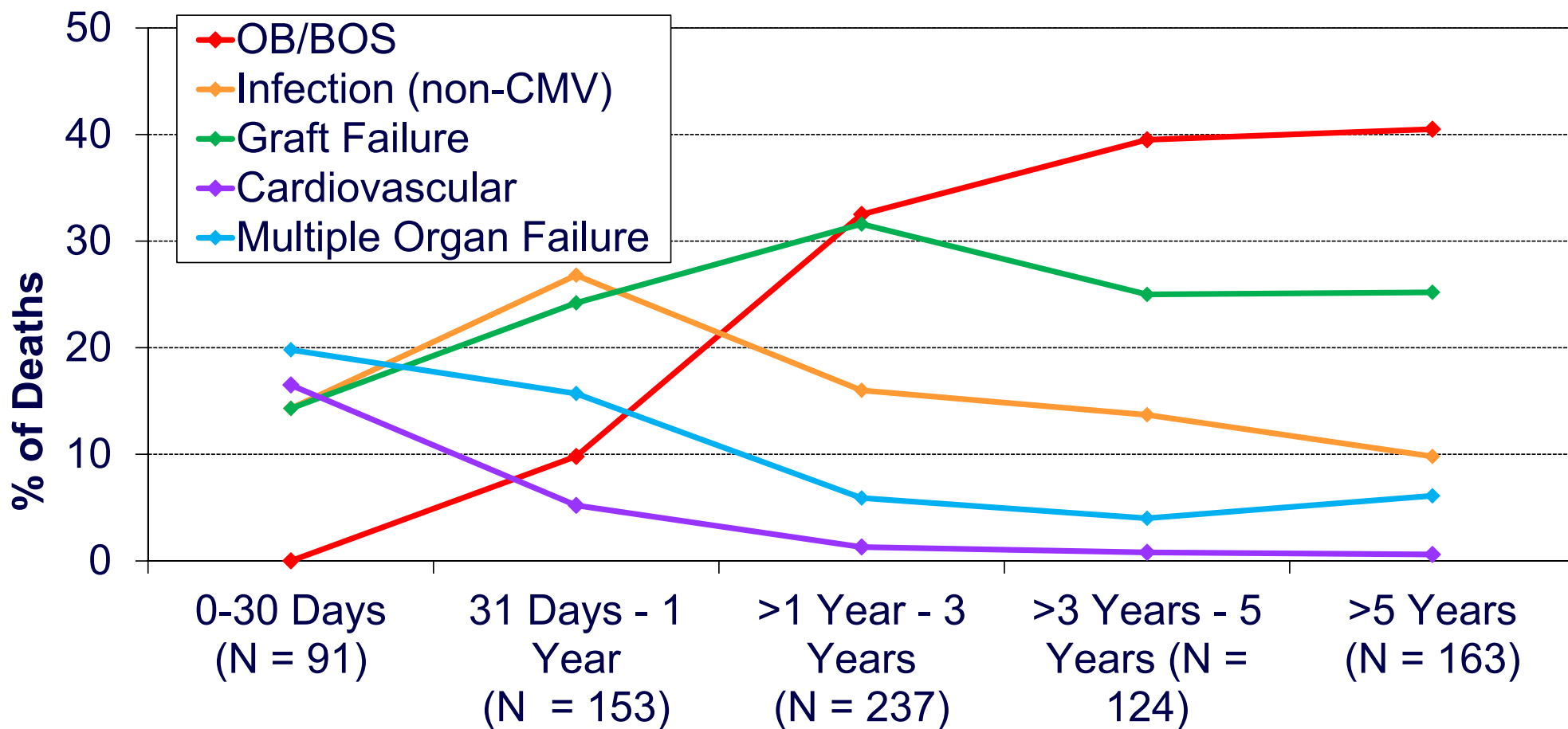


(Transplants: January 1990 – June 2016)

Pediatric Lung Transplants: Kaplan-Meier Survival by Era



Pediatric Lung Transplants: Relative Incidence of Leading Causes of Death



(Deaths: January 2000 – June 2017)

Complications - Overview

Three Phases of Transplant

- Immediate (First Week)
- Early (1 Week to 3 Months)
- Late (after 3 Months)

Four Complication Categories

- Immunologic (rejection)
- Infectious
- Surgical
- Other

Immediate Complications

- Hyperacute Rejection
 - Rarely seen
- Early Graft Dysfunction
 - Aka “reimplantation response”, “ischemia/reperfusion injury”
- Infection
- Surgical Complications
 - Bleeding
 - Anastomosis Breakdown
 - Vascular complications

Post-Transplant Case #1

- You are caring for a 12 y/o patient with pulmonary hypertension who had a lung transplant 6 hours ago.
 - Ischemic times 7:00 R, 7:45 L
 - Pre-transplant PRA 0%
- In the past 2 hours he has developed:
 - diffuse pulmonary infiltrates
 - poor lung compliance
 - moderate gas exchange abnormalities

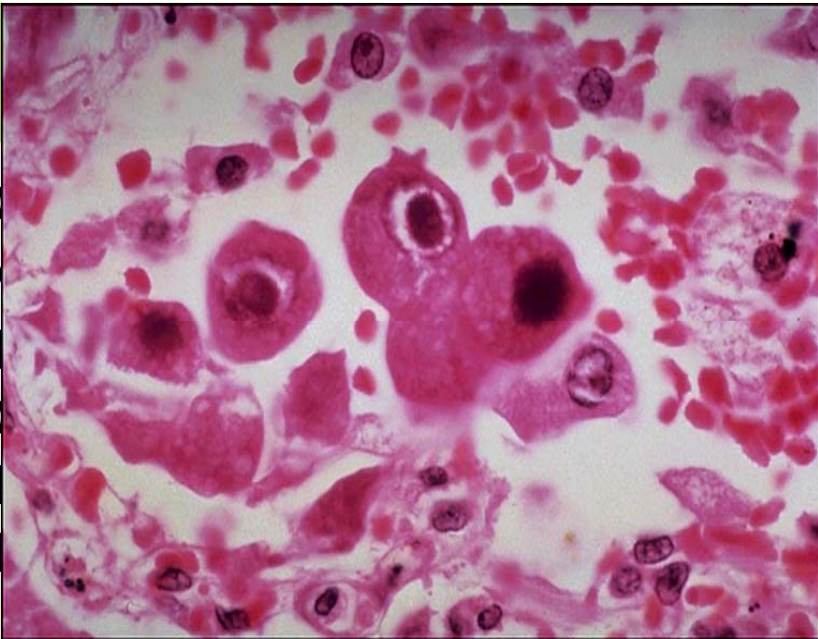
Post-Transplant Case #1

- What is the most likely diagnosis for this lung transplant recipient with severe graft dysfunction:
 - a) Acute rejection
 - b) Donor viral infection
 - c) Pulmonary vein obstruction
 - d) Primary Graft Dysfunction

Post-Transplant Case #1

- What is the most likely diagnosis for this lung transplant recipient with severe graft dysfunction:
 - a) Acute rejection
 - b) Donor viral infection
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 - d) **Primary Graft Dysfunction**

Early Complications - Infection



Viruses

- CMV (ganciclovir prophylaxis)
- Adenovirus
- RSV

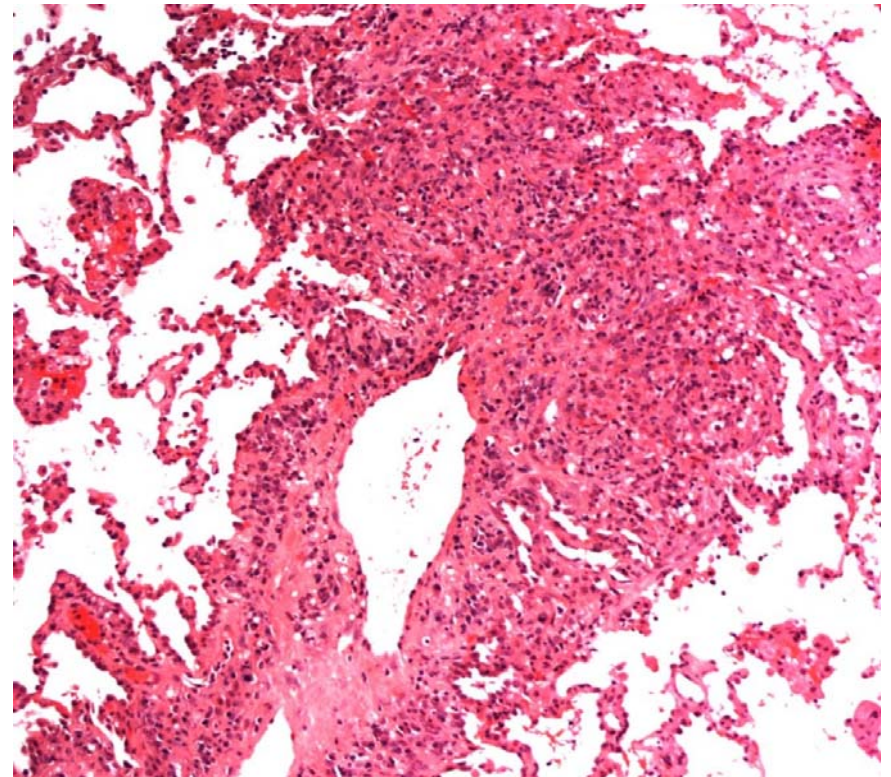
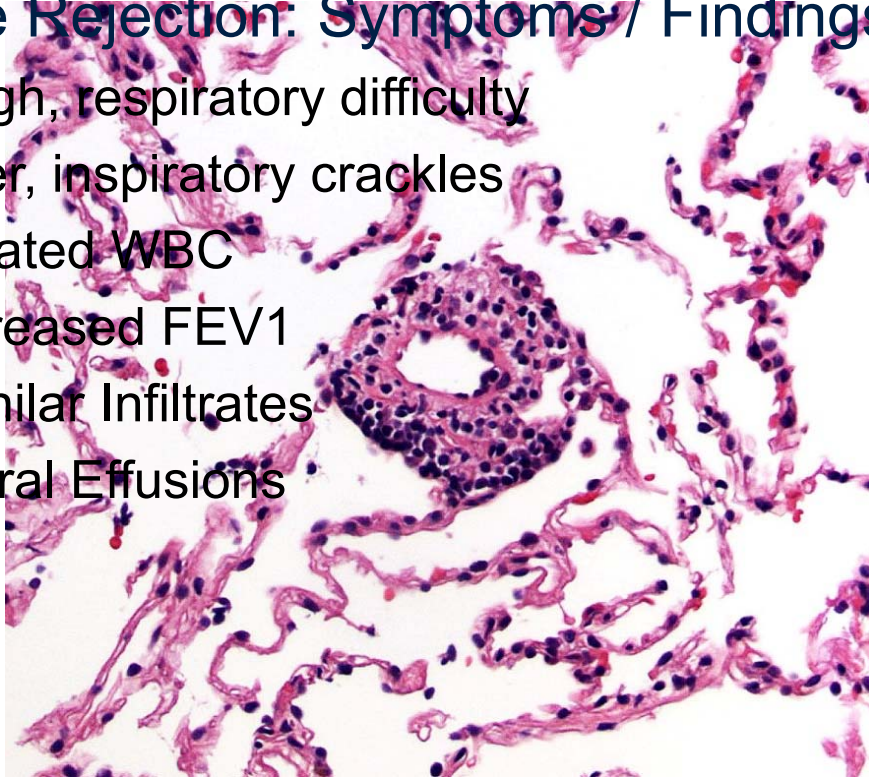
Opportunistic

- PJP

Photo: Yousem, S. 3rd Banff
Conference on Allograft Pathology

Early Complications – Acute Rejection

- Acute Rejection: Symptoms / Findings
 - Cough, respiratory difficulty
 - Fever, inspiratory crackles
 - Elevated WBC
 - Decreased FEV1
 - Perihilar Infiltrates
 - Pleural Effusions



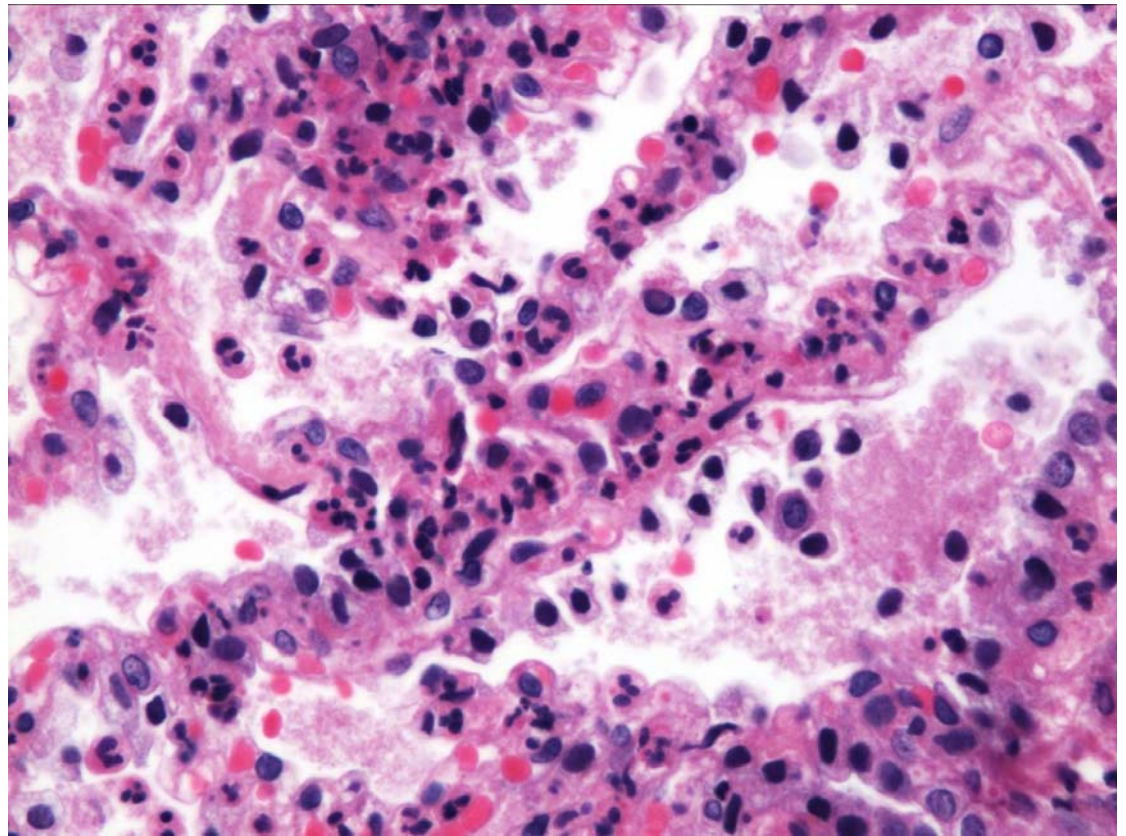
A2 Images Courtesy F. White, Washington University **A3**

Early Complications – Acute Rejection

- Acute Rejection – Treatment
 - Pulse steroids (methylprednisolone 10 mg/kg IV x 3 doses)
 - Reassess (i.e. biopsy 2 wk post rx)
 - Consider additional therapy if worse (more steroids, Antithymocyte globulin)

Early Complications – Humoral Rejection

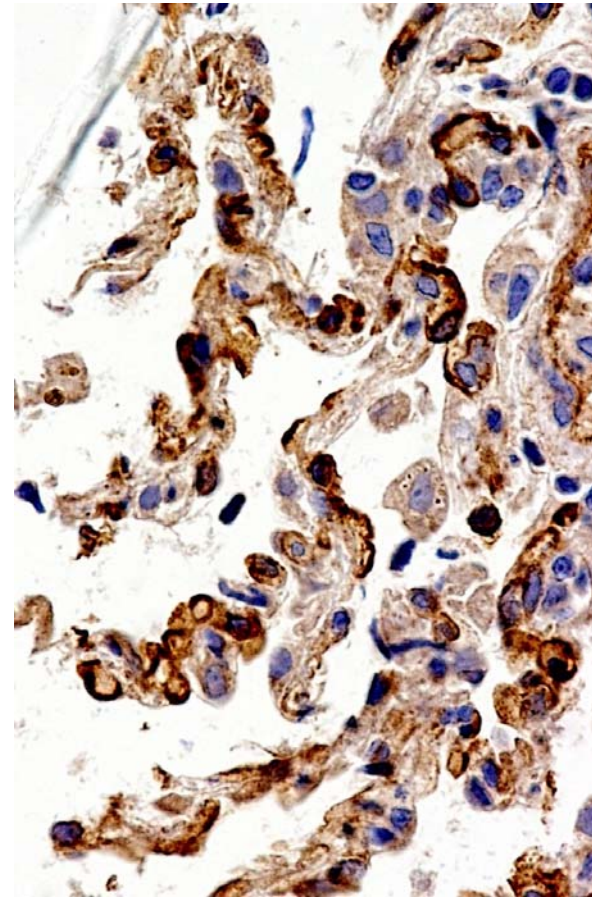
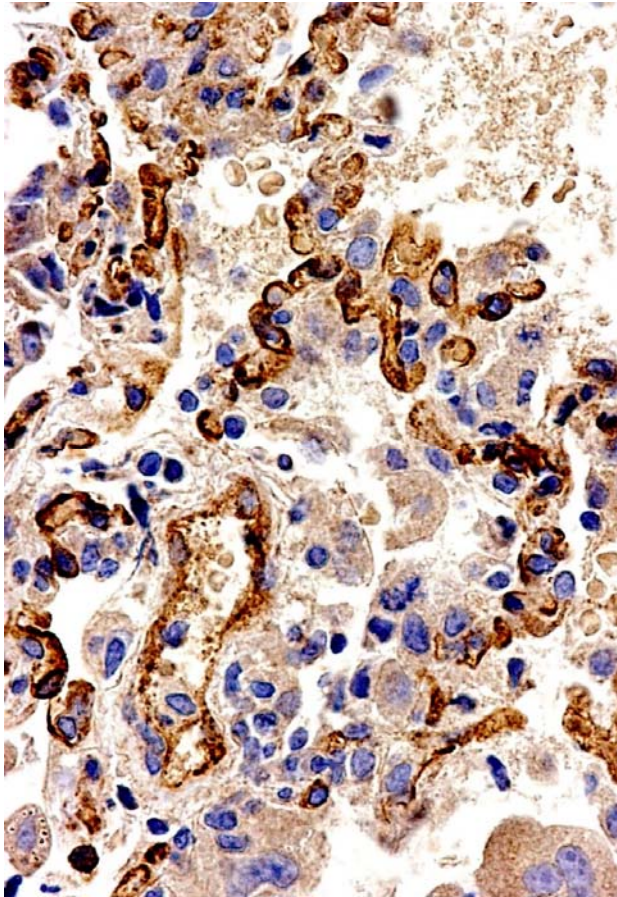
- Humoral Rejection – Symptoms / Findings
 - Can be asymptomatic
 - Inspiratory crackles
 - Decreased FEV1
 - Presence of donor specific HLA antibodies
 - Positive C4d capillary loop staining



Capillaritis

Image Courtesy F. White, Washington University

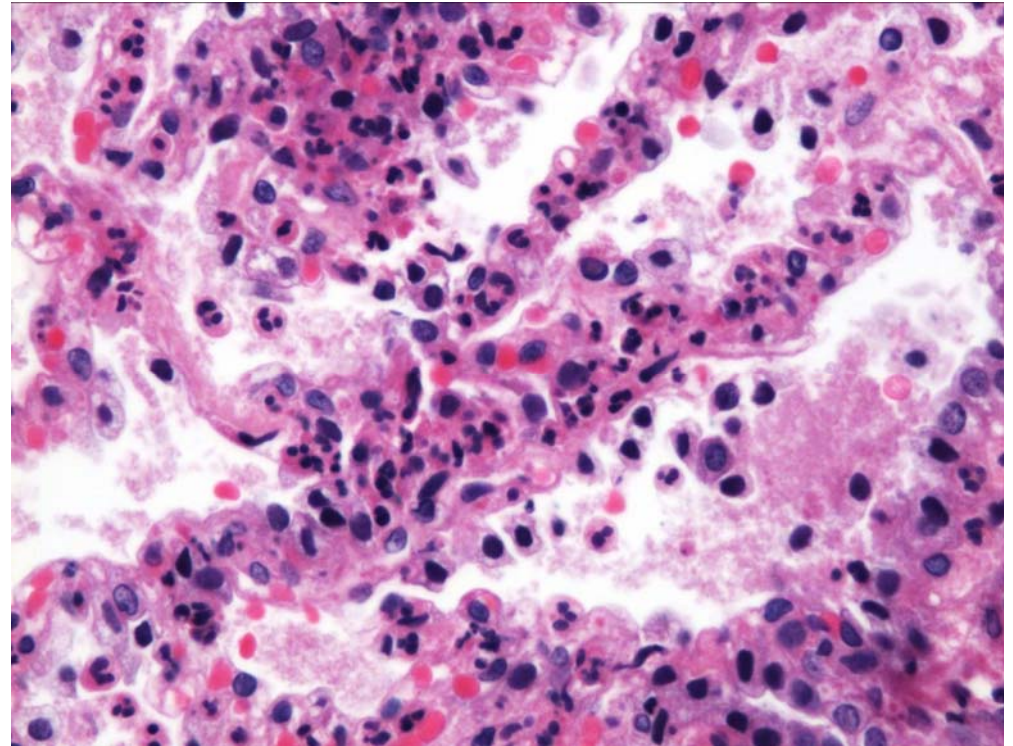
Positive C4d Staining



Images
Courtesy F.
White,
Washington
University

Early Complications – Humoral Rejection

- Humoral Rejection – Treatment
 - Many options - Controversial
 - Plasma Exchange
 - Proteasome Inhibitors (carfilzomib)
 - B-Cell depletion (rituximab)
 - Complement Inhibition (eculizumab)
 - Pulse Steroids
 - Antithymocyte globulin



Capillaritis

Image Courtesy F. White, Washington University

Early Complications

- **Surgical Complications**

- **Airway anastomosis narrowing / malacia:**

- More common in infants, related to ischemic injury to mainstem bronchi
 - Present with respiratory difficulty, obstruction on spirometry
 - Treated by serial dilation with balloon catheter
 - Rarely require placement of endobronchial stent

- **Airway dehiscence:**

- Can be asymptomatic
 - Can present with pneumomediastinum on CXR / CT

- **Diaphragm Paresis**

- Cases with recurrent infection/atelectasis treated with plication

- **Vocal Cord Paresis**

Early Complications

- Other Complications
 - Hypertension – common side effect of CNI use
 - Seizures / posterior reversible encephalopathy syndrome (PRES)
 - Associated with elevated CNI levels
 - Renal Failure
 - Usually in patients with preexisting renal dysfunction
 - Gastrointestinal
 - Delayed Gastric Emptying
 - May make reflux more likely
 - Aspiration can be a major issue
 - DIOS in CF Patients
 - Arrhythmias
 - Often SVT

Post-Transplant Case #2

- You are evaluating an 8 y/o with CF, 2 months post transplant with fever and cough
 - Vitals: tachypnea, SaO₂: 92-94% RA
 - PFTs: refuses at home, down in lab
 - Exam: mild distress, crackles at bases
 - CBC: WBC 18K, no left shift CXR: perihilar infiltrates, small right pleural effusion
 - Bronchoscopy: anastomoses intact and patent, no airway mucus, BAL gram stain – moderate polys, no organisms

Post-Transplant Case #2

- What is the most likely diagnosis for this transplant recipient with fever and cough :
 - a) Community acquired pneumonia
 - b) Acute Cellular Rejection
 - c) Viral Pneumonia
 - d) Bacteremia

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- What is the most likely diagnosis for this transplant recipient with fever and cough :
 - a) Community acquired pneumonia
 - b) **Acute Cellular Rejection**
 - c) Viral Pneumonia
 - d) Bacteremia

Late Complications

- Infection, Acute and/or Humoral Rejection...
- Developmental delay (particularly in infants)
- Renal Failure
- Diabetes
- Malignancy
- Chronic Lung Allograft Dysfunction (CLAD)

Pediatric Lung Transplants

Cumulative Morbidity Rates in Survivors within 1, 5 and 7 Years Post-Transplant (Transplants: January 1994 – June 2016)

Outcome	<u>Within 1 Year</u>	Total N with <u>known</u> response	<u>Within 5 Years</u>	Total N with <u>known</u> response	<u>Within 7 Years</u>	Total N with <u>known</u> response
Severe Renal Dysfunction¹	2.0%	(N = 843)	6.1%	(N = 327)	7.8%	(N = 204)
<i>Creatinine > 2.5 mg/dl</i>	1.5%		4.3%		5.9%	
<i>Chronic Dialysis</i>	0.4%		1.2%		1.0%	
<i>Renal Transplant</i>	0.1%		0.6%		1.0%	
Diabetes²	18.8%	(N = 848)	28.6%	(N = 336)	-	
Bronchiolitis Obliterans Syndrome	9.3%	(N = 794)	36.9%	(N = 260)	45.1%	(N = 153)

¹ Severe renal dysfunction = Creatinine > 2.5 mg/dl (221 µmol/L), dialysis or renal transplant

² Data are not available 7 years post-transplant.

Late Complications

- Infection, Acute and/or Humoral Rejection...
- Developmental delay (particularly in infants)
- Renal Failure
- Diabetes
- **Malignancy**
 - Post Transplant Lymphoproliferative Disease (PTLD)
 - Other malignancies
- **Chronic Lung Allograft Dysfunction (CLAD)**
 - Bronchiolitis Obliterans (OB)
 - Restrictive Allograft Syndrome (RAS)

Pediatric Lung Transplants

Cumulative Post-Transplant Malignancy Rates in Survivors

(Transplants: January 1994 – June 2016)

Malignancy/Type		1-Year Survivors	5-Year Survivors	7-Year Survivors
No Malignancy		814 (95.0%)	316 (90.8%)	203 (90.2%)
Malignancy (all types combined)		43 (5.0%)	32 (9.2%)	22 (9.8%)
<i>Malignancy Type*</i>	<i>Lymphoma</i>	<i>40</i>	<i>31</i>	<i>21</i>
	<i>Other</i>	<i>2</i>	<i>1</i>	<i>0</i>
	<i>Skin</i>	<i>1</i>	<i>0</i>	<i>1</i>
	<i>Type Not Reported</i>	<i>0</i>	<i>1</i>	<i>0</i>

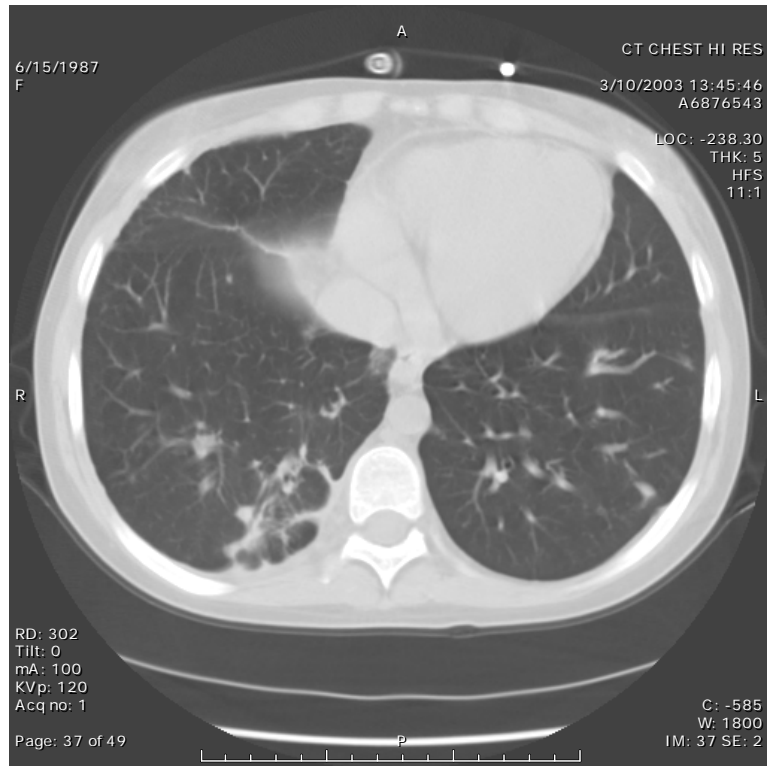
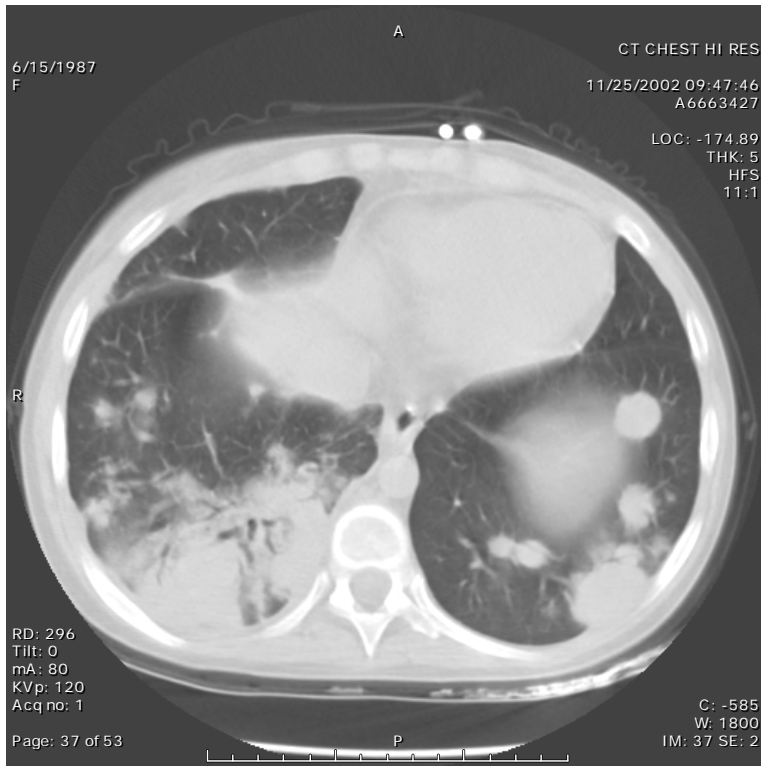
“Other” includes liver and primitive neuroectodermal tumor.

* Recipients may have experienced more than one type of malignancy so the sum of individual malignancy types may be greater than the total number with malignancy.

Malignancies

- PTLD
 - Usually B-cell non-Hodgkins lymphoma
 - 5-15% of patients
 - Associated with EBV infection
 - Risk factors include CF and acute rejection episodes
 - Elevated EBV PCR sensitive but not specific
 - Initial therapy: rituximab ± low dose cyclophosphamide / prednisone
 - Some patients require chemotherapy
- Other malignancies
 - Skin Cancer

PTLD

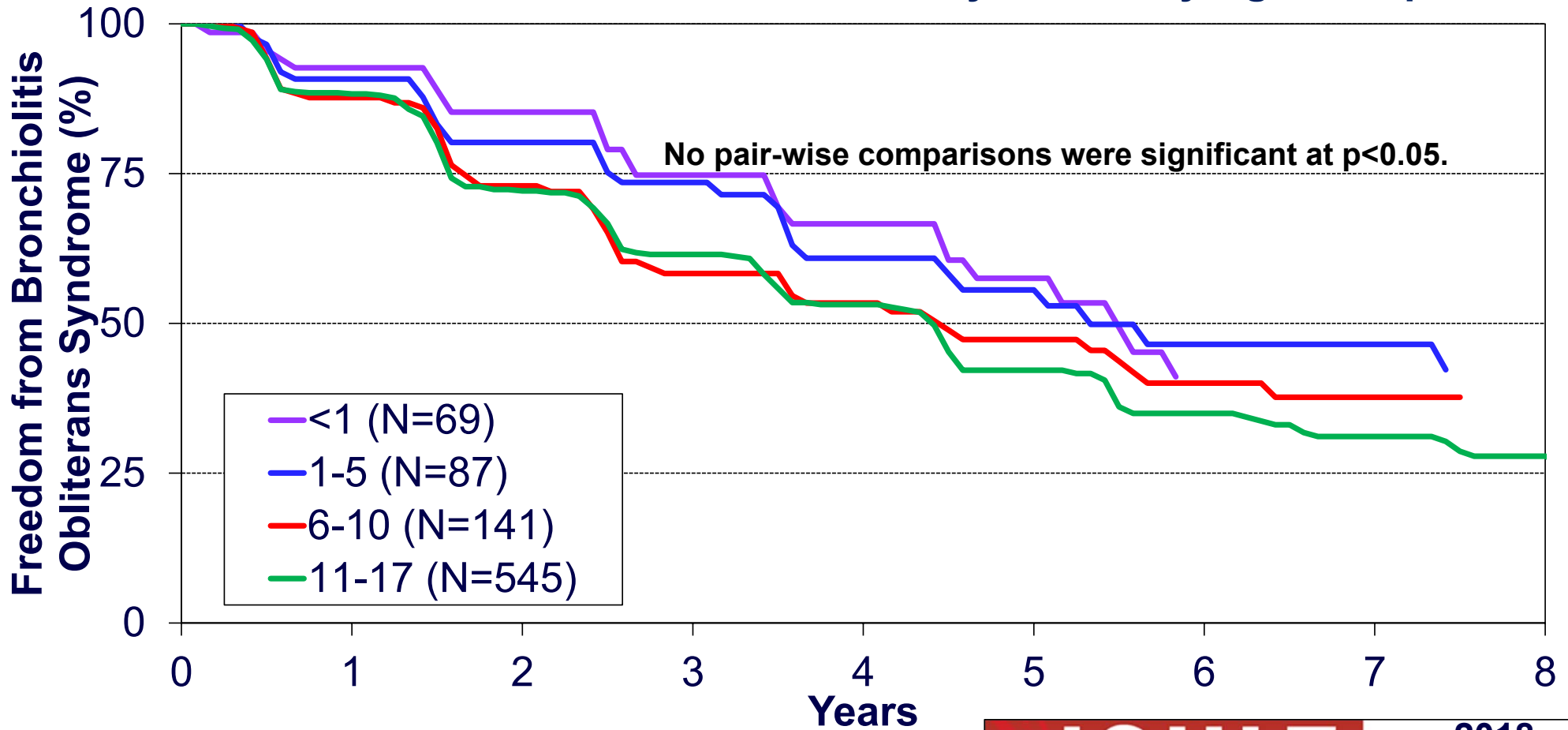


Late Complications

- Infection, Acute and/or Humoral Rejection...
- Developmental delay (particularly in infants)
- Renal Failure
- Diabetes
- Malignancy
 - Post Transplant Lymphoproliferative Disease (PTLD)
 - Other malignancies
- **Chronic Lung Allograft Dysfunction (CLAD)**
 - Bronchiolitis Obliterans (OB)
 - Restrictive Allograft Syndrome (RAS)

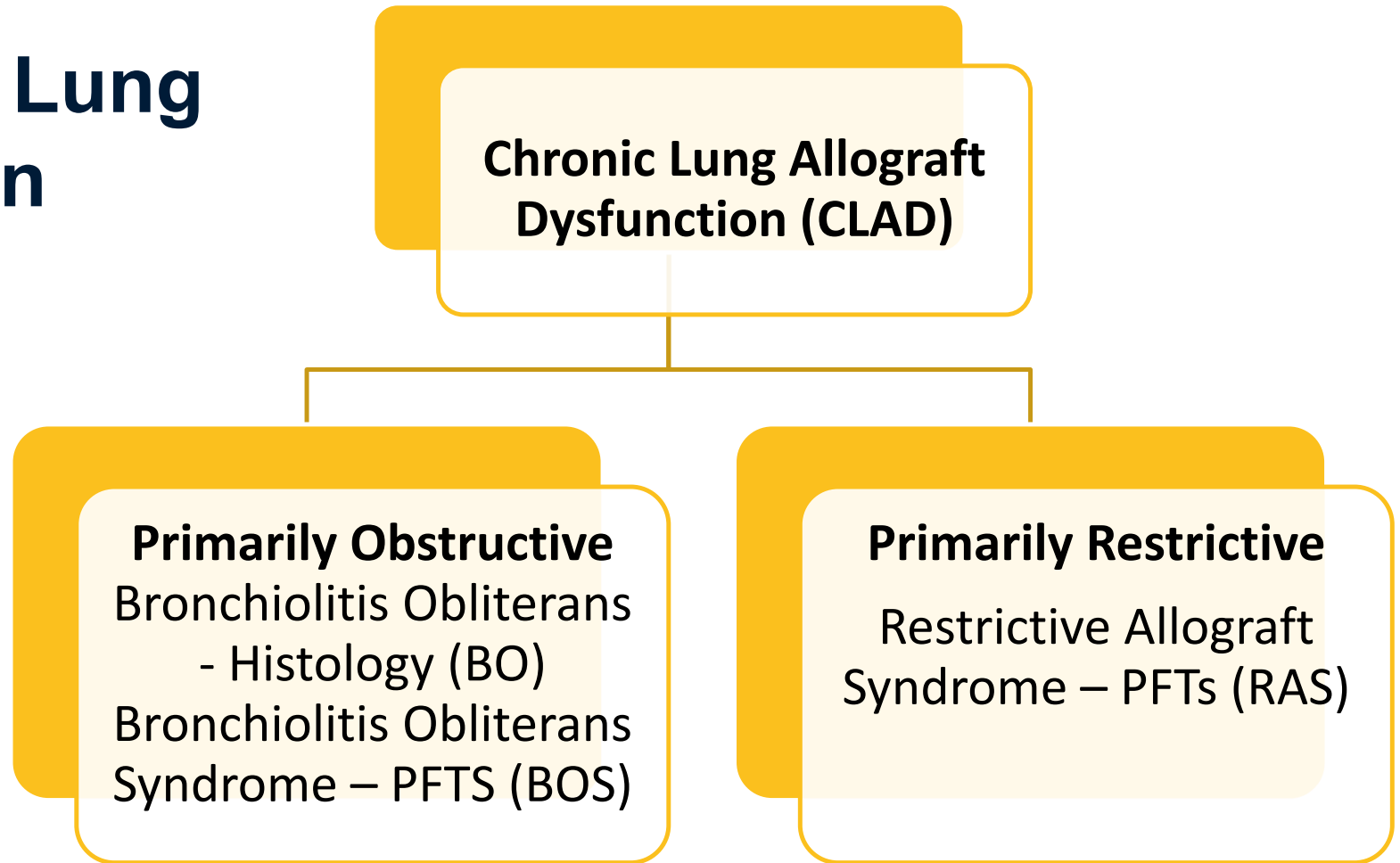
Pediatric Lung Transplants

Freedom from Bronchiolitis Obliterans Syndrome by Age Group



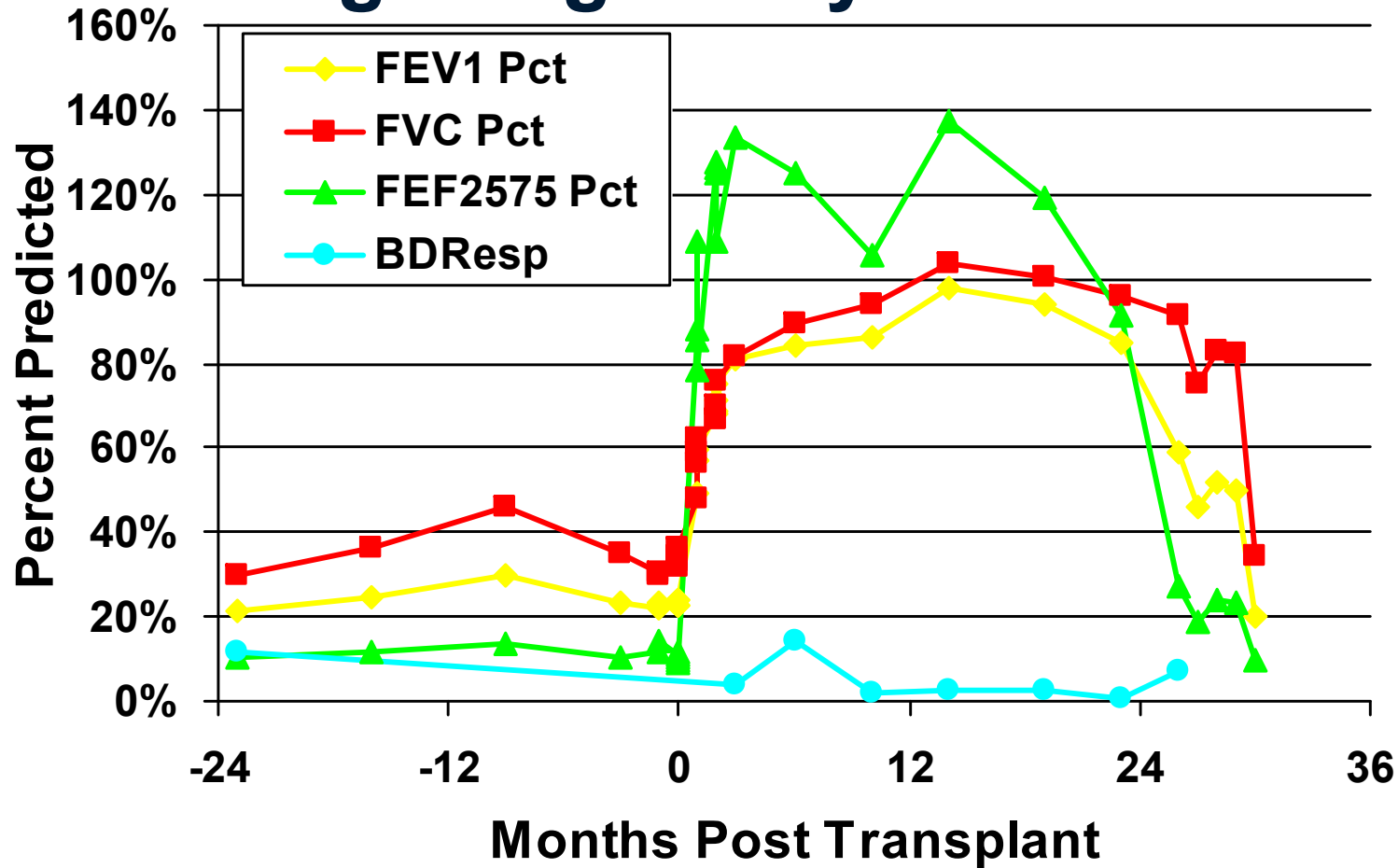
(Transplants: January 1994 – June 2016)

Chronic Lung Rejection

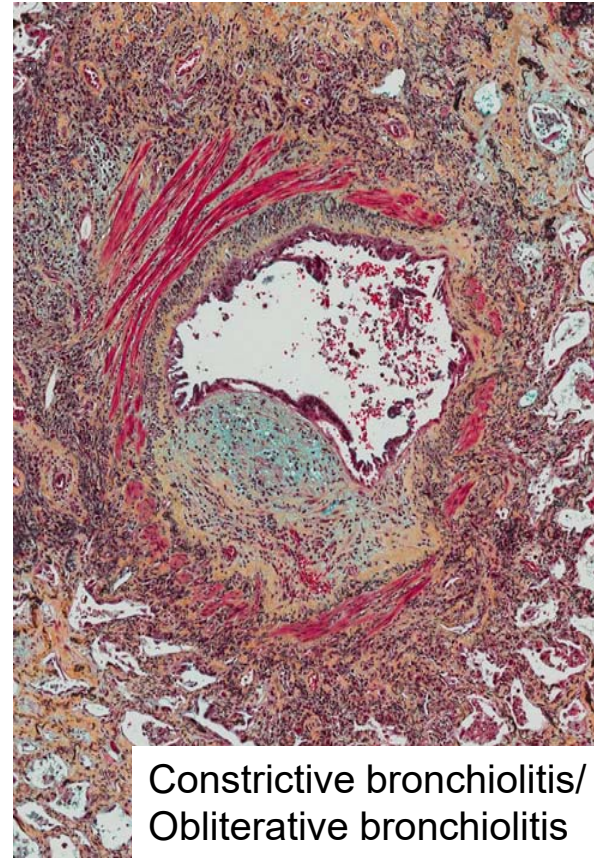
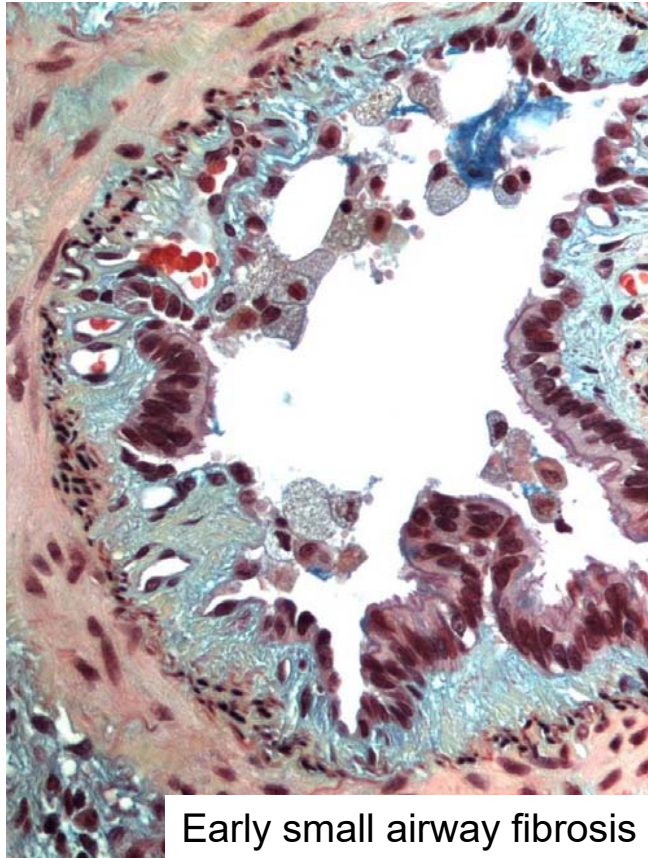


J Heart Lung Transplant 2014;33:127–133

Chronic Lung Allograft Dysfunction

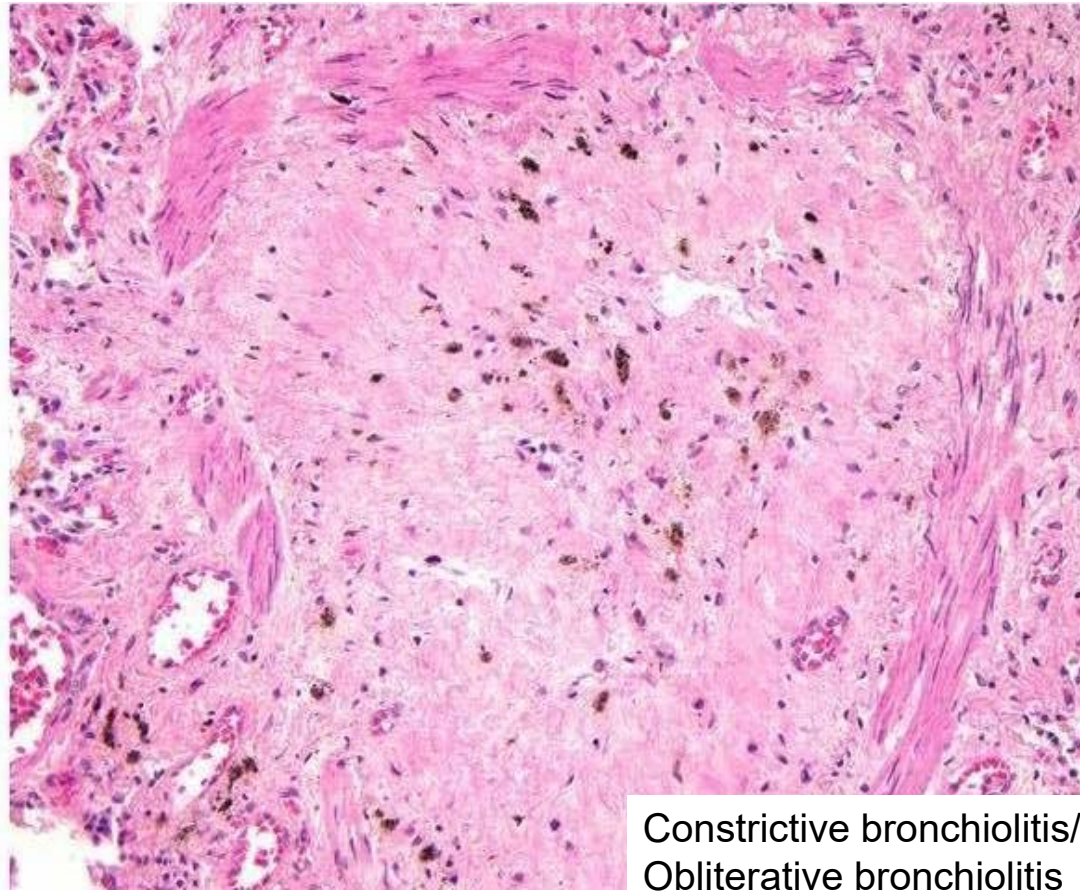


Bronchiolitis Obliterans



Images Courtesy F. White, Washington University

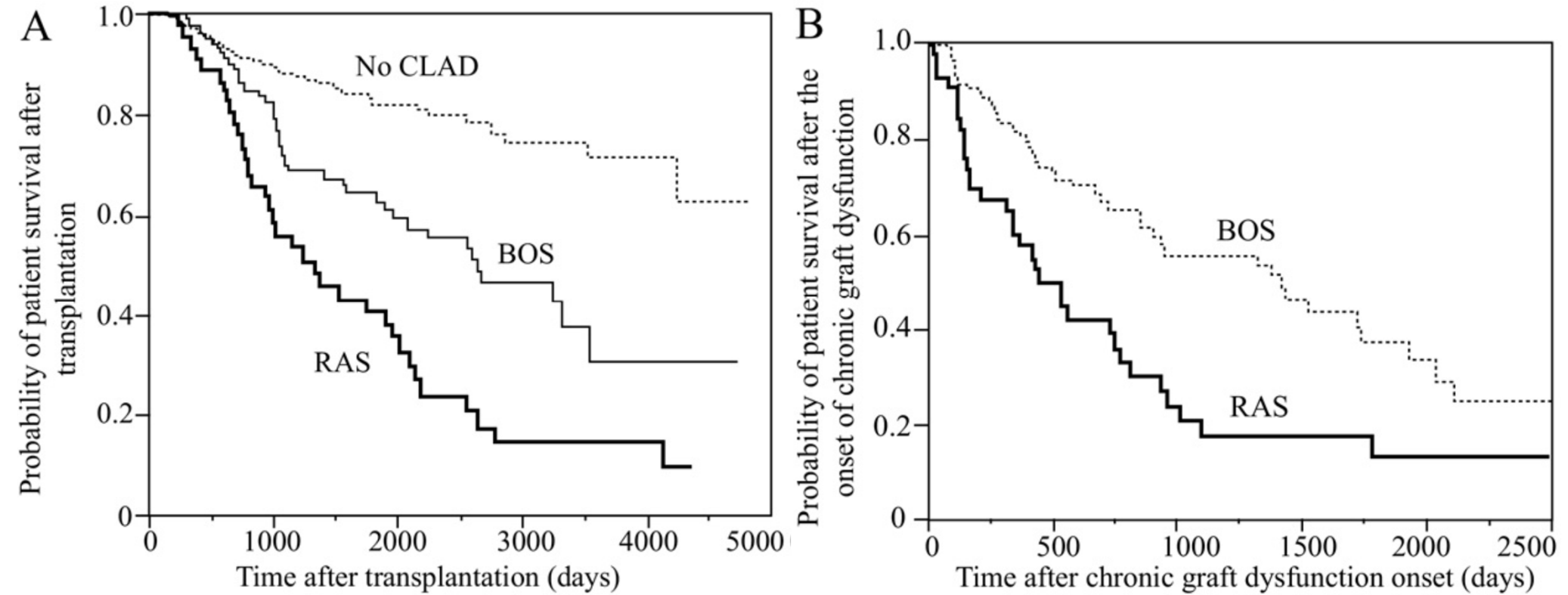
Bronchiolitis Obliterans



Constrictive bronchiolitis/
Obliterative bronchiolitis

Image Courtesy F. White, Washington University

CLAD Outcomes



Sato et al., *J HeartLungTransplant* 2011;30:735–42

CLAD – Risk Factors

- Acute Rejection Episodes
- Lymphocytic Bronchitis / Bronchiolitis
- Gastroesophageal Reflux
- HLA / Donor Specific Antibodies
- Autoantibodies (K- α 1-tubulin, Collagen V)
- Infections
- Primary Graft Dysfunction

CLAD – Treatment

- Augmented Immunosuppression
(T-cell directed Cytolytic therapy)
- Azithromycin
- Address GERD
- Photopheresis
- Retransplant

NO CONSISTENTLY EFFECTIVE THERAPY

Post-Transplant Case #3

- You are seeing a 16 m/o who is 9 months post transplant who presents with persistent fever, poor PO intake
 - Treated x 3 in last two months for otitis, bronchitis.
 - Exam: SaO₂: 95-97%. Irritable but consolable. Lungs Clear. Abdomen slightly distended and tender. No organomegaly.
 - CXR: nothing new, WBC normal
 - EBV PCR elevated (since 3 months post transplant)
 - Bronch: Mild right sided narrowing. Some mucus on right.
 - BAL :Gram stain negative. Culture 20 K alpha strep.
 - TBBx: Lymphocytic bronchitis, no rejection
 - CT Chest / Abdomen: focal nodules in left base, and kidney. Mesenteric thickening

Post-Transplant Case #3

- What is the most likely diagnosis for this transplant recipient with persistent fever:
 - a) Acute Rejection
 - b) Post-Transplant Lymphoproliferative Disorder
 - c) Bronchiolitis Obliterans
 - d) Fungal Pneumonia

Post-Transplant Case #3

- What is the most likely diagnosis for this transplant recipient with persistent fever:
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Pediatric lung transplant - Overview

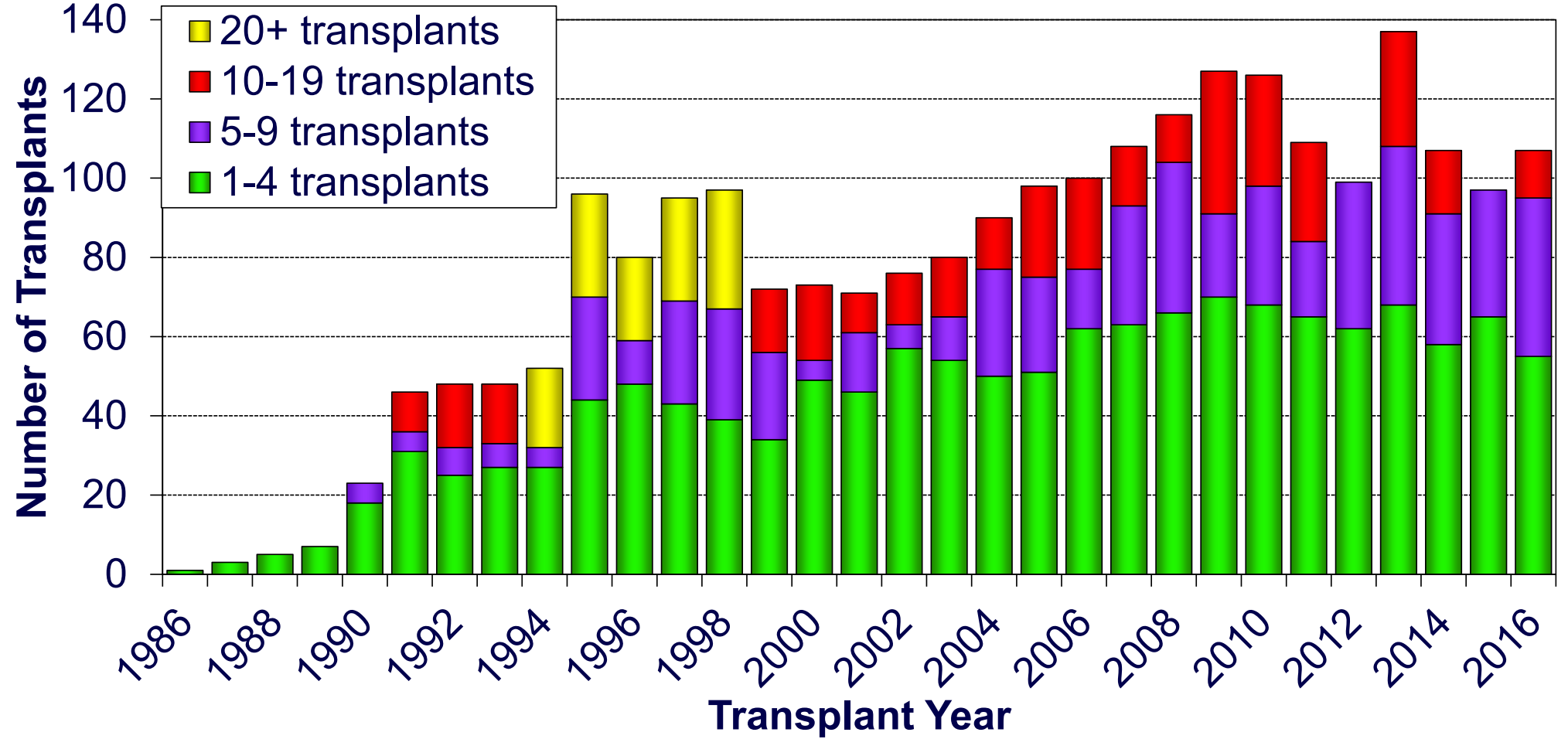
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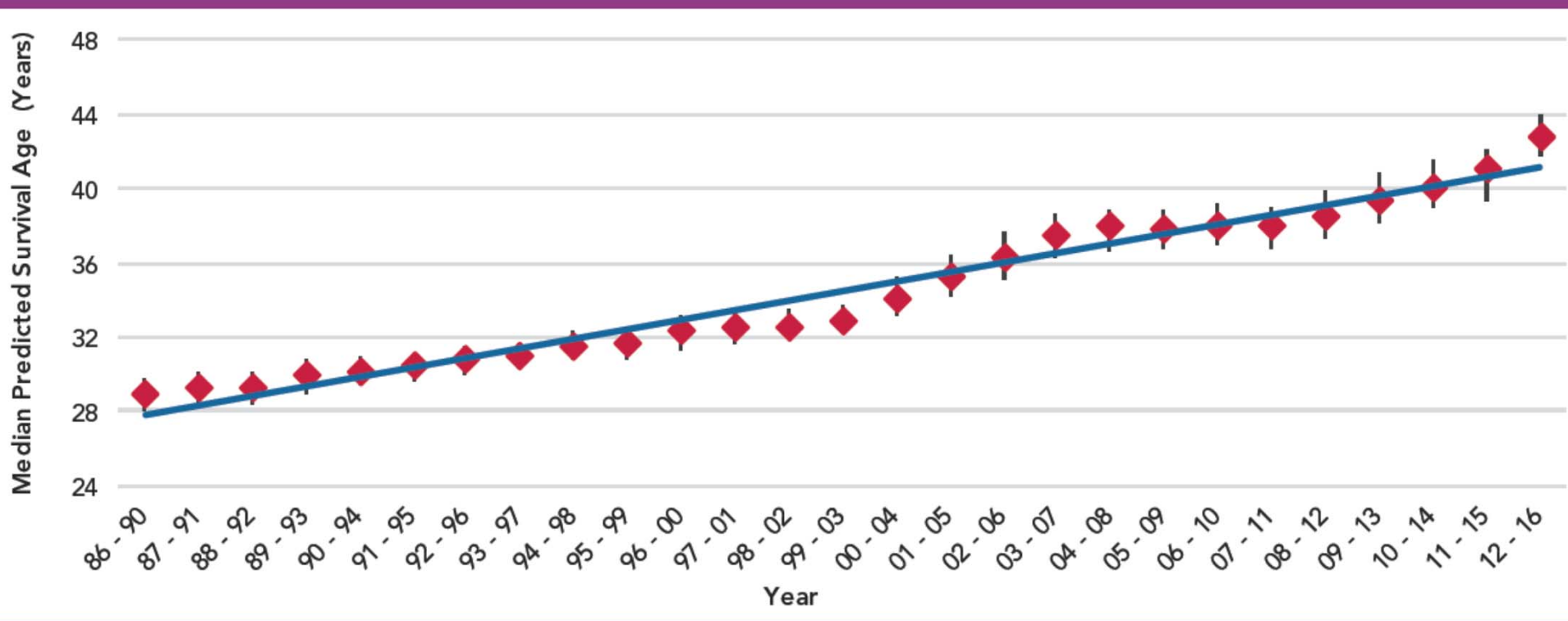
Pediatric Lung Transplants: Number of Transplants by Pediatric Center Volume



Analysis includes deceased and living donor transplants.

Cystic Fibrosis Median Survival

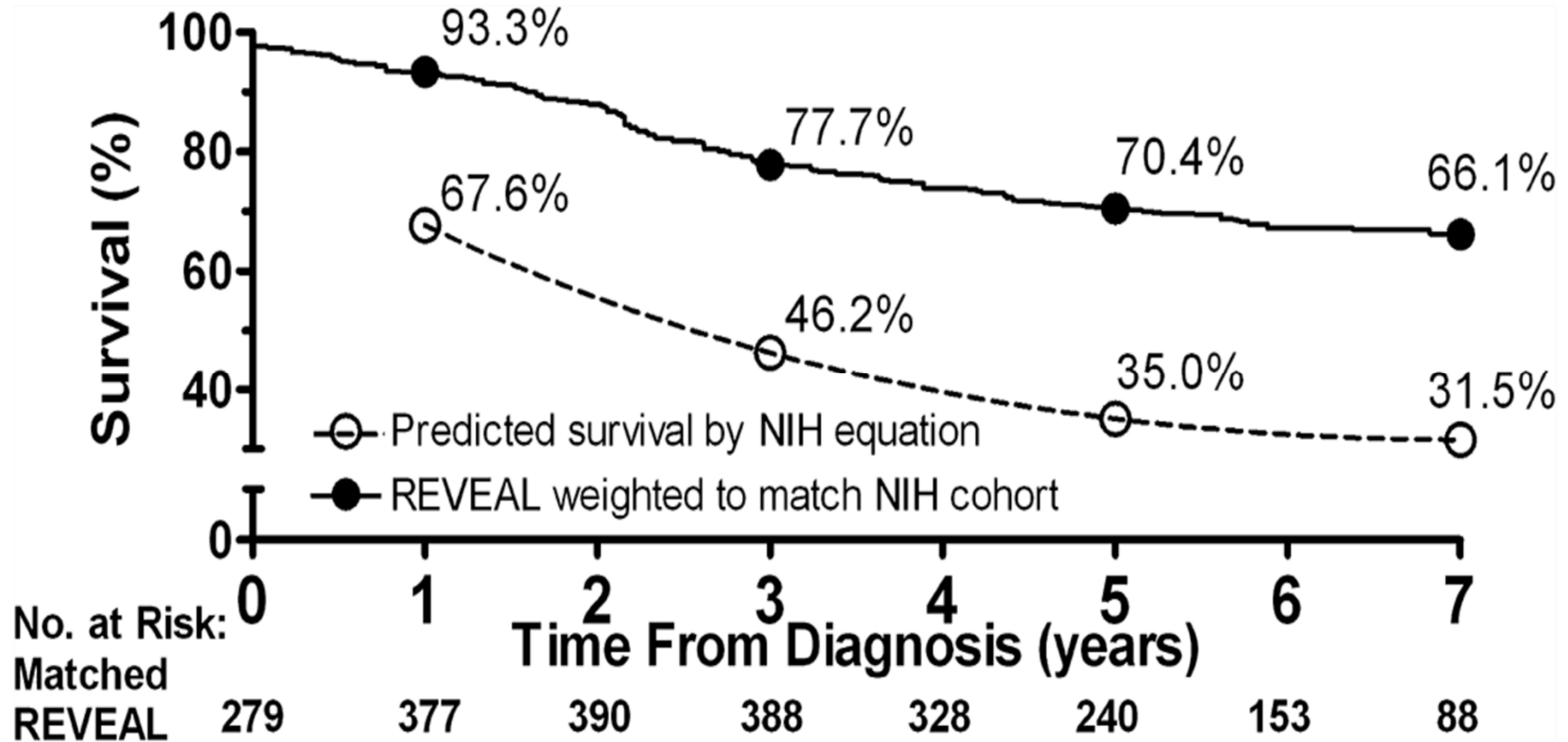
Median Predicted Survival Age, 1986–2016 In Five Year Increments



**Using the currently recommended method for calculating median predicted survival.*

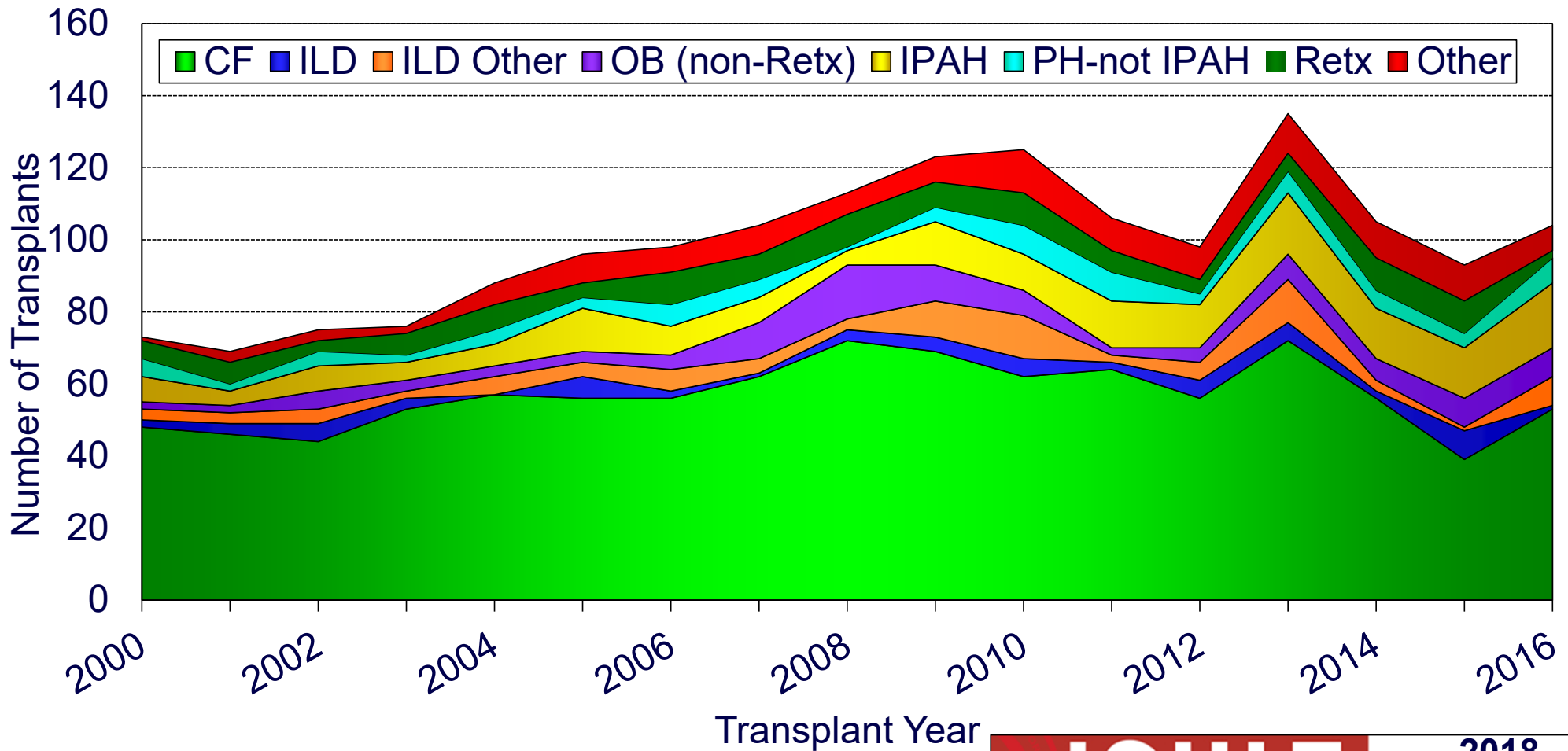
Cystic Fibrosis Foundation 2016 Registry Report

Pulmonary Hypertension Survival

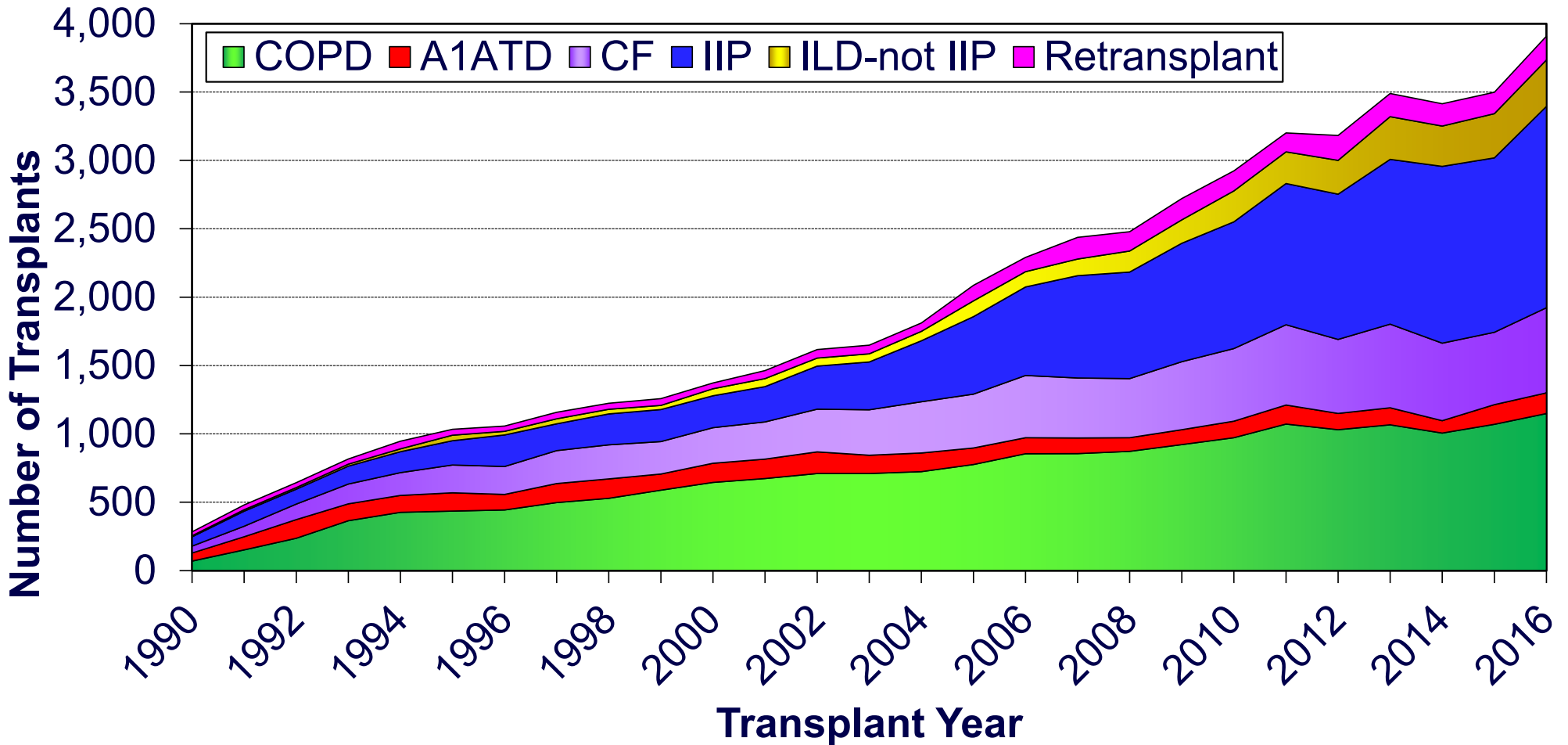


Chest. 2012;142(2):448-456.

Pediatric Lung Transplants: Diagnosis by Year (Number)



Adult Lung Transplants: Major Diagnoses by Year (Number)

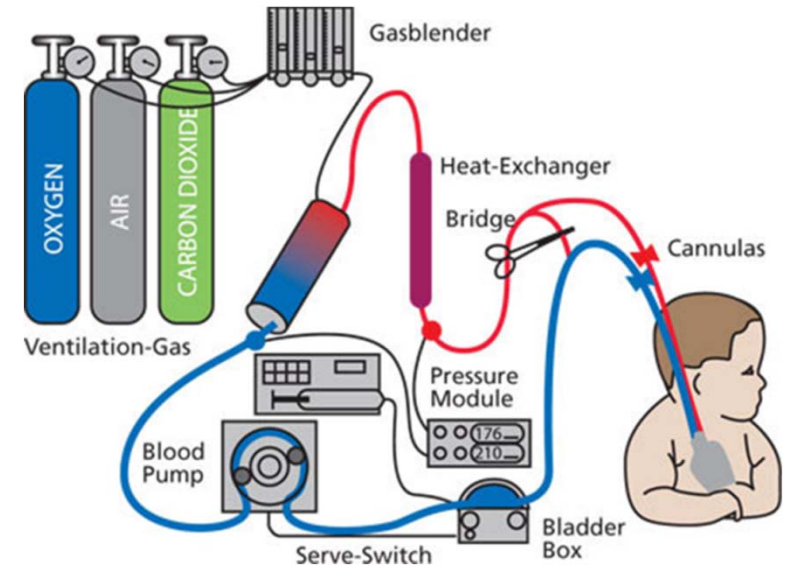


Challenges

- More even distribution of pediatric transplants across centers
- Population of pediatric lung transplant candidates changing (less CF, less IPH)
- Increasing competition for adult transplant (numbers, high acuity candidates)
- Increasing Candidate Acuity
- Ultimately, Patient Outcomes are at Risk

Bridges to Transplant

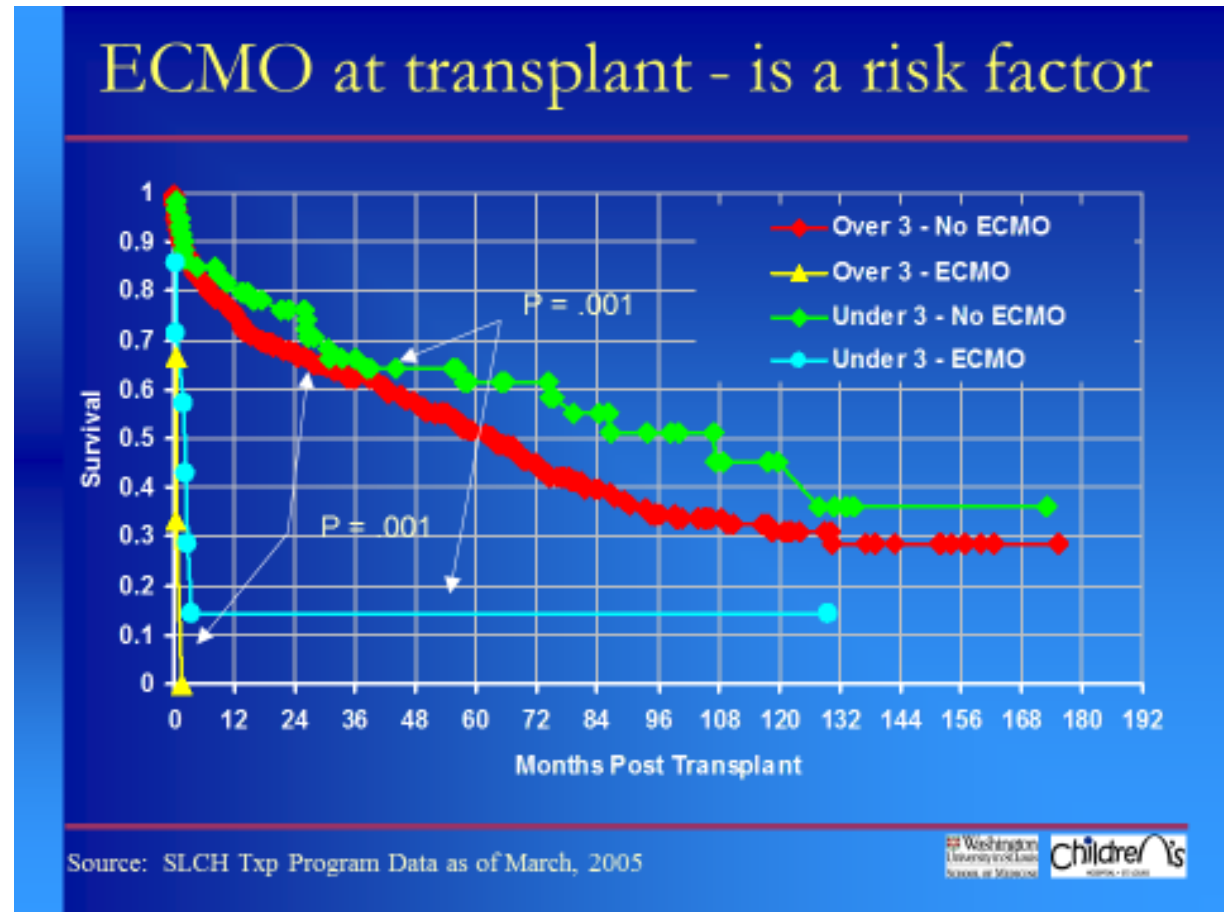
- Historical Paradigm –
 - End Stage Lung Disease
 - Respiratory Failure
 - Mechanical Ventilation with escalating support
 - Extracorporeal Life Support (ECLS)
 - Historically meant VA ECMO
 - Complication rate increases with time
 - Sedation / muscle relaxant requirements may limit rehabilitation potential
 - Outcomes poor...



Bridges to Transplant

Evolving Approach

- *Historically Dismal Outcomes with VA ECMO*



Bridges to Transplant

Evolving Approach

- *VV ECMO in Selected Cases*
 - Early Tracheostomy when Possible
 - Active Rehabilitation (a work in progress)
 - Several successful cases
- *Pumpless Oxygenator for Refractory Pulmonary Vascular Diseases – PA to LA configuration*
 - Four patients, one bridged to recovery, one successfully transplanted
 - All with significant vascular complications

Gazit et al. *J Thorac Cardiovasc Surg* 2011; 141(6) e48-e50

Hogansen et al. *J Thorac Cardiovasc Surg*. 2014;147(1):420-6

Virtual Table Exercise (10 minutes)

- Introduce yourselves
- Identify a spokesperson
- Discuss and develop answers to the assigned case from the materials provided
- Be prepared to provide answers and rationale

Key Points

- Pediatric lung transplantation is an accepted therapy
- Long term outcomes remain an issue
- Increasing competition for organs drives
 - Need to increase lung donor utilization
 - Evolution of bridging strategies

Thanks!

