Pediatric Lung Transplantation: Basic Concepts and Complications

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Rev. 11/2015

Disclosures

- Unfortunately, I have no financial disclosures.
- I have a lot of slides…
- I am primarily a clinician and I’m definitely not a transplant immunologist!

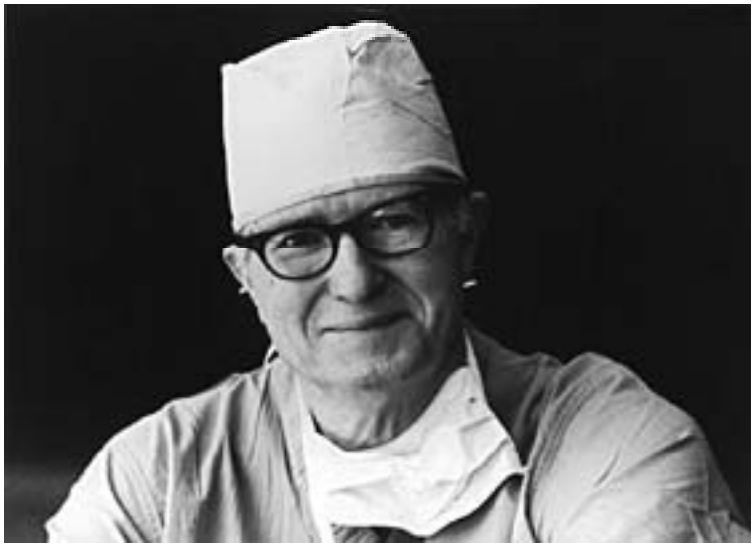
Objectives

- (Brief) history of lung transplantation
- Indications/Contraindications
- The “Basics” of Transplant Immunology and Immunosuppressive Treatment
- Complications (limited)
- Controversies and Challenges


THE ROAD TO ENLIGHTENMENT IS LONG AND DIFFICULT, WHICH IS WHY I ASKED YOU TO BRING SANDWICHES AND A CHANGE OF CLOTHING.

History of Lung Transplantation II

- 1963: First human lung transplant by J.D. Hardy. Deceased donor. Recipient died of renal failure, 18 days (Minimal rejection, although A-B incompatible!)



J.D. Hardy, MD. 1918-2003: First human lung transplant (1963); first animal to human heart transplant (1964)

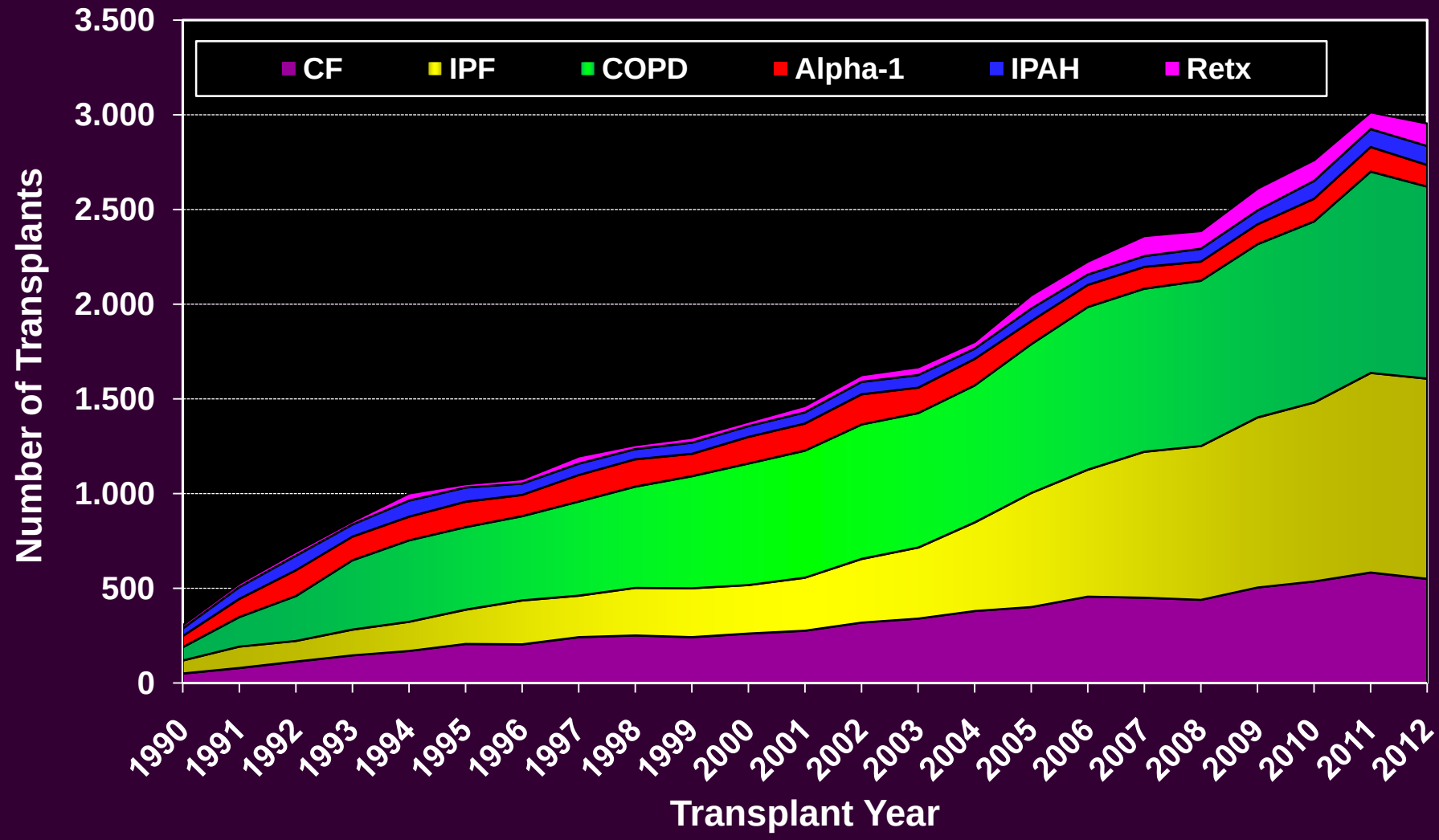
History of Lung Transplantation II

- 1963-1982:
  - First attempted pediatric lung transplant 1968
  - Research on surgical techniques leading to improved bronchial anastomotic healing.
  - Immunosuppressives: Azathioprine, irradiation, and corticosteroids
  - By 1978: of 38 reported recipients, only 9 lived more than 14 days, none more than 1 year.

History of Lung Transplantation III

- After 1978
  - The CYCLOSPORINE A “Revolution”…
  - Calne: renal 1978
  - Starzl: liver 1981
  - Reitz: heart-lung 1981

Adult Lung Transplants
Major Indications by Year (Number)



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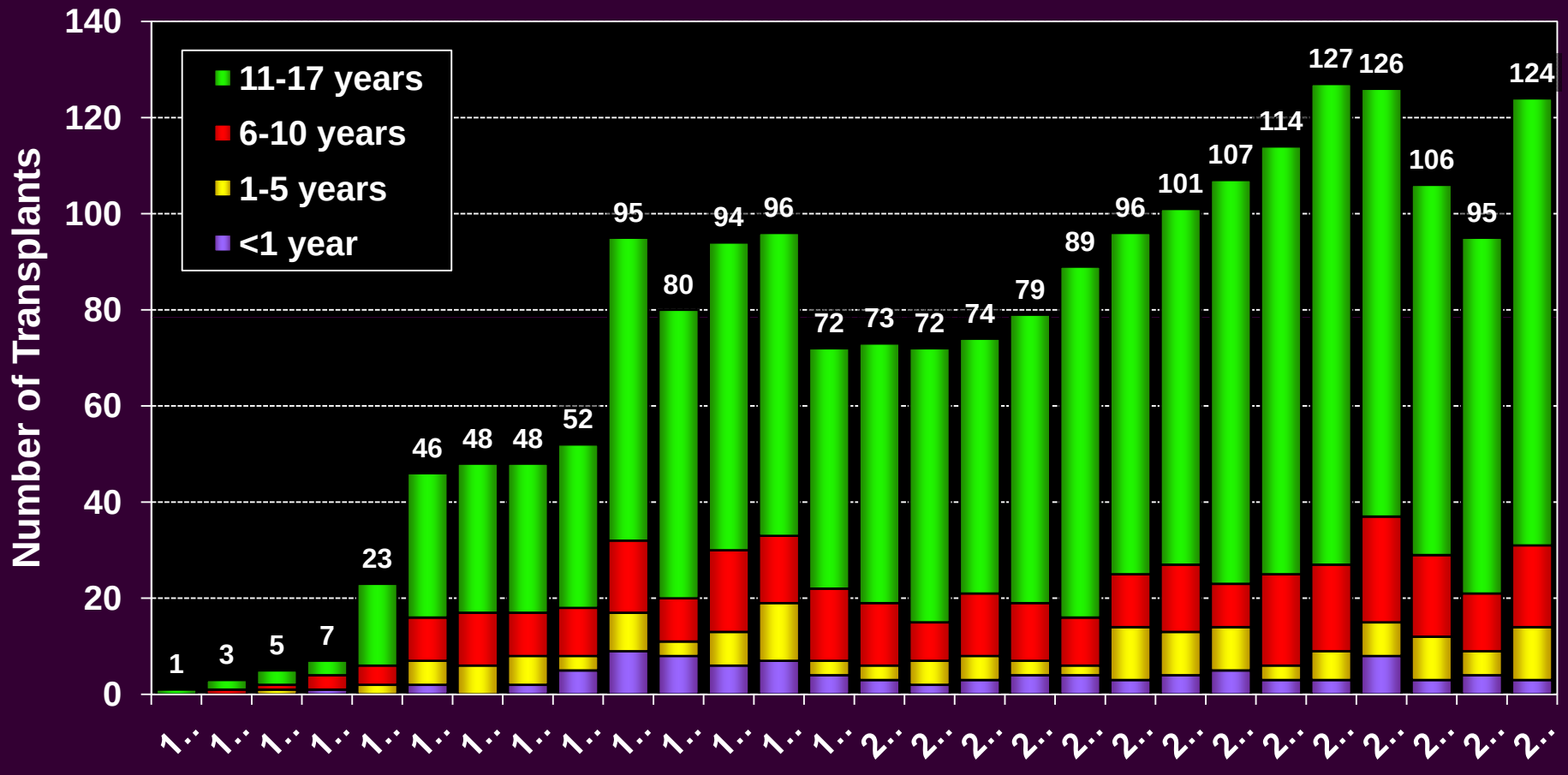
2014

JHLT. 2014 Oct; 33(10): 1009-1024

For some retransplants, diagnosis other than retransplant was reported, so the total number of retransplants may be greater.

Pediatric Lung Transplants
Recipient Age Distribution by Year of Transplant



NOTE: This figure includes only the pediatric lung transplants that are reported to the ISHLT Transplant Registry. Therefore, these numbers should not be interpreted as the rate of change in pediatric lung procedures performed worldwide.

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JHLT. 2015 Oct; 34(10): 1255-1263

Analysis includes deceased and living donor transplants.

Adult Lung Transplants
Indications (Transplants: January 1995 – June 2013)

Diagnosis	SLT (N = 15,321)	BLT (N = 26,579)	TOTAL (N = 41,900)
COPD/Emphysema	6,594 (43.0%)	7,078 (26.6%)	13,672 (32.6%)
Idiopathic Pulmonary Fibrosis	5,354 (34.9%)	4,825 (18.2%)	10,179 (24.3%)
Cystic Fibrosis	234 (1.5%)	6,628 (24.9%)	6,862 (16.4%)
Alpha-1	771 (5.0%)	1,572 (5.9%)	2,343 (5.6%)
Idiopathic Pulmonary Arterial Hypertension	92 (0.6%)	1,158 (4.4%)	1,250 (3.0%)
Pulmonary Fibrosis, Other	677 (4.4%)	970 (3.6%)	1,647 (3.9%)
Bronchiectasis	62 (0.4%)	1,069 (4.0%)	1,131 (2.7%)
Sarcoidosis	280 (1.8%)	776 (2.9%)	1,056 (2.5%)
Retransplant: Obliterative Bronchiolitis	312 (2.0%)	379 (1.4%)	691 (1.6%)
Connective Tissue Disease	177 (1.2%)	409 (1.5%)	586 (1.4%)
Obliterative Bronchiolitis (Not Retransplant)	105 (0.7%)	351 (1.3%)	456 (1.1%)
LAM	138 (0.9%)	302 (1.1%)	440 (1.1%)
Retransplant: Not Obliterative Bronchiolitis	205 (1.3%)	227 (0.9%)	432 (1.0%)
Congenital Heart Disease	58 (0.4%)	291 (1.1%)	349 (0.8%)
Cancer	7 (0.0%)	29 (0.1%)	36 (0.1%)
Other	255 (1.7%)	515 (1.9%)	770 (1.8%)

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Pediatric Lung Transplants

Indications by Age Group (Transplants: January 2000 – June 2014)

Diagnosis	< 1 Year		1-5 Years		6-10 Years		11-17 Years	
Cystic Fibrosis	0		5	5.7%	99	50.5%	726	69.1%
Idiopathic Pulmonary Arterial Hypertension	7	13.0%	19	21.8%	20	10.2%	83	7.9%
Retransplant: Obliterative Bronchiolitis	0		4	4.6%	6	3.1%	33	3.1%
Congenital Heart Disease	8	14.8%	7	8.0%	3	1.5%	8	0.8%
Idiopathic Pulmonary Fibrosis	4	7.4%	11	12.6%	8	4.1%	29	2.8%
Obliterative Bronchiolitis, Not Retx	0		8	9.2%	21	10.7%	48	4.6%
Retransplant, Not OB	0		4	4.6%	3	1.5%	24	2.3%
Interstitial Pneumonitis	0		2	2.3%	2	1.0%	1	0.1%
Pulmonary Vascular Disease	2	3.7%	5	5.7%	2	1.0%	1	0.1%
Eisenmenger's Syndrome	0		1	1.1%	1	0.5%	4	0.4%
Pulmonary Fibrosis, Other	7	13.0%	10	11.5%	15	7.7%	28	2.7%
Surfactant Protein B Deficiency	11	20.4%	4	4.6%	0		0	
COPD/Emphysema	0		0		1	0.5%	6	0.6%
Bronchopulmonary Dysplasia	4	7.4%	2	2.3%	3	1.5%	3	0.3%
Bronchiectasis	0		0		0		14	1.3%
Other	11	20.4%	5	5.7%	12	6.1%	43	4.1%

Analysis includes deceased and living donor transplants. For some retransplants, a diagnosis other than retransplant is reported, so the total percentage of retransplants may be greater.

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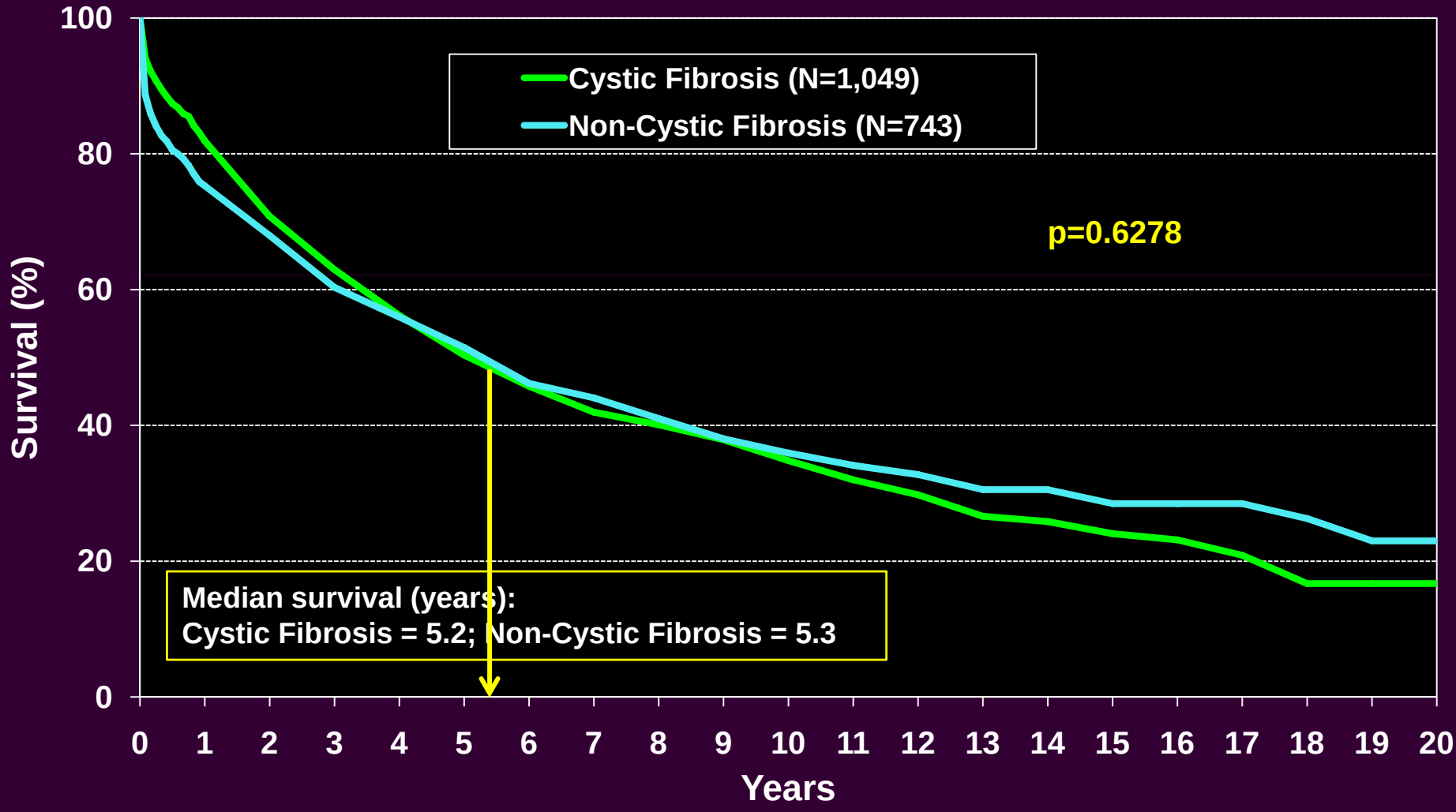
The Before

- When do I refer to a transplant center?
- How do we decide who can be listed for a transplant?
- When do we decide to list?
- How long to people need to wait for a transplant?
- How do patients prepare for transplantation?

Recipient Selection

- Is the patient sick enough to justify the risks of lung transplantation?
- Is the patient likely to benefit from lung transplantation?
- Are there contraindications that will absolutely preclude lung transplantation?

Pediatric Lung Transplants
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 – June 2013)



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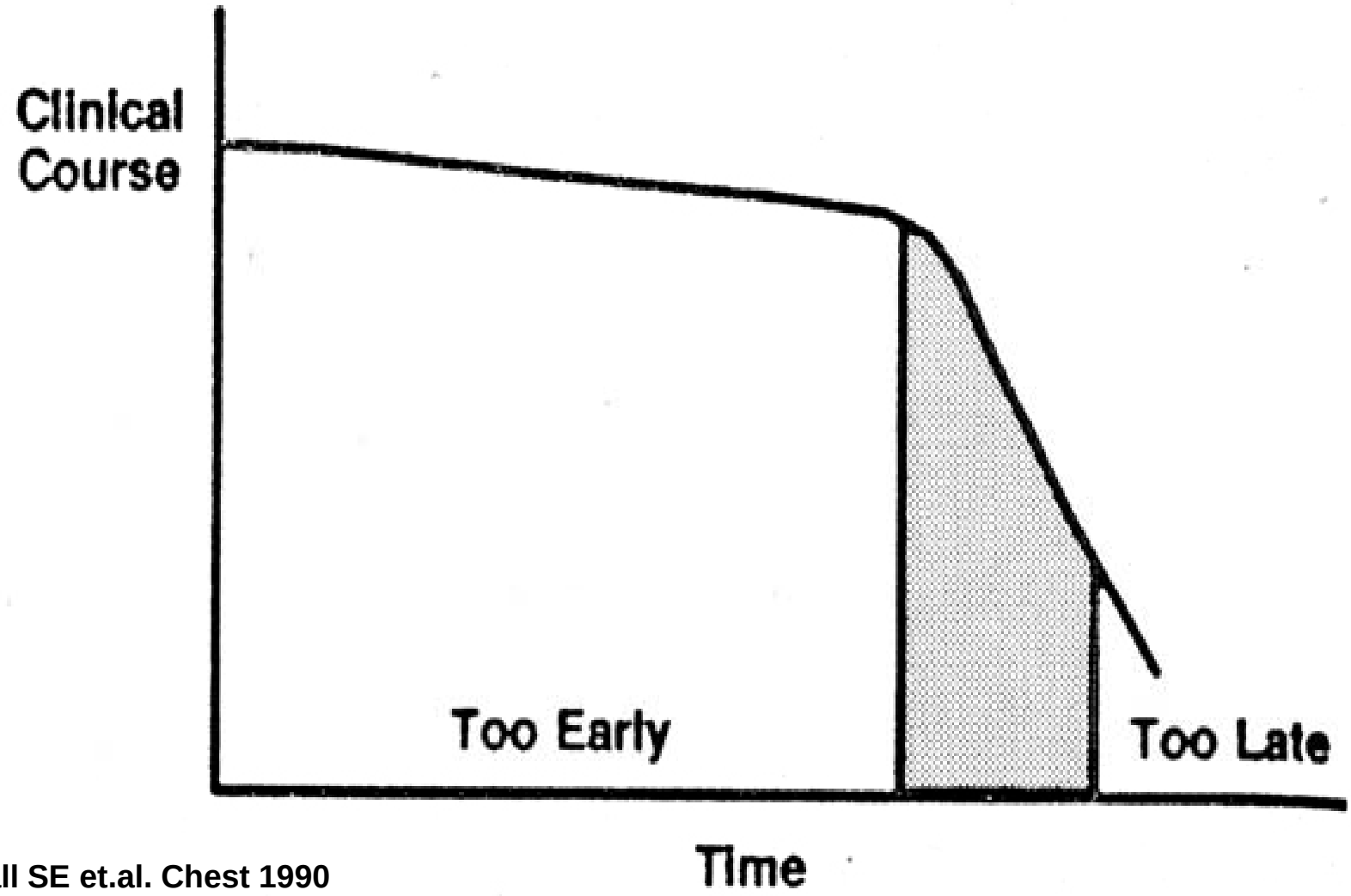
"TRANSPLANT WINDOW"



Marshall SE et.al. Chest 1990 Dec;98(6):1488-94

Guidelines for Candidate Selection

- **Optimal medical therapy**
- **Known limited survival**
- **Optimal treatment of comorbid conditions (e.g. DM, HTN)**
- **Age limits:**
  - **Heart-lung: 55 yrs.**
  - **Single lung: 65 yrs.**
  - **Double lung: 60 yrs.**

Subject to change based on recipient physiology and co-morbidities

Disease-specific Criteria for Lung Transplantation

COPD and alpha-1 anti-trypsin deficiency	Post-bronchodilator FEV1 <25% predicted +/- $PaCO_2 \geq 55$mmHg +/- elevated PA pressures +/- progressive deterioration
ILD	Symptomatic and progressive disease FVC <60-70% predicted or DLCO <50-60% predicted PaO_2 <55mmHg and $PaCO_2$ >45mmHg Desaturation <88% during 6-MWT
Bronchiectasis/CF	FEV1 <30% predicted PaO_2 <55mmHg and $PaCO_2$ >45mmHg Progressive disease, pulmonary hypertension Increasing resistance of bacteria Severe, life-threatening complications (hemoptysis, pneumothorax)
Pulmonary vascular disease	Progressive disease despite medical therapy and NHYA Class III or IV Mean PA pressure >55mmHg Mean RA pressure >15mmHg CI <2.0L/min/M^2

FEV1 = forced expiratory volume at 1 second; PA = pulmonary artery; FVC = forced vital capacity; DLCO = diffusion of carbon monoxide; 6-MWT = six minute walk test; RA = right atrium; CI = cardiac index

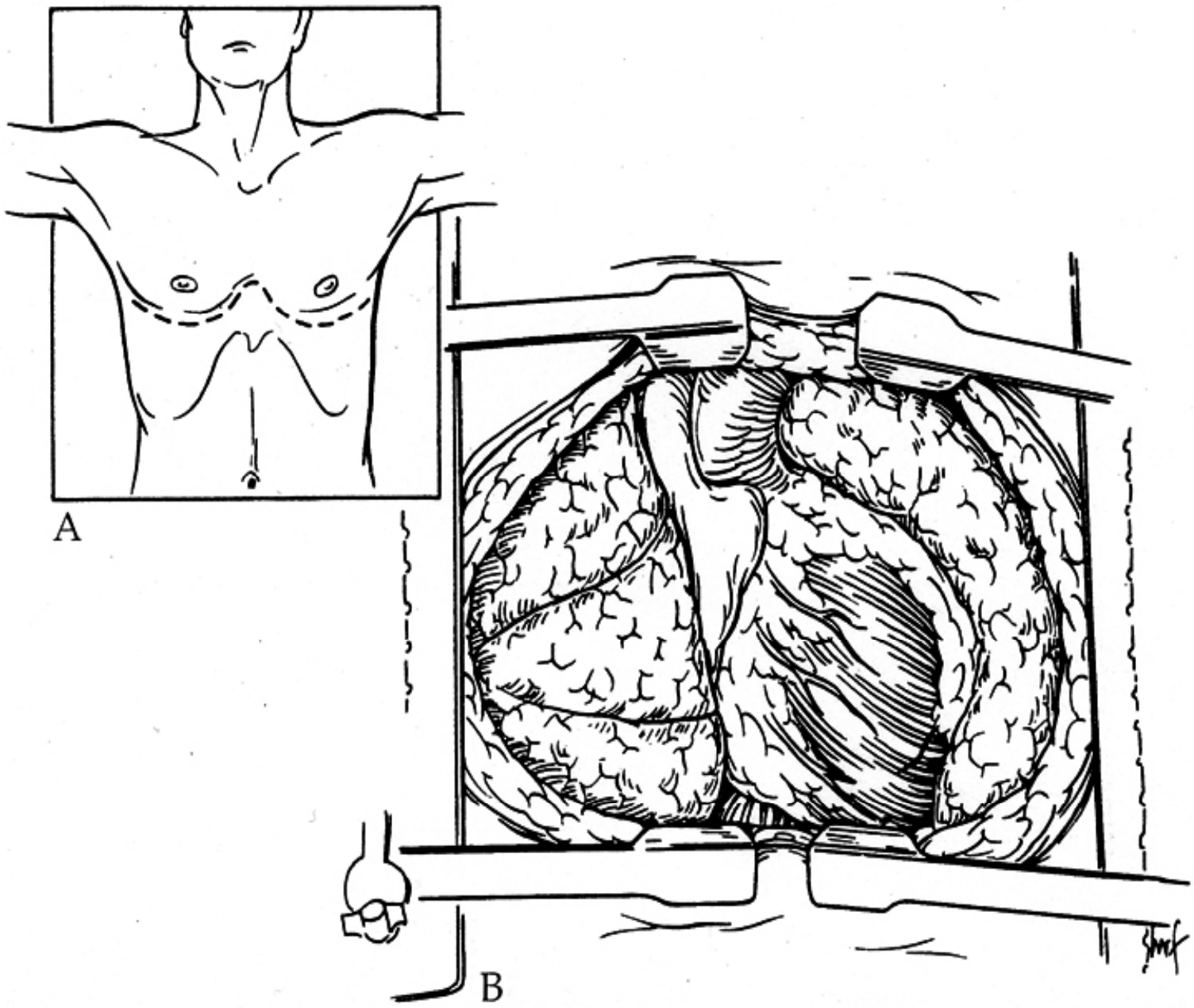
Absolute Contraindications	**Relative Contraindications**
Malignancy within 2 years, with the exception of cutaneous squamous and basal cell tumors Untreatable, advanced dysfunction of another major organ system Non-curable chronic extrapulmonary infection (HIV, HepB, HepC) Significant chest wall and/or spinal deformity Documented nonadherence **Immunodeficiency**** Untreatable psychiatric or psychologic condition that will impair compliance with medical therapy No reliable social support system Substance addiction within past 6 months	Critical or unstable condition Severely limited functional status with poor rehabilitation potential Colonization with highly resistant or highly virulent microorganisms Severe obesity (BMI >30 kg/m^2) Severe malnutrition Severe or symptomatic osteoporosis Mechanical ventilation Suboptimally treated serious medical condition

Evaluation for Pediatric Lung Transplantation

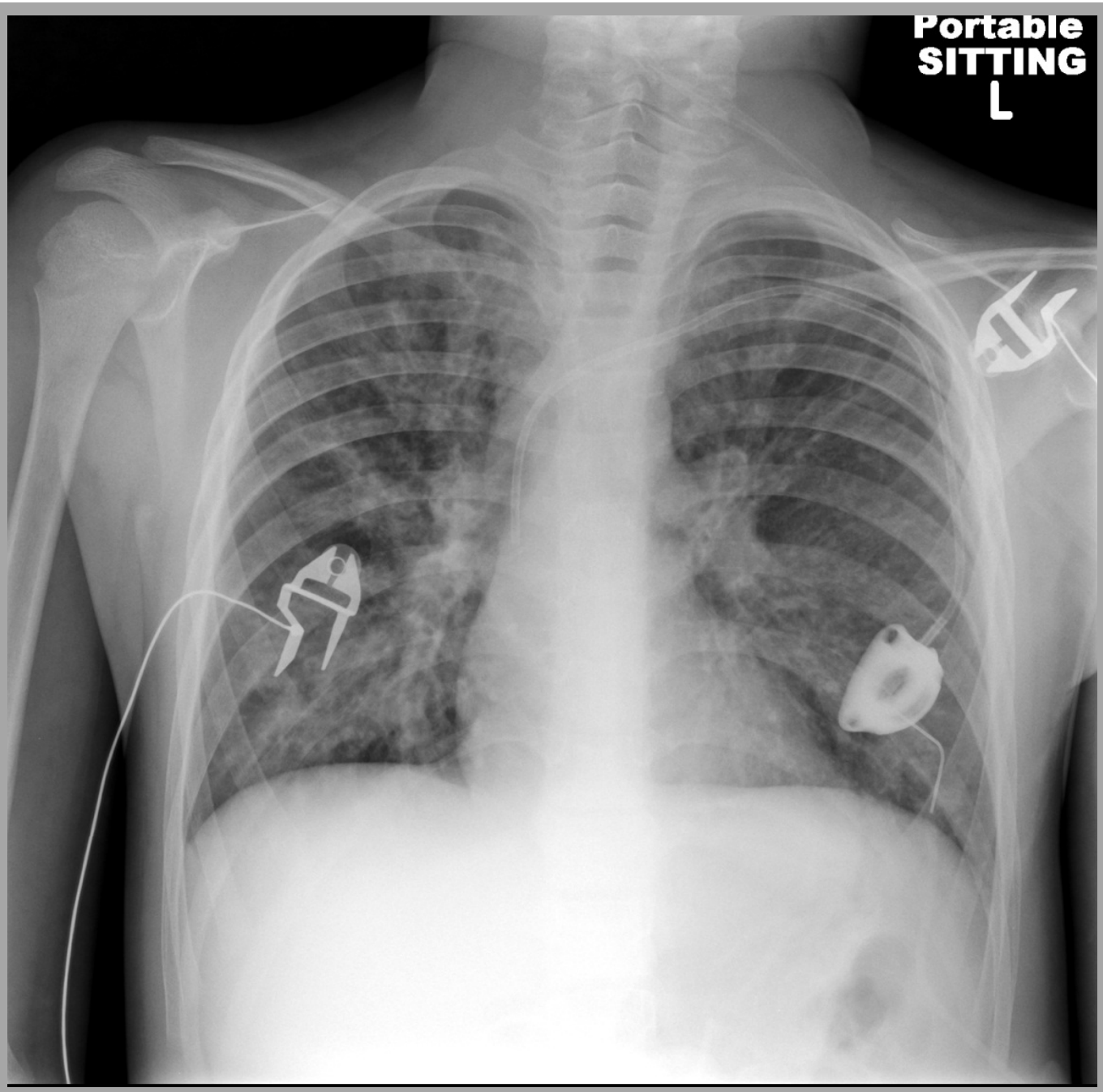
- Consideration
  - Underlying disease
  - Contraindications?
  - Assessed level of illness/ risk of death
- Evaluation
  - Meet the team: *Transplant Coordinator* Pulmonology/Cardiology/I.D./CT Surgery/ Psychology/Social Work et. al.
  - Understanding of process of transplantation

Pediatric Lung Transplantation

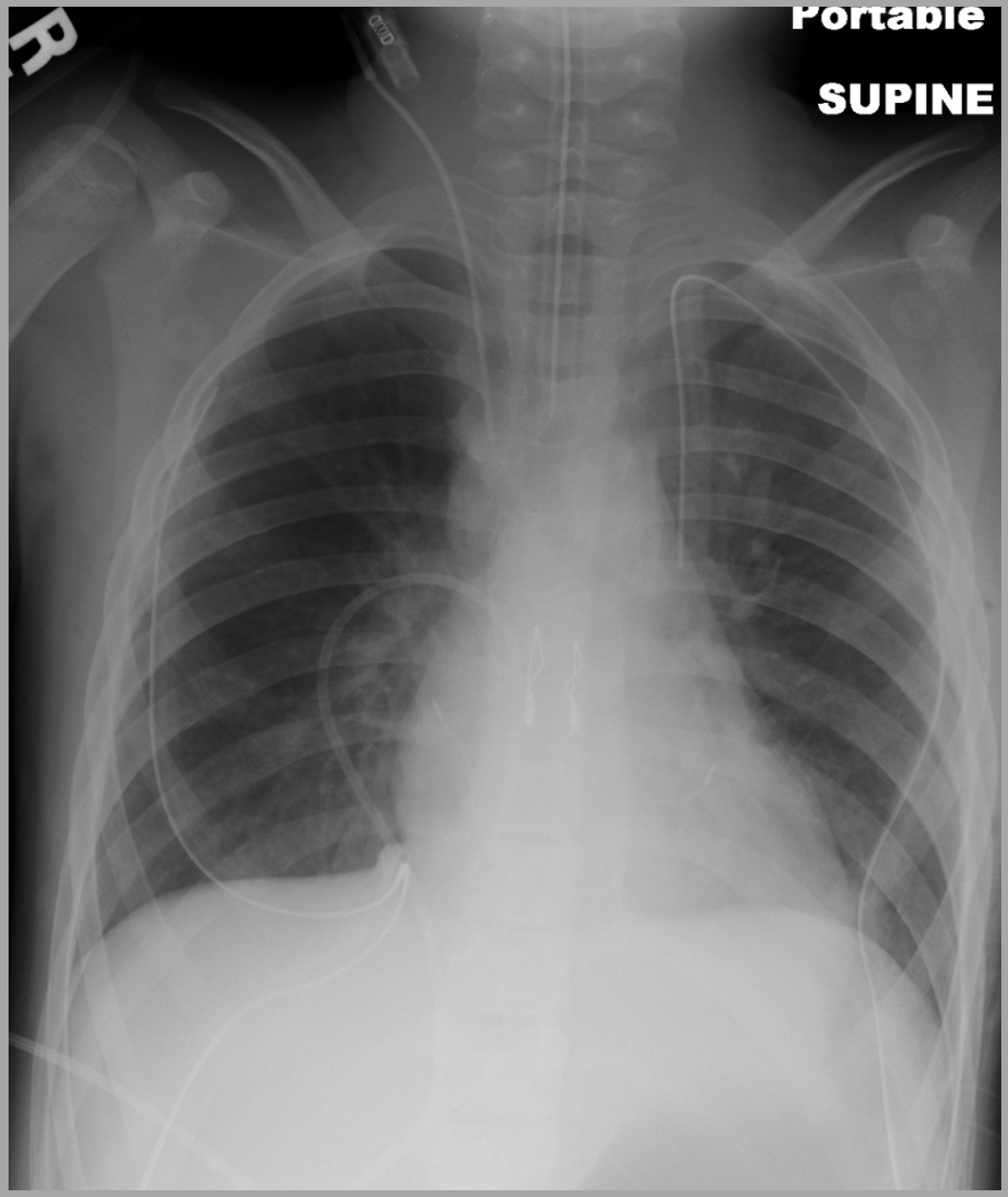
- Surgical approach is usually bilateral sequential lung transplantation with bi-bronchial anastamoses.
  - Transverse inframammary thoracic incision
  - Bronchial arterial re-implantation usually not performed
- Lung harvesting: hypothermic pulmonary artery flush,50 to 60 mL/kg, low potassium Dextran-glucose soln.



*ig. 6. **A:** A transverse sternothoracotomy is performed with the patient supine. The incision* (dashed line) *ollows the inframammary crease. **B:** The fourth or fifth interspace is opened, and the sternum is divided.*



CF Patient Immediately Pre-Transplant



CF Patient Immediately Post-Transplant

Pediatric Lung Transplantation

- The surgery, although technically challenging, is not the most difficult aspect of pediatric lung transplantation.
- Recovery post-transplant and “life after lung transplantation” are the real test of the patient , the family…and the care team
  - Immunosuppression: Life-long compliance
  - Risk of complications: e.g. Rejection; Infection

“Lung transplantation is a treatment, not a cure, and it is not a panacea.”

Trulock EP. Am J Resp Crit Care Med 1997; 155: 789-818

Lung transplantation means trading one disease for another disease…except in the case of cystic fibrosis where one trades only *part* of one disease for another disease.

Complications of Transplantation Generally are the Rule Rather than the Exception

The lessons learned in transplantation have been taught to us at great expense by our Patients

The immune system can be defined as a system of biological structures and processes within an organism that protects the organism from disease resulting from specific pathogens.

The immune system identifies an allograft as "foreign" and thus a potential pathogen. The task of transplant science is to control the immune system in a way that will preserve the graft, but not lose the ability to protect against true pathogens.

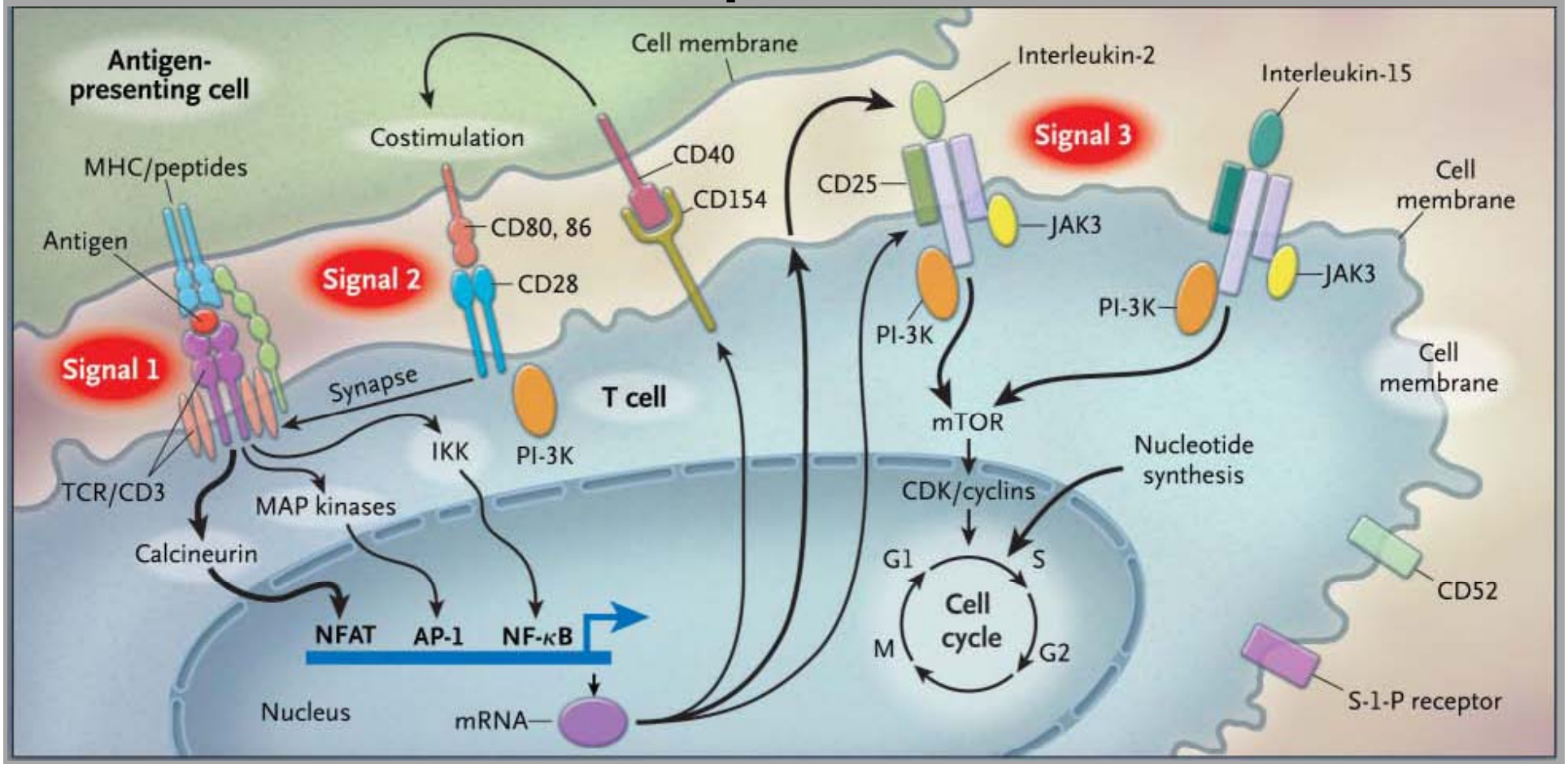
Graft Rejection I

- "**Older View**": T-cell dependent, adaptive immunity was felt to be the key (?only?) immune response
- "**Newer View**": Combination of innate and adaptive immunity important.
  - Pattern recognition receptors (PPRs), detecting Pathogen-associated molecular patterns (PAMPs) can also detect and bind to Damage-associated molecular patterns (DAMPs).
    - DAMPs can result from tissue/organ harvesting: release of markers of injury
    - PPRs sensing DAMPs leads to local inflammatory cascade affecting the graft.
- **Other effectors** leading to graft dysfunction:
  - Complement system
  - Antibodies to mismatched HLA

Graft Rejection II: …back to T-cells

- "Three Signal" concept of T-cell activation
  - Signal 1 (**Priming**): interaction of T-cell receptor with donor MHC antigen(s) presented by APC.
  - Signal 2 (**Costimulation**): interaction of CD28-CD86 or CD80 AND CD154-CD40
  - Signal 3 (**Transduction**): downstream effects of Ca^{+2} increase, activation of calcineurin, and increased NFAT and NFκB…leading to increased release of IL-2

T-Cell Activation: A 3 step Process



Halloran P. N Engl J Med 2004; 351:26

Graft Rejection IV

- The Effector mechanism of graft rejection involves allograft-independent and –dependent mechanisms-- examples:
  - Organ ischemia leads to a non-specific inflammatory response--can magnify the recognition of the graft as foreign
  - Cytotoxic T-lymphocytes (CTLs) recognize “foreign” cells and interact with them. Granzymes injected into target cells, triggering apoptosis.

A “history” of immunosuppressive agents

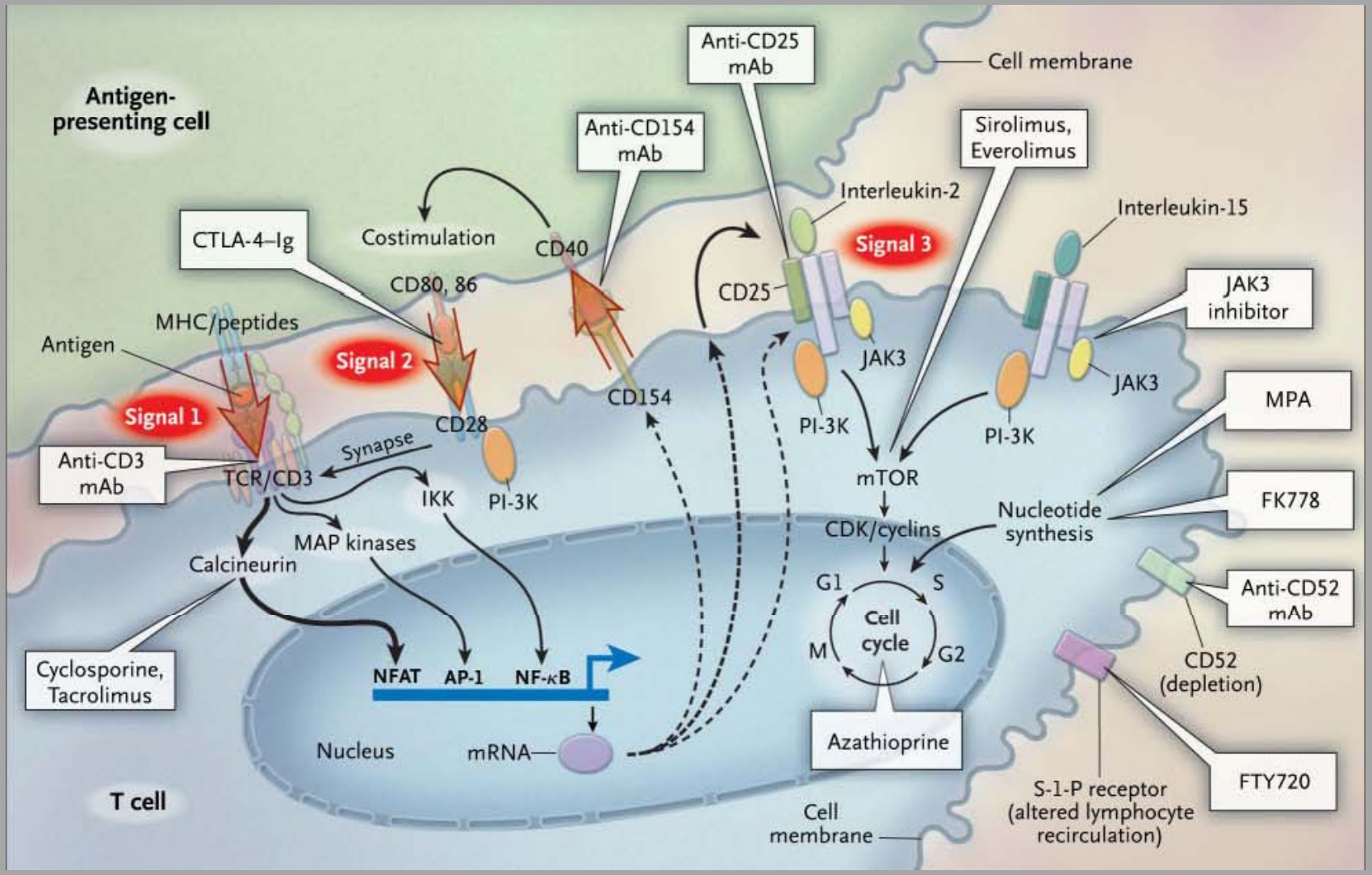
Date	Compound	Authors
1949	Cortisol	Hench et al. (1949)
1959	Cyclophosphamide	Stender et al. (1959)
1959	6-mercaptopurine	Schwartz and Dameshek (1959)
1961	Methotrexate	Friedman et al. (1961)
1975	Mizoribine	Sakaguchi et al. (1975)
1976	Cyclosporin A	Borel et al. (1976)
1977	Rapamycin	Martel et al. (1977)
1978	Leflunomide	Schleyerbach (1978)
1987	Tacrolimus	Kino et al. (1987)
1991	Mycophenolate mofetil	Allison et al. (1991)

Allison AC Immunopharmacology 2000; 47: 63-83

Other Immunosuppressives (Biologics)

- Anti-thymocyte globulin:*Thymoglobulin [Rabbit]* and ATGAM [Equine]
- Anti-CD3 monoclonal (OKT3)
- *Anti-CD25 monoclonal (Basiliximab)*
- Anti-CD52 monoclonal (Alemtuzumab)

Sites of Action of Immunosuppressive Agents



Halloran P. N Engl J Med 2004; 351:26

Immunosuppression
Long Term Management

- Corticosteroids
- Tacrolimus (alternative: Cyclosporine A)
- Mycophenolate mofetil or Azathioprine

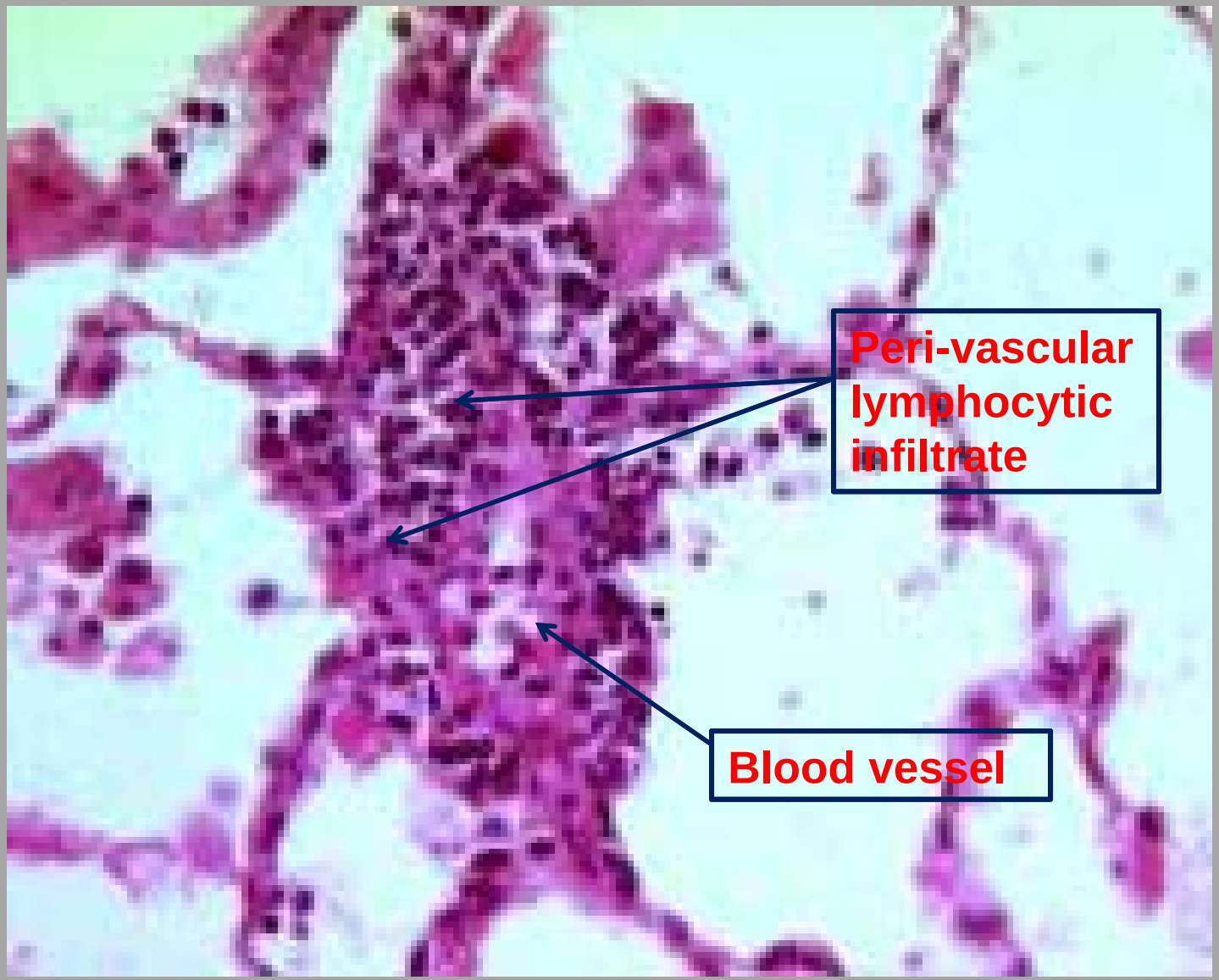
(Selected) Surgical Complications

- Primary graft dysfunction
- Diffuse alveolar damage/ischemia-reperfusion injury
- Anastomotic complications: vascular or airway
- Phrenic/vocal cord paresis
- Gastroparesis

(Selected) Medical Complications I

- Acute Rejection
- Infection: viral, bacterial, fungal, protozoal
- Toxicity of immunosuppressives:
  - Nephrotoxicity, Hypertension
  - Hirsutism
  - Gingival hyperplasia
  - PRES (Posterior Reversible Encephalopathy Syndrome)
- Diabetes

Acute Cellular Rejection

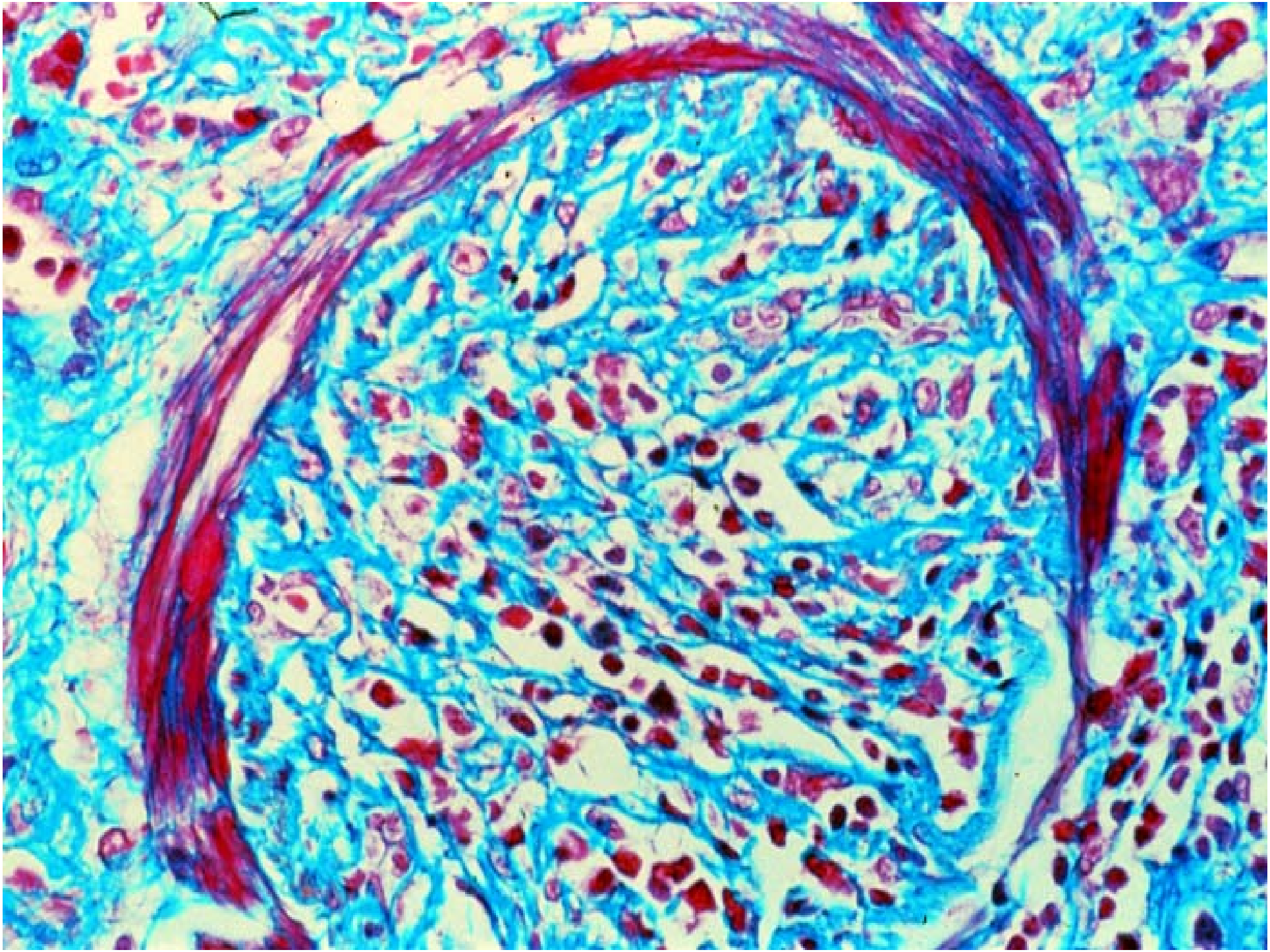


(Selected) Medical Complications II

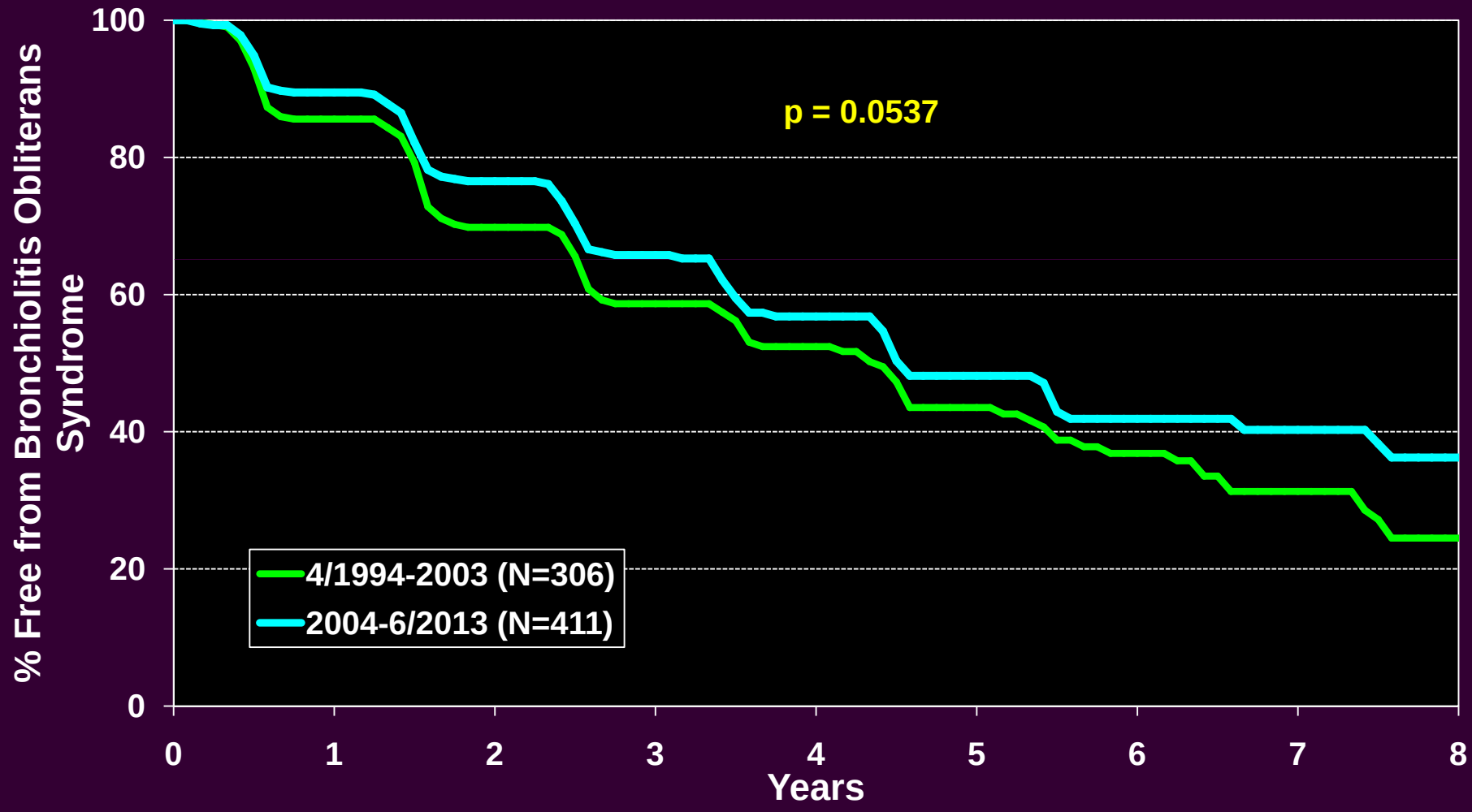
- Hyperlipidemia
- Post-Transplant Lymphoproliferative Disease (PTLD)
  - B-cell driven lymphoma
  - EBV-related
- Obliterative Bronchiolitis
- Other malignancy

Obliterative Bronchiolitis

- “The thorn in the side of transplantation.”
- “…a riddle wrapped in a mystery inside an enigma”
- Is obliterative bronchiolitis truly chronic rejection?
  - Affects airways, not vessels
- Difficult to diagnosis on biopsy---BOS
- Does not respond well to steroids (or other therapy)



Pediatric Lung Transplants
Freedom from Bronchiolitis Obliterans Syndrome by Era
(Transplants: April 1994 – June 2013)



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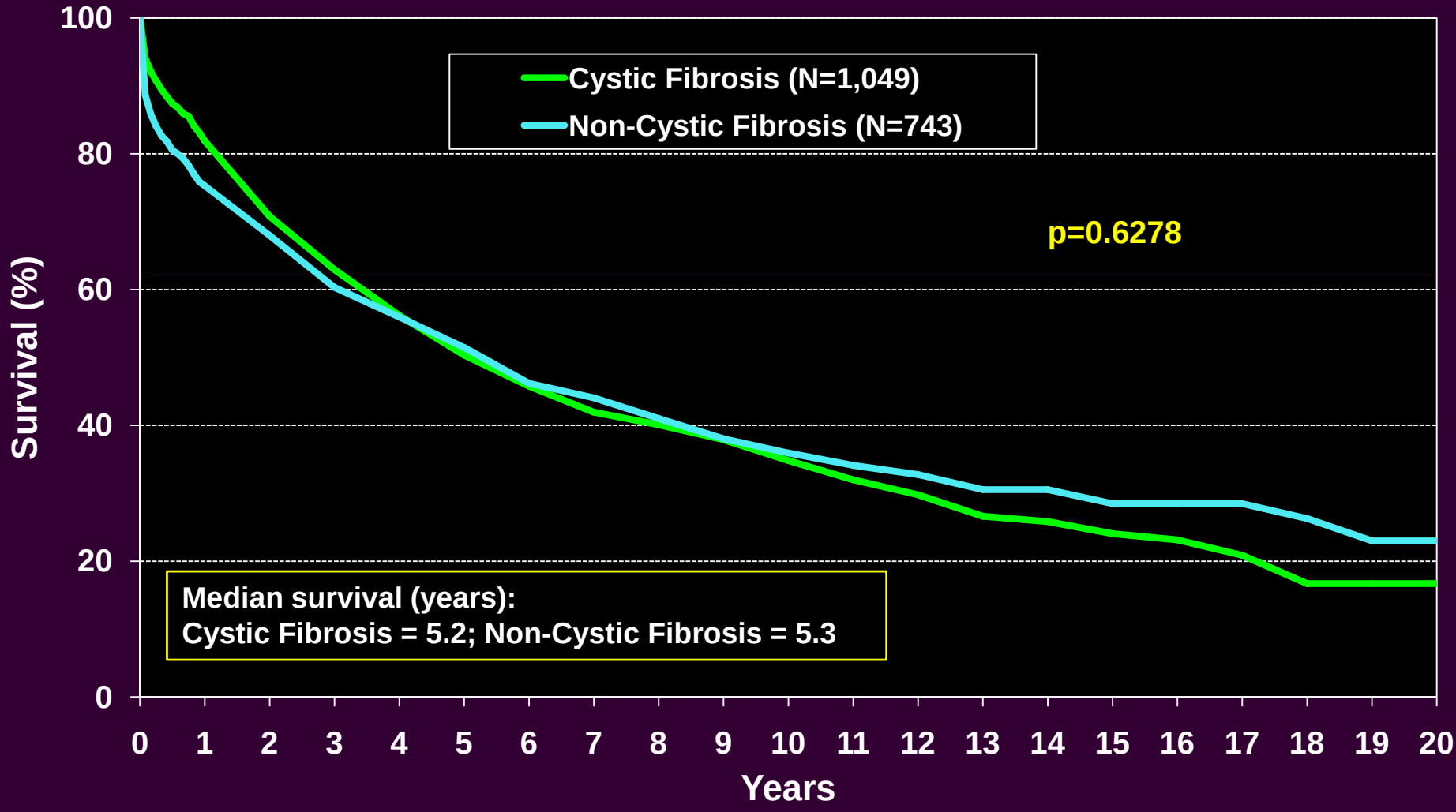
Pediatric Lung Transplants
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 – June 2013)



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Why are lungs so “delicate” ?

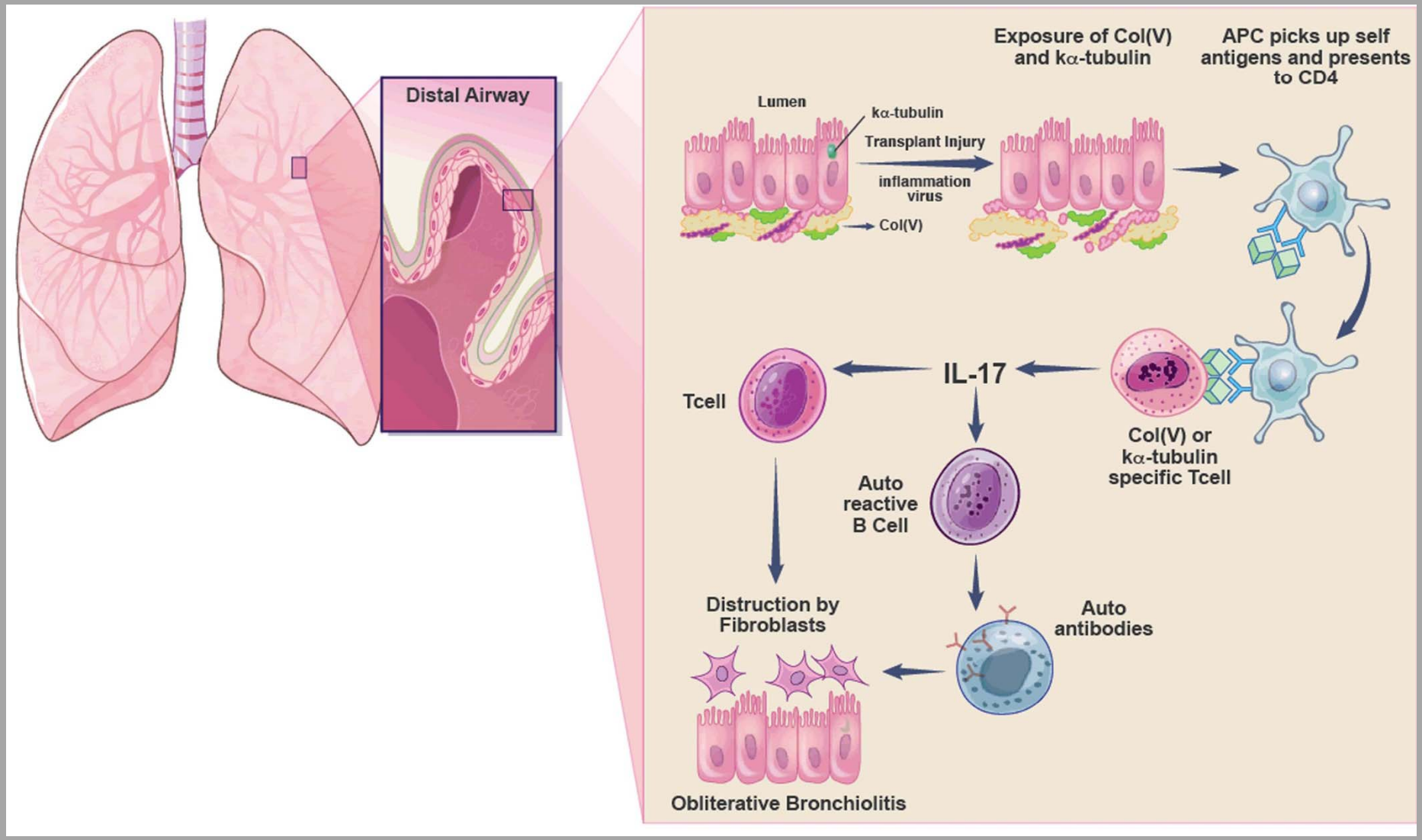
- A scaffolded and “collapsible” system with interdependent features
- Two blood supplies normally, reduced to one with transplantation
- Receives entire cardiac output
- Immunologically active organ; AMs are derived from monocytes (donor origin)
- Exposure to external environment
- Reliance on external muscles for function
- Denervated lungs post-transplant

What is the underlying “cause” of BOS

- Many factors have been associated with the development of BOS
  - Primary graft dysfunction
  - CMV mismatch and CMV pneumonitis
  - Respiratory viral illness
  - Gastroesophageal reflux and/or aspiration
  - Multiple episodes of acute rejection
  - Development of Donor HLA-specific Abs by recipient

Bronchiolitis Obliterans: Recent Experimental Evidence

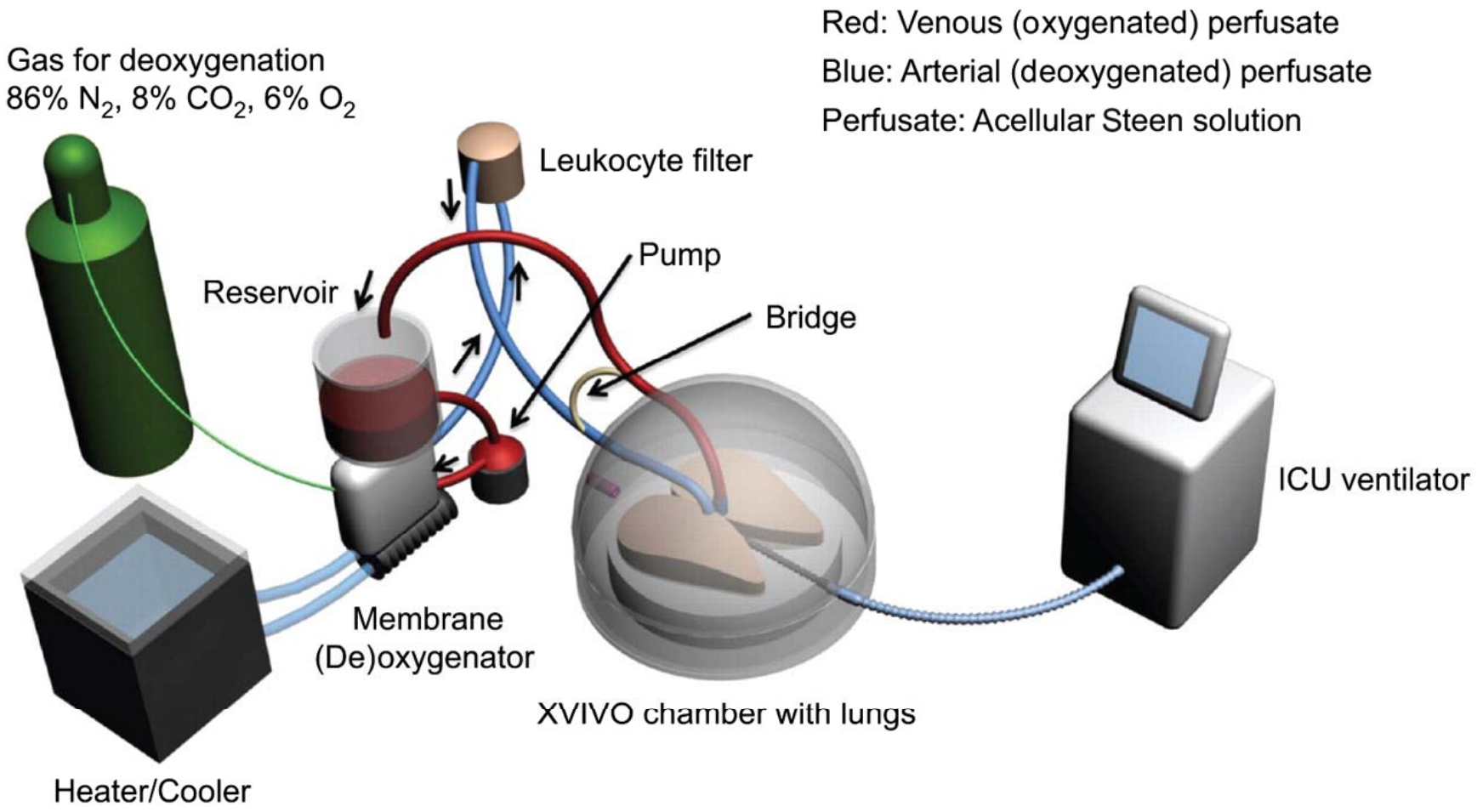
- "Uncovering" of a usually hidden potential antigen, possibly secondary to organ harvesting or ischemia-reperfusion injury
  - Collagen Type V, κα1-Tubulin?
- Possible role of IL-17 in perpetuating airway damage?



Weber DJ. Am J Physiol Lung Cell Mol Physiol 2013; L304: L307-L311

How do we increase the number of available lungs (and decrease the damage during harvesting)?

Ex-Vivo Lung Perfusion



Immunodeficiency

- Recurrent infections, including lung infections, with opportunistic pathogens
- Resultant chronic lung disease including bronchiectasis
- Contraindication to lung transplantation?

Potential Solution

- Donor partially HLA matched to Recipient (2-3/6 haplotypes)
- Obtain donor marrow at time of lung harvest
- Carry out lung transplant with lowered immunosuppression
- T-cell deplete donor marrow

Potential Solution (2)

- Carry out modified (mild) marrow ablation on recipient 6 weeks to 6 months following lung transplant
- Administer T-cell depleted donor marrow
- Expected result:
  - Resolution of immunodeficiency
  - Lung and bone marrow from same donor, therefore lowered risk of lung rejection

Lung Transplantation: A “Team Effort”, with thanks

- Transplant Coordinators
- Cardiology and C.T. Surgery
- Pulmonology
- I.D.
- Psychology and Social Work
- Pathology, Radiology, Immunology, Clinical/Micro Labs

Acknowledgements:

(With key current physicians/staff in Red)

- Many patients and families, nurses, CTICU attendings
- Jim Dauber, Irv Paradis, Joe Pilewski
- Brenda Stinner, Pam Berman, Dana Parker, Megan Platz, Lynne Cipriani, Kathy Iurlano
- Jonathan Spahr, Peter Michelson, Shruti Phadke, Blake Noyes
- Victor Morell, Pete Wearden, Bartley Griffith, John Armitage
- Susan Miller, Brian Feingold, Steve Webber
- Marian Michaels, Mike Green
- Diana Shellmer
- Jennifer Picarsic, Csaba Galambos,

Thanks

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“Probably the most interesting period of medicine has been that of the last few decades. So rapid has been this advance, as new knowledge developed, that the truth of each year was necessarily modified by new evidence, making the truth an ever-changing factor.”

Charles H. Mayo, M.D., 1919

Other References for GER/Aspiration and Lung Transplant

- Mohammed A. Gastroesophageal Reflux Disease and Graft Failure Following Lung Transplantation Transplant Rev 2010; 24: 99-103
- Garrity ER. Gastroesophageal reflux disease and bronchiolitis obliterans syndrome: Where are we today? J Heart Lung Transpl 2013; 32: 577-580
- Abassi-Ghadi N. Anti-reflux surgery for lung transplant recipients…J Heart Lung Transpl 2013; 32: 588-595
- Griffin SM. Aspiration and allograft injury secondary to GER…Ann Surg 2013; 258:705-712

U.S. Lung Allocation Score: Patients >12 yrs old, since 2005.

- Waitlist Urgency:
  - Predicts survival on the wait list over the next year
- Post-Transplant Survival
  - Predicts survival over the year following transplantation
- Both used to calculate a Raw Score, leading to the actual LAS (0-100).

Patient data required for LAS

- 6 minute walk distance
- Modified NYHA Class
- Diabetes (Y/N)
- Assisted ventilation (Y/N)
- Serum creatinine
- O_2 (Y/N; amt)
- FVC (# and % pred.)
- PCO_2
- PA systolic; PAP; PCWP

Data updated every 6 months

Score range: 0 (healthiest) -100 (sickest)

Recent Changes to UNOS Policy

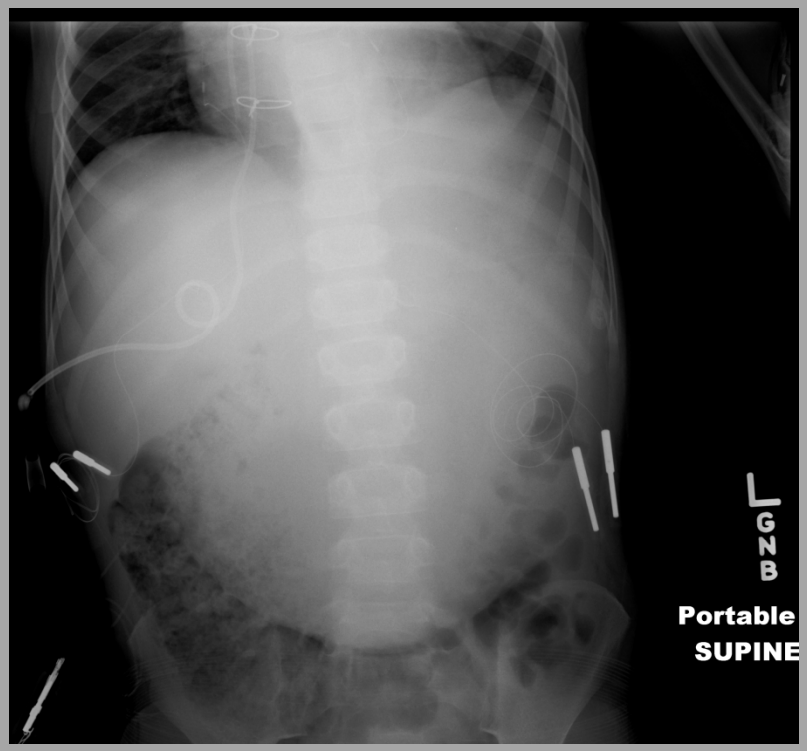
- Pediatric Donor Lungs are preferentially directed to Pediatric Recipients over a broader geographic area
- Adolescent Lung Candidates may not be large enough for lungs from previously healthy adolescent donors and thus may benefit by increased availability of lungs from younger donors.

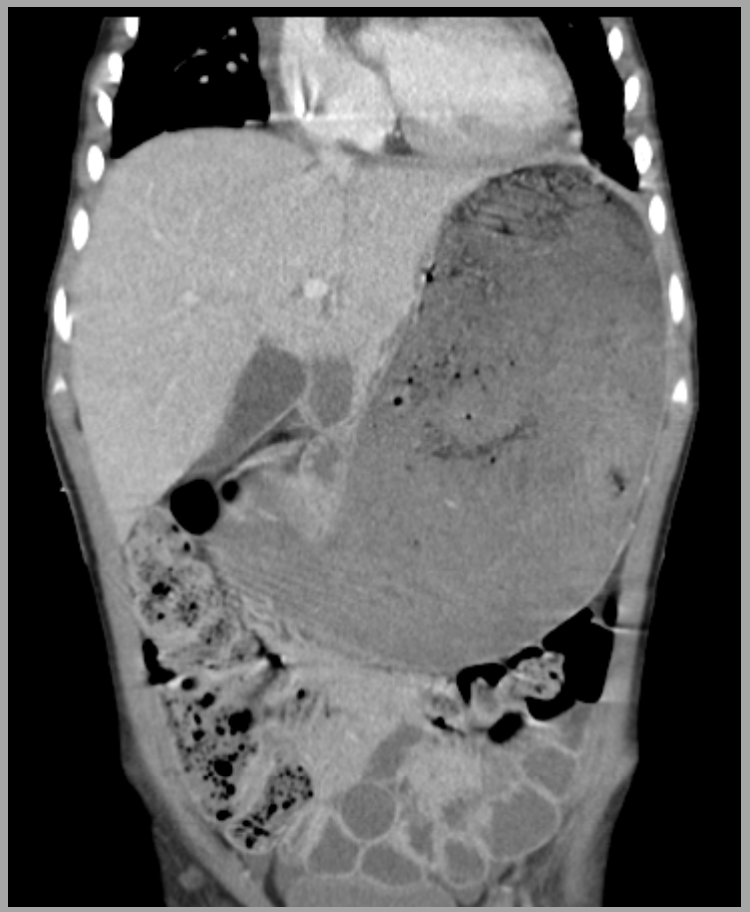
Acute Cellular Rejection

- Determined with TBBx or OLB
- Peri-vascular lymphocytic infiltration
- Treatment: High-dose methylprednisolone succinate (Solu-Medrol), 10 mg/kg I.V. daily X 3 days

GER and Lung Transplantation: Inconvenience or Complication?

8 y/o boy 5 days post H-L Txplt with abdominal pain and a “mass”



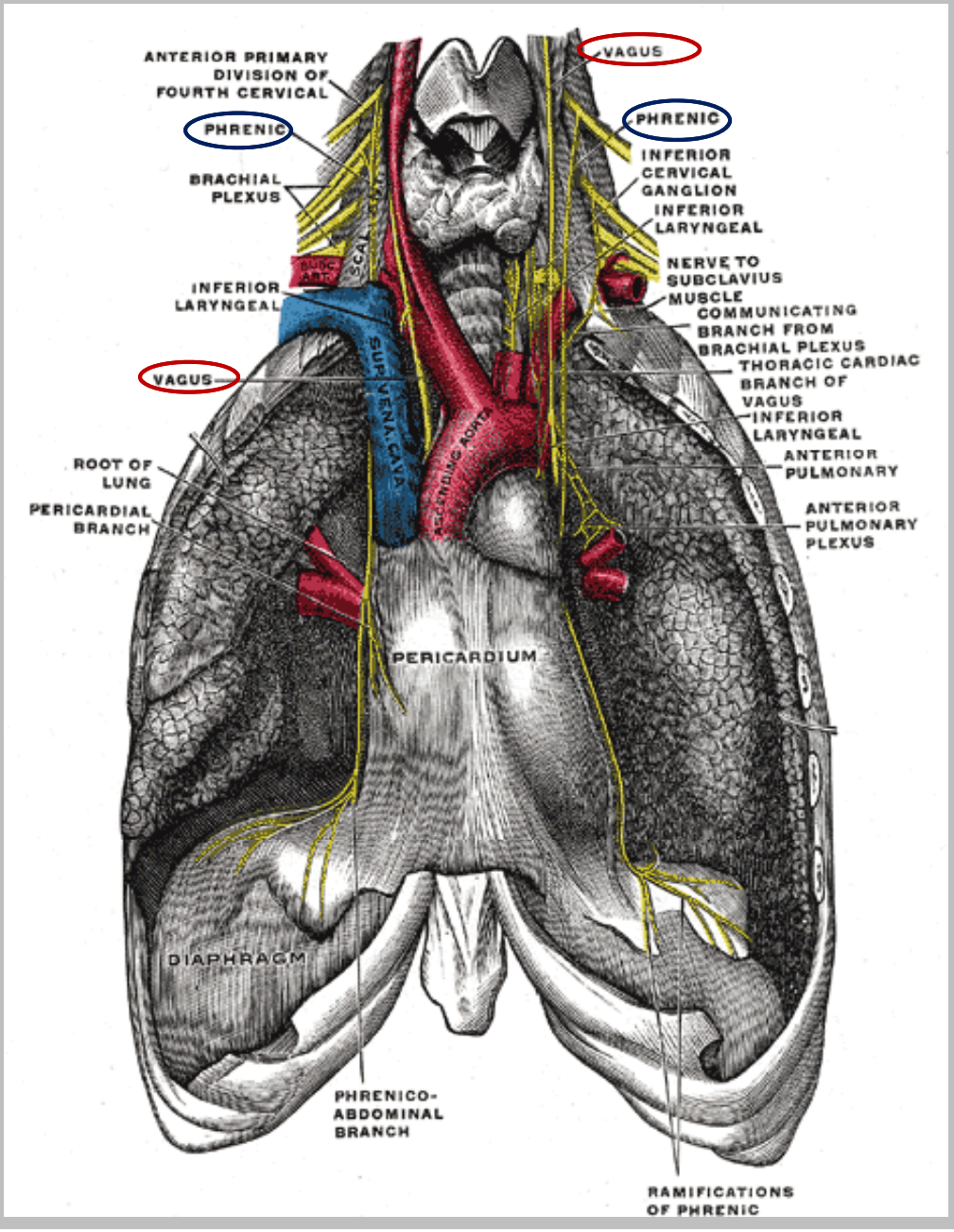


Gastroparesis following lung transplantation

- 3-year follow up of 38 adult lung or heart-lung recipients.
- 16/38 (42%) experienced GI complaints (pain, dyspepsia, N/V, satiety)
- Evaluation led to 27 diagnoses in the 16 patients
- Gastroparesis confirmed with endoscopy (retained food after fasting) and scintigraphy in 9/16
- 44% of patients with gastroparesis developed OB vs 29% in those without gastroparesis

Berkowitz N. Chest 1995; 108:1602-07

The phrenic and vagus nerves course through the thorax

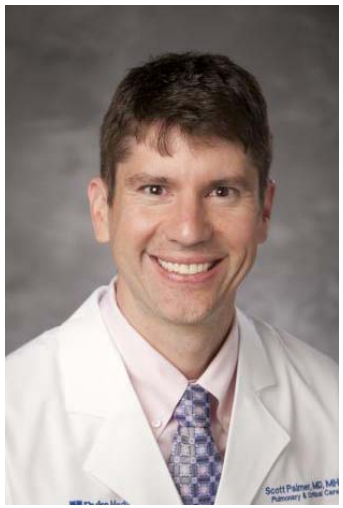


What about GER?

Lung Transplantation Exacerbates Gastroesophageal Reflux Disease*

Lisa R. Young, MD; Denis Hadjiliadis, MD, MHS; R. Duane Davis, MD, FCCP; and Scott M. Palmer, MD, MHS, FCCP

Chest 2003; 124: 1689-1693

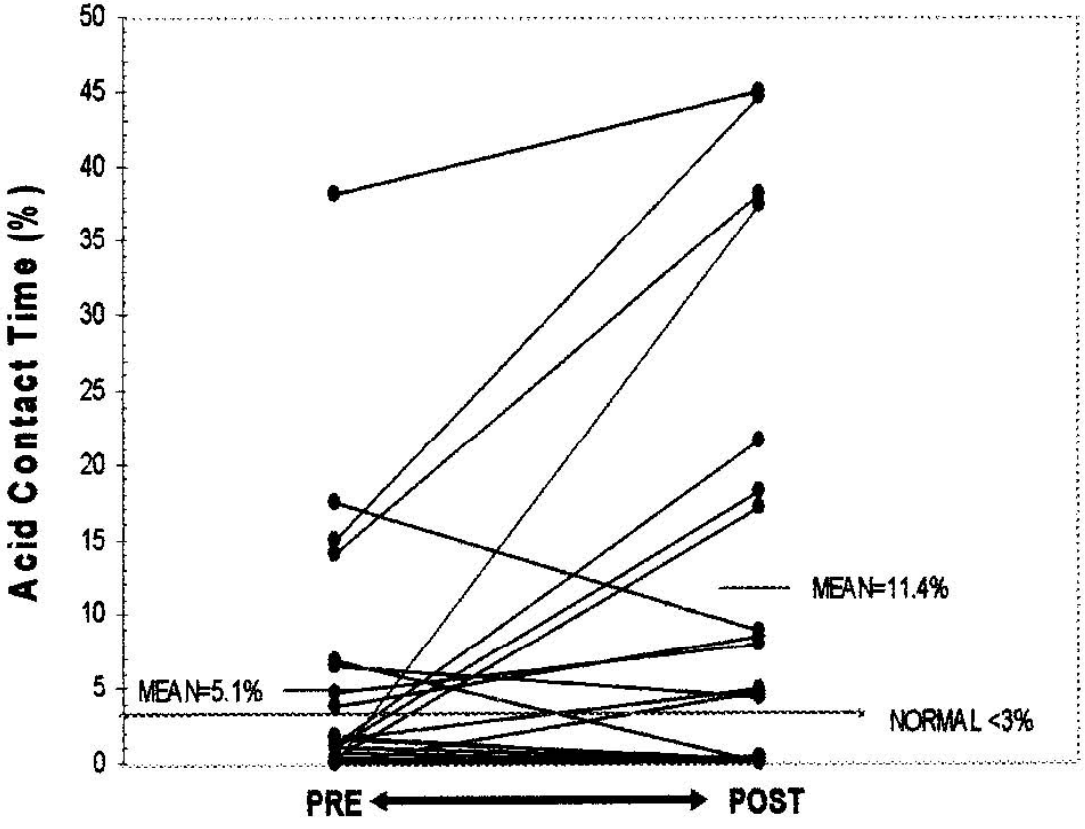


GER Increases following Lung Transplantation

- Duke study, 2003: 23 patients (mean age 51.5 yrs) studied with pH probe, esophageal manometry, and gastric emptying pre- and post-transplant (median 100 days)
- Emphysema (11), CF (4), and IPF (3) most common diagnoses.
- GER present pre-transplant in 8/23 (35%), but in 15/23 (65%) post-transplant. 80% of patients were asymptomatic!

Young LR et. al. Chest 124:1689-1693, 2003

Increased Esophageal Acid Contact Time Following Lung Transplant



Supine Acid Contact Time by Patient

Young LR et. al. Chest 124:1689-1693, 2003

Can Prevention of GER Improve Transplant Outcome?

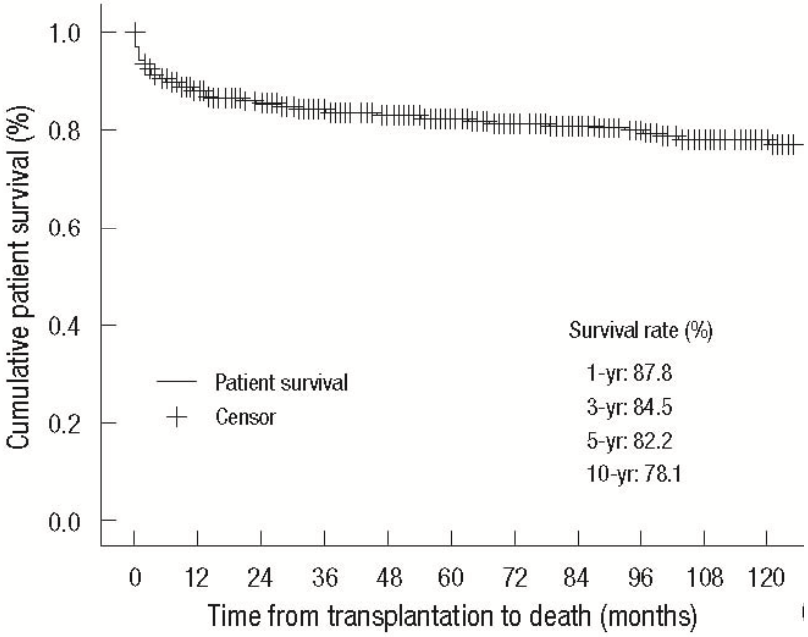
Early Fundoplication Prevents Chronic Allograft Dysfunction in Patients With Gastroesophageal Reflux Disease

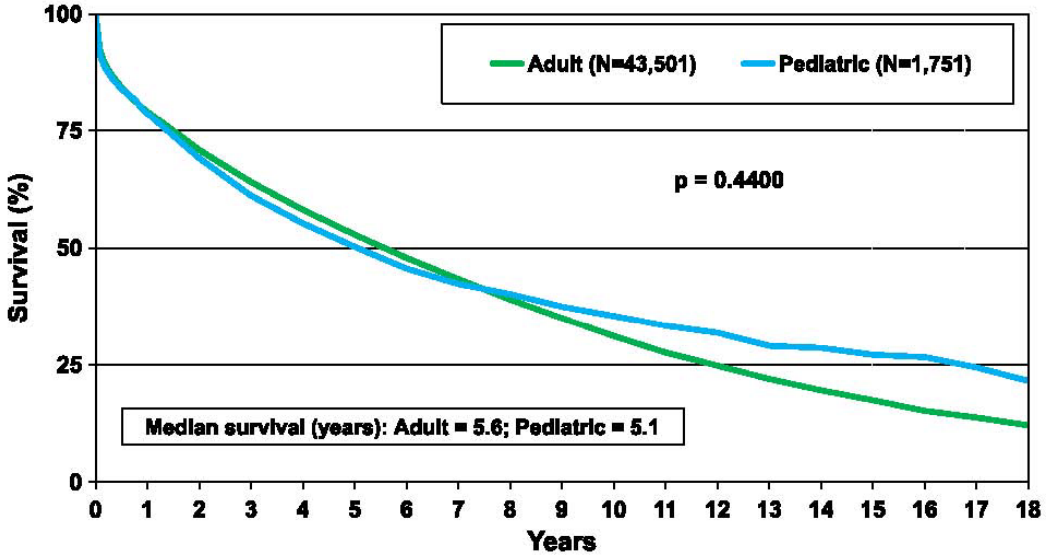
Edward Cantu III, MD, James Z. Appel III, MD, Matthew G. Hartwig, MD, Hiwot Woreta, BA, Cindy Green, PhD, Robert Messier, MD, PhD, Scott M. Palmer, MD, MPH, and R. Duane Davis, Jr, MD

Department of Surgery, Department of Medicine, Duke University Medical Center; Duke Clinical Research Institute, Durham, North Carolina

Ann Thorac Surg 2004;78:1142–51

Why are lungs so “delicate” ?





Kim JM J Korean Med Sci 28: 42-47, 2013

Benden C J Heart Lung Transpl 33: 1025-1033, 2014

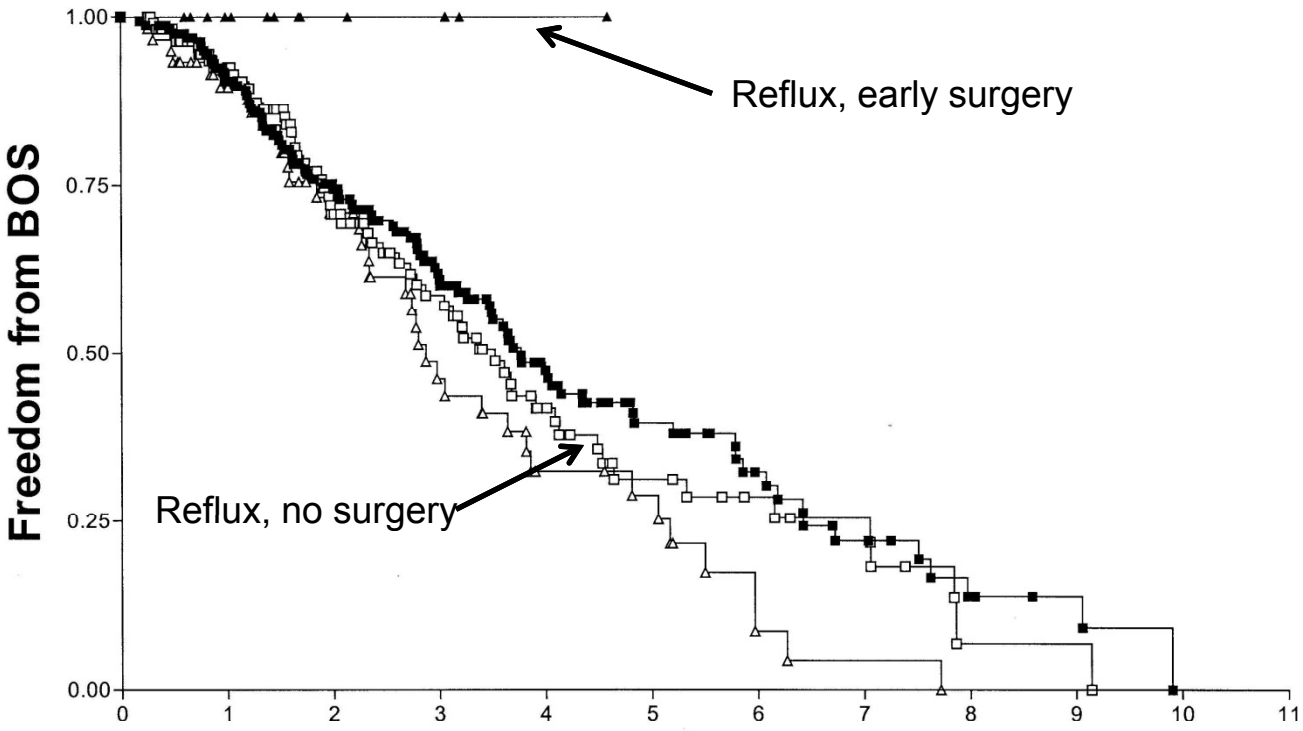
Early Fundoplication and Graft Dysfunction

- Duke retrospective study (4/1992-7/2003; 457 patients). GER studies only since 1997; initially only symptomatic patients until 3/1998.
- Stratified first by ICD-9 code for GER
  - No history of reflux n=180
  - History of reflux, no fundoplication n=125
  - History of reflux and early (<90 Days) fundoplication n=14
  - History of reflux and late fundoplication n=62

Cantu E et. al. Ann Thoracic Surg 78: 1142-51, 2004

Effect of Fundoplication on BOS

Fig 2. Freedom from BOS in ICD-9 segregated groups. ■ = no history of reflux; □ = reflux, no surgery; ▲ = reflux, early surgery; △ = reflux, late surgery. (BOS = bronchiolitis obliterans syndrome; ICD = international classification of diseases.)



Patients at risk at year	0	1	2	3	4	5	6	7	8	9	10
No History of Reflux	180	160	130	93	62	37	23	16	9	4	3
Reflux no Surgery	125	110	84	50	35	20	12	9	6	1	1
Reflux Early Surgery	14	12	8	5	3	1	0	0	0	0	0
Reflux Late Surgery	62	57	44	30	17	10	8	2	1	0	0

Cantu E et. al. Ann Thoracic Surg 78: 1142-51, 2004

Are CF patients at higher risk for GER post transplant?

Gastroesophageal reflux disease in lung transplant patients with cystic fibrosis

Bernardino M. Mendez, M.D.[a], Christopher S. Davis, M.D., M.P.H.[a], Cynthia Weber, M.D.[a], Raymond J. Joehl, M.D., F.A.C.S.[a,b], P. Marco Fisichella, M.D., F.A.C.S.[a,b,*]

[a]Department of Surgery, Loyola University Chicago, Stritch School of Medicine, 2160 South First Avenue, Room 3226, Health Sciences Campus, Maywood, IL 60153, USA; [b]Hines VA Hospital, Hines, IL, USA

Am J Surg 2012; 204: e21-26

CF and lung transplantation: Higher risk for GER?

- pH probe monitoring, esophageal manometry, gastric emptying scans, and Ba swallow studies in patients with CF (n=10) compared with patients without CF (n=78). Average time from transplant to GER studies was 30 months.
- Prevalence of GERD in CF patients was 90% (vs 54% in non-CF recipients). Proximal reflux in 70% of CF vs 29% of non-CF recipients.

Mendez BM Am J Surg 204: e21-6, 2012

What about other diseases and biomarkers as a risk for GER?

Pepsin concentrations are elevated in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis after lung transplantation

Christopher S. Davis, MD, MPH,[a] Bernardino M. Mendez, MD,[a] Diana V. Flint, MD,[a] Karen Pelletiere, RN, BSN,[b] Erin Lowery, MD, MS,[b] Luis Ramirez, BS,[a] Robert B. Love, MD, FACS, FRCS,[c] Elizabeth J. Kovacs, PhD,[a] and P. Marco Fisichella, MD, FACS[a,]*

[a] *Department of Surgery, Loyola University Chicago Health Sciences Campus, Maywood, Illinois*

[b] *Division of Pulmonary and Critical Care Medicine, Department of Medicine, Loyola University Chicago Health Sciences Campus, Maywood, Illinois*

[c] *Department of Thoracic and Cardiovascular Surgery, Loyola University Chicago Health Sciences Campus, Maywood, Illinois*

J Surg Res 2013; 185: E101-8

Pepsin in BAL fluid post-transplant

- Gastric pepsin measured in 252 BAL samples from 100 recipients.
- Correlation of pepsin with biopsy results, Ba swallows, esophageal functional studies, and gastric emptying scans was sought—but <50% of patients were studied…
- Underlying disease leading to transplant was another variable studied.

Davis CS J Surg Research 185: E101-E108, 2013

Pepsin levels in lung recipients

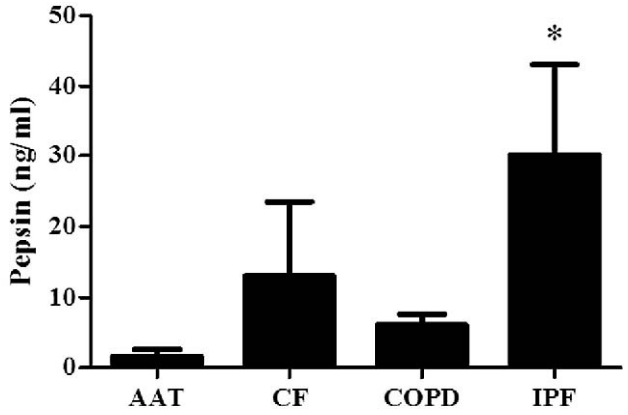


Fig. 2 – Bronchoalveolar lavage fluid pepsin concentrations among the most common indications for lung transplantation: AAT ($n = 7$), CF ($n = 14$), COPD ($n = 38$), and IPF ($n = 24$). *$P < 0.05$ *versus* all other groups (Kruskal-Wallis post-hoc analysis).

- In IPF patients, those with higher pepsin levels had increased frequency of acute rejection
- Effect on chronic rejection /BOS not reported.

Davis CS J Surg Research 185: E101-E108, 2013

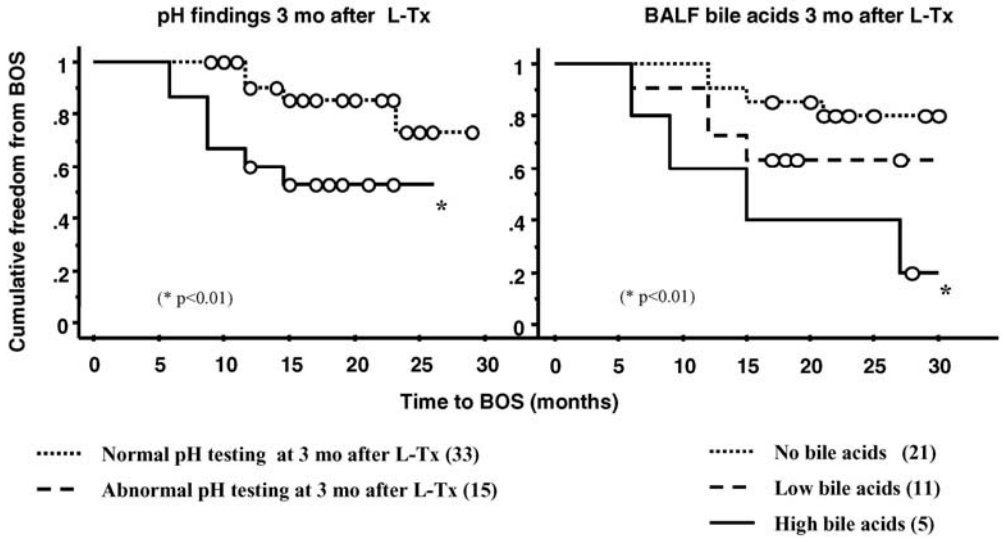
GER common post-transplant despite the underlying diagnosis…

- All 4 groups had high prevalence of GERD and delayed gastric emptying post-transplant
- Patients with CF and AAT had highest incidence of proximal (high) GER
- All 4 groups had high incidence of delayed gastric emptying.
- IPF patients had higher incidence of acute rejection
- However: BOS, mortality, and length of follow-up was not different among the 4 groups.

Davis CS J Surg Research 185: E101-E108, 2013

Is pepsin a satisfactory biomarker for GER post-transplant?

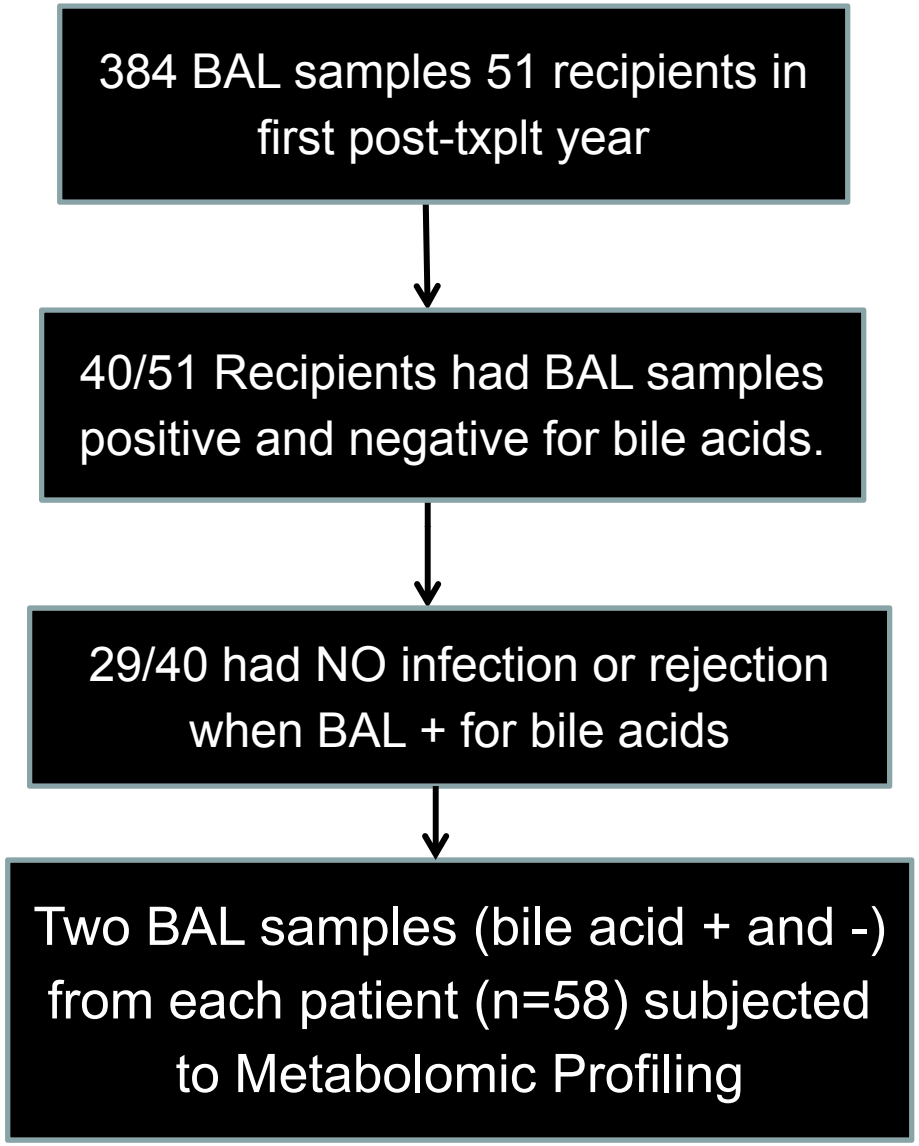
- Possibly:
  - Pepsin found in BAL samples post-transplant, with negative findings in BAL from healthy controls. (Ward C. Thorax 2005; 60:872)
- Are there alternative biomarkers?
  - Bile acids: (D'Ovidio F. Am J Transplant 2006; 6: 1930)



Mechanisms of graft injury associated with GER/Aspiration.

- Bile acids in BAL fluid may be more sensitive and specific markers for aspiration
- Could they also be a surrogate marker of inflammation leading to airway damage/BOS?
- Might they be the cause/mechanism of damage leading to BOS?

Neujahr DC Am J Transplantation. 2014; 14:841



Neujahr DC Am J Transplantation. 2014; 14:841

Metabolomic Profiling

- Liquid chromatography coupled to high-resolution mass spectrometry.
- Molecules identified using mass/charge (m/z) ratio and a specific software
- False discovery rate (FDR) analysis used to control the expected proportion of incorrectly rejected null hypotheses (“false discoveries”). This is a commonly used technique in settings of large data sets…

Neujahr DC Am J Transplantation. 2014; 14:841

Metabolomic Profiling (2)

- 7608 individual metabolic peaks seen with LC-MS
- Using FDR, 2302 molecules identified that were significantly different. Most of these were small (m/z 80-500).
- Refinement to 472 was done by identifying top 5% of metabolites that contributed to 95% separation of bile acid + and – samples.

Neujahr DC Am J Transplantation. 2014; 14:841

Metabolomic Profiling (3)

- Many of the molecules identified as increased in Bile acid + BAL were associated with:
  - Microbial metabolism
  - Biomarkers of lung injury including
    - T-cell Granzyme B level
    - Chemoattractants CXCL9 and CXCL10
- This suggests that aspiration leads to upregulation of inflammatory mediators, potentially leading to graft damage or dysfunction

Neujahr DC Am J Transplantation. 2014; 14:841

Limitations/Questions

- Vast majority of studies involve adults
- Some studies show that GER is common post-transplant but is *not* linked to development of BOS. (see Blondeau Eur Resp J 31:707, 2008)
- Limited information/studies on medical management options for gastroparesis or GER (see Lidor AO Domperidone for delayed gastric emptying post transplant Prog. Transplantation 2014; 24: 27 or Mertens V Azithromycin reduces GER and aspiration post-transplant Dig. Dis. Sci. 2009; 54:972)
- Should all potential lung recipients be evaluated for GER prior to transplant?
- When is optimal time for surgical management of GER?
- Interruption of the consequences of aspiration: Is it feasible? Will it help prevent BOS?