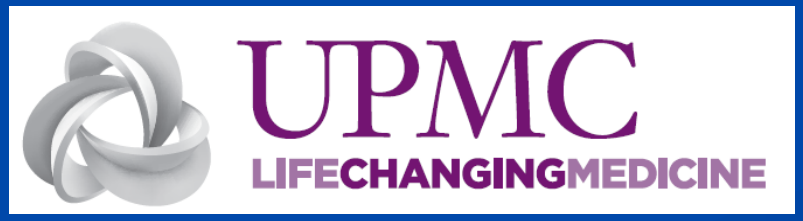
Overview of Lung Transplantation

Matthew Ricks Morrell, M.D.
Medical Director Lung Transplantation
Division of Pulmonary, Allergy and Critical Care

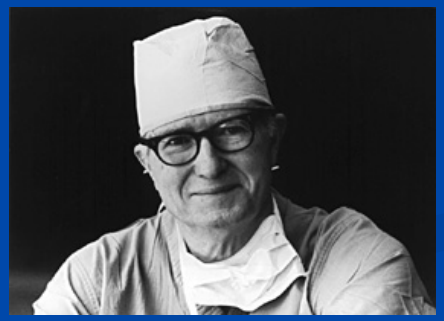


Outline

- Background
- Process/Description
- History
- Mechanisms of Action
- Safety and Tolerability
- Use in Solid-Organ Transplantation
- Preliminary Research

First Lung Transplant

- Performed on June 11, 1963 at the University of Mississippi
  - Recipient: non-resectable left lung CA
  - Donor: massive myocardial infarction
- Treated with azathioprine, prednisone and mediastinal radiation
- Died due to progressive renal failure and malnutrition
  - Survived 18 days



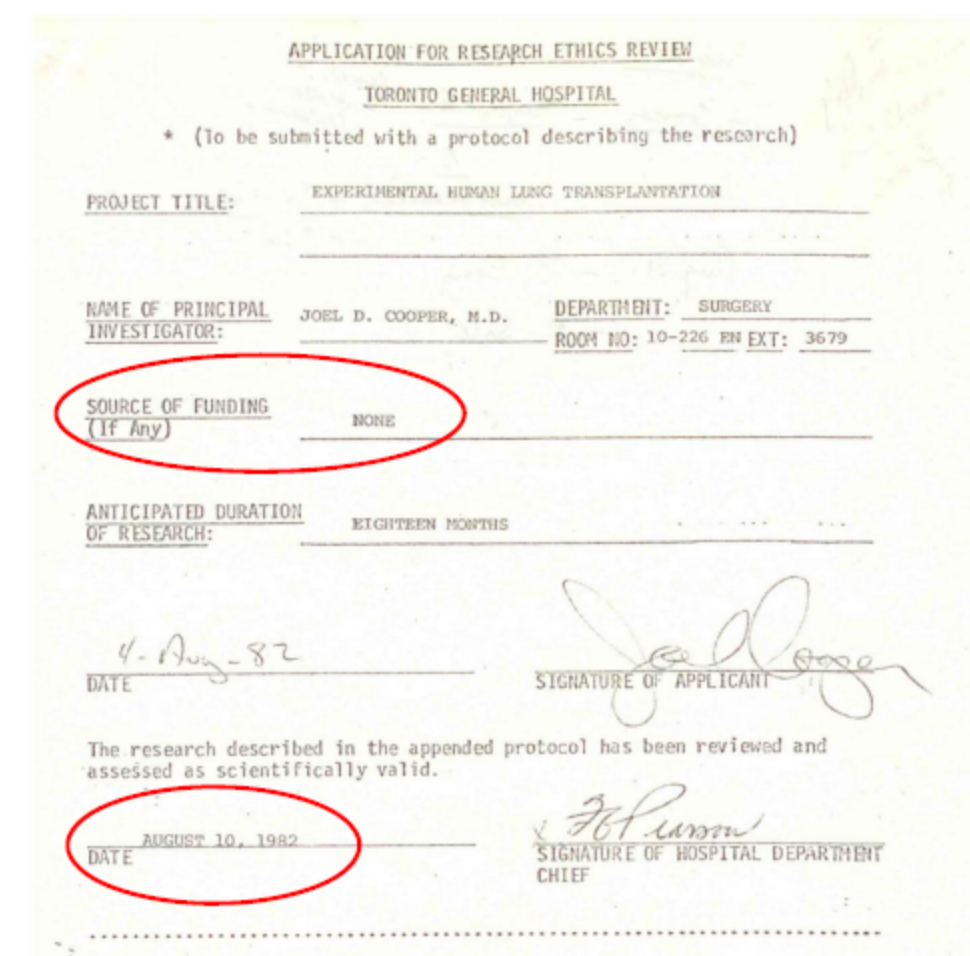
JAMA®
The Journal of the American Medical Association

Hardy, JD, Webb, WR, Dalton, ML Jr, Walker, GR Jr. Lung homotransplantation in man. JAMA 1963; 186:1065

Lung Transplantation History

- 1963-1981: Nearly 40 lung transplants were attempted
  - Longest survival of 6-8 months
  - Complicated by dehiscence, graft failure

Lung Transplant Research



APPLICATION FOR RESEARCH ETHICS REVIEW

TORONTO GENERAL HOSPITAL

* (To be submitted with a protocol describing the research)

PROJECT TITLE: EXPERIMENTAL HUMAN LUNG TRANSPLANTATION

NAME OF PRINCIPAL INVESTIGATOR: JOEL D. COOPER, M.D.

DEPARTMENT: SURGERY

ROOM NO: 10-226 EN EXT: 3679

SOURCE OF FUNDING (If Any): NONE

ANTICIPATED DURATION OF RESEARCH: EIGHTEEN MONTHS

4-Aug-82
DATE

SIGNATURE OF APPLICANT

The research described in the appended protocol has been reviewed and assessed as scientifically valid.

AUGUST 10, 1982
DATE

SIGNATURE OF HOSPITAL DEPARTMENT CHIEF

www.humboldtcanada.com/presentations_air/chow.pdf

Selection Criteria

III Selection Criteria

Potential candidates will include patients, preferably under 50 years of age, with end-stage, disabling primary pulmonary pathology. This will include patients with end-stage interstitial lung disease and patients with end-stage primary pulmonary hypertension, who have already experienced at least one syncopal episode. Patients with pulmonary failure due to systemic sclerosis will be considered if there is no evidence for circulating immune complexes. Patients with cystic fibrosis will not be considered.

Potential candidates should be individuals who are totally disabled, unable to perform any tasks and with limited ability to ambulate. Patients requiring home oxygen because of respiratory symptoms will be included. Patients with chronic infection, previous myocardial infarction, or other major organ failure (other than cor pulmonale) will be excluded.

Patients should be judged to have less than six months to live. All

www.humboldtcanada.com/presentations_air/chow.pdf

First Successful Single Lung Tx

1983

Tom Hall with wife, Barbara
1st successful lung transplant

Ron Grossman MD

Tom was an incredibly brave guy.....I told him what the odds were. 43 human lung transplants had been done to date. No one survived longer than 6 month and in fact, most never left hospital. I remember like it was yesterday. He told me, "It would be a privilege to be patient 44." *8 May 2011 – Ron Grossman*

First Successful Double Lung Tx

1986 – First Bilateral Lung Transplant
Toronto: Alex Patterson

15 yrs later

www.humboldtcanada.com/presentations_air/chow.pdf

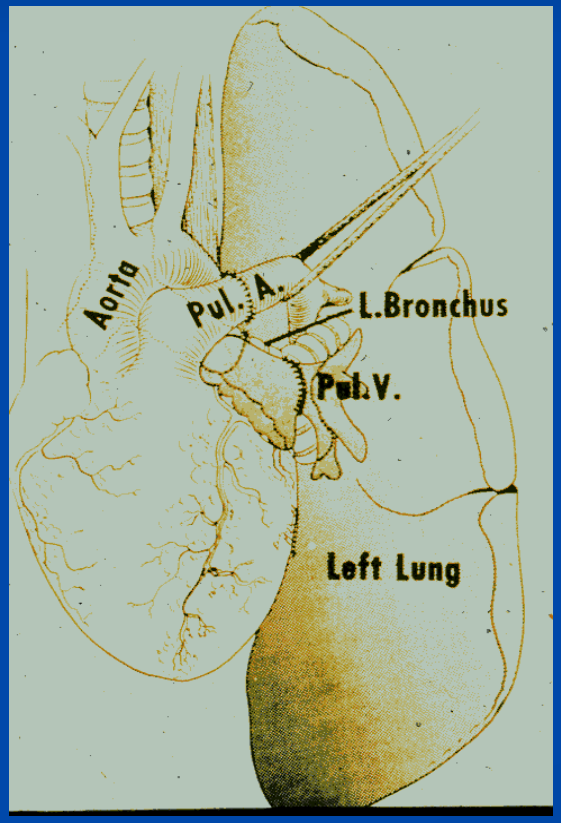
Lung Transplant at UPMC

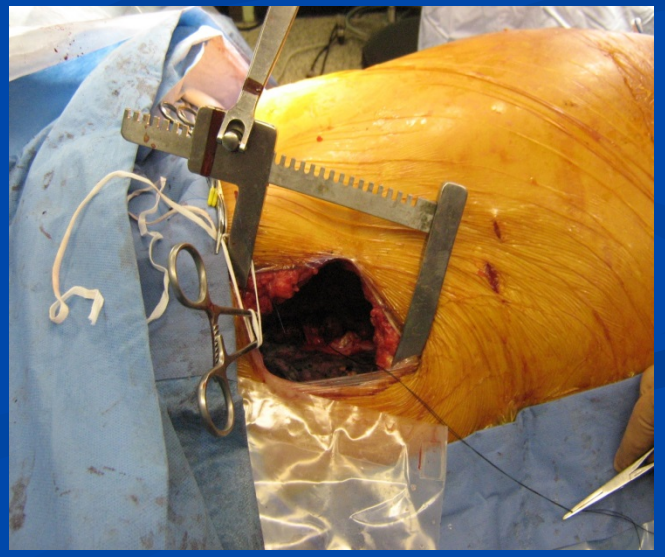
- 1982: Region's first and world's second heart-lung transplant
- 1985: Region's first single lung transplant
- 1989: Nation's first pediatric double lung transplant

Bartley Griffith

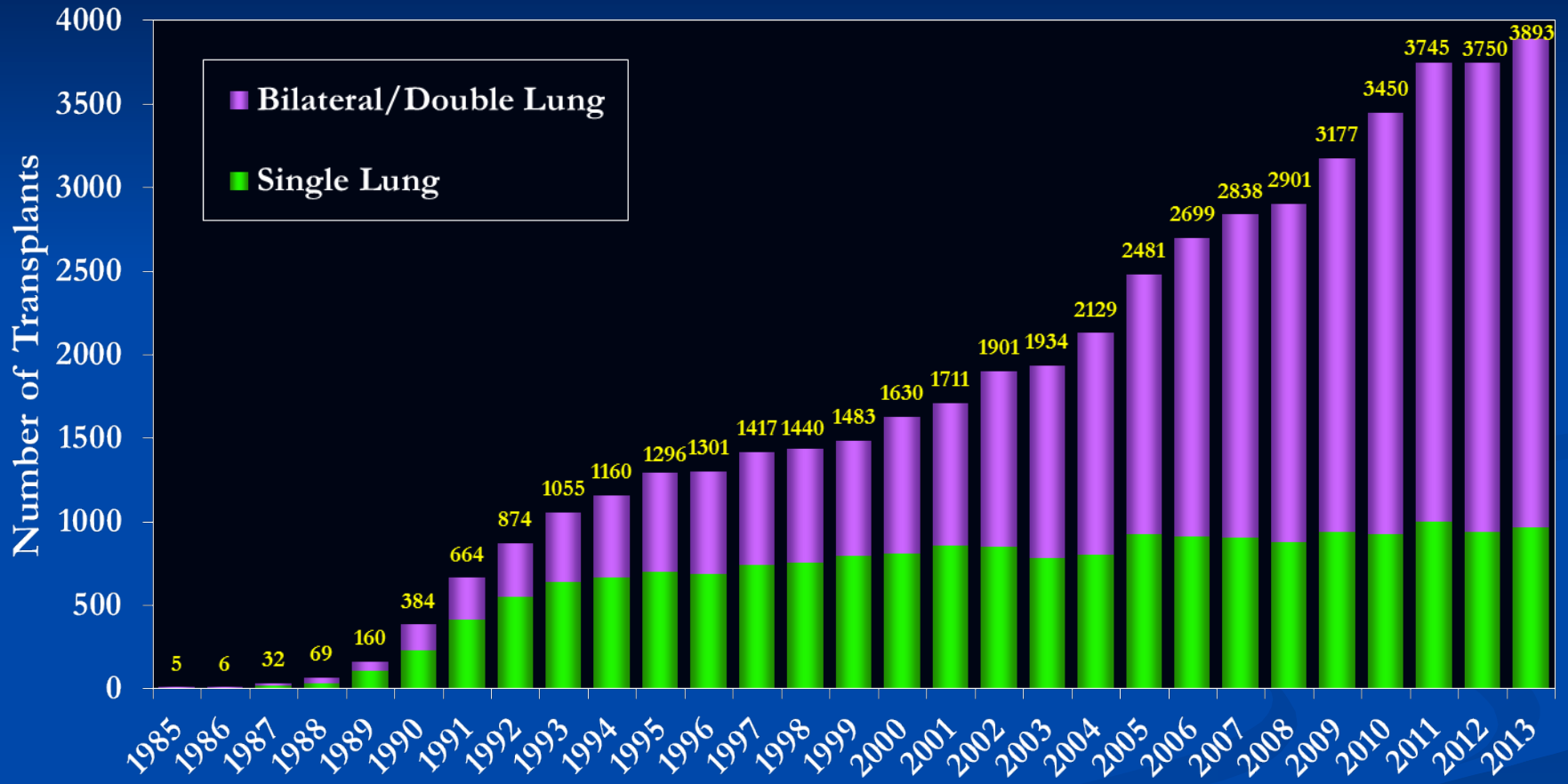
Surgical Technique

- 1990: Bilateral sequential double lung transplant



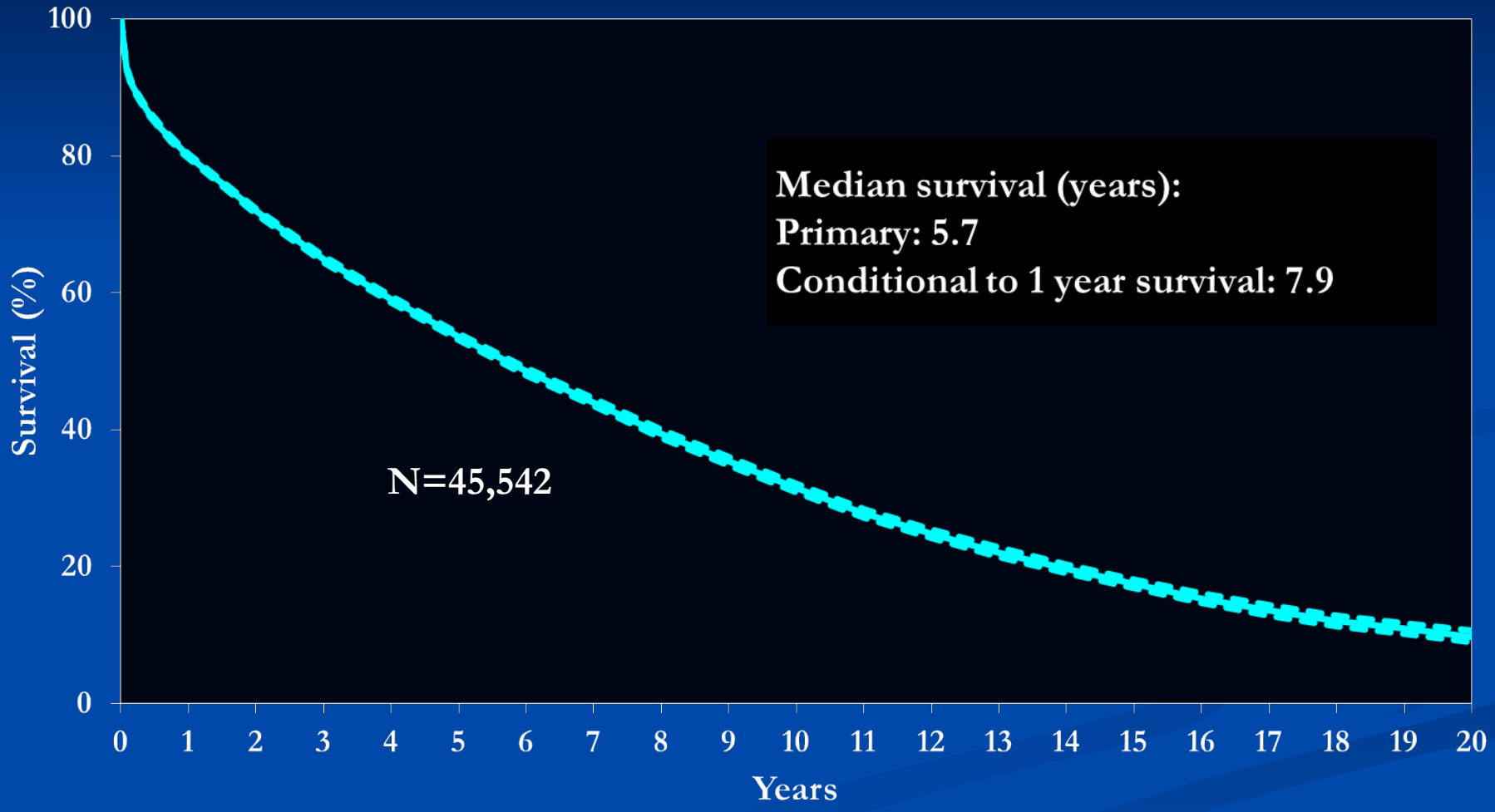


Adult Lung Transplants
Number of Transplants by Year and Procedure Type



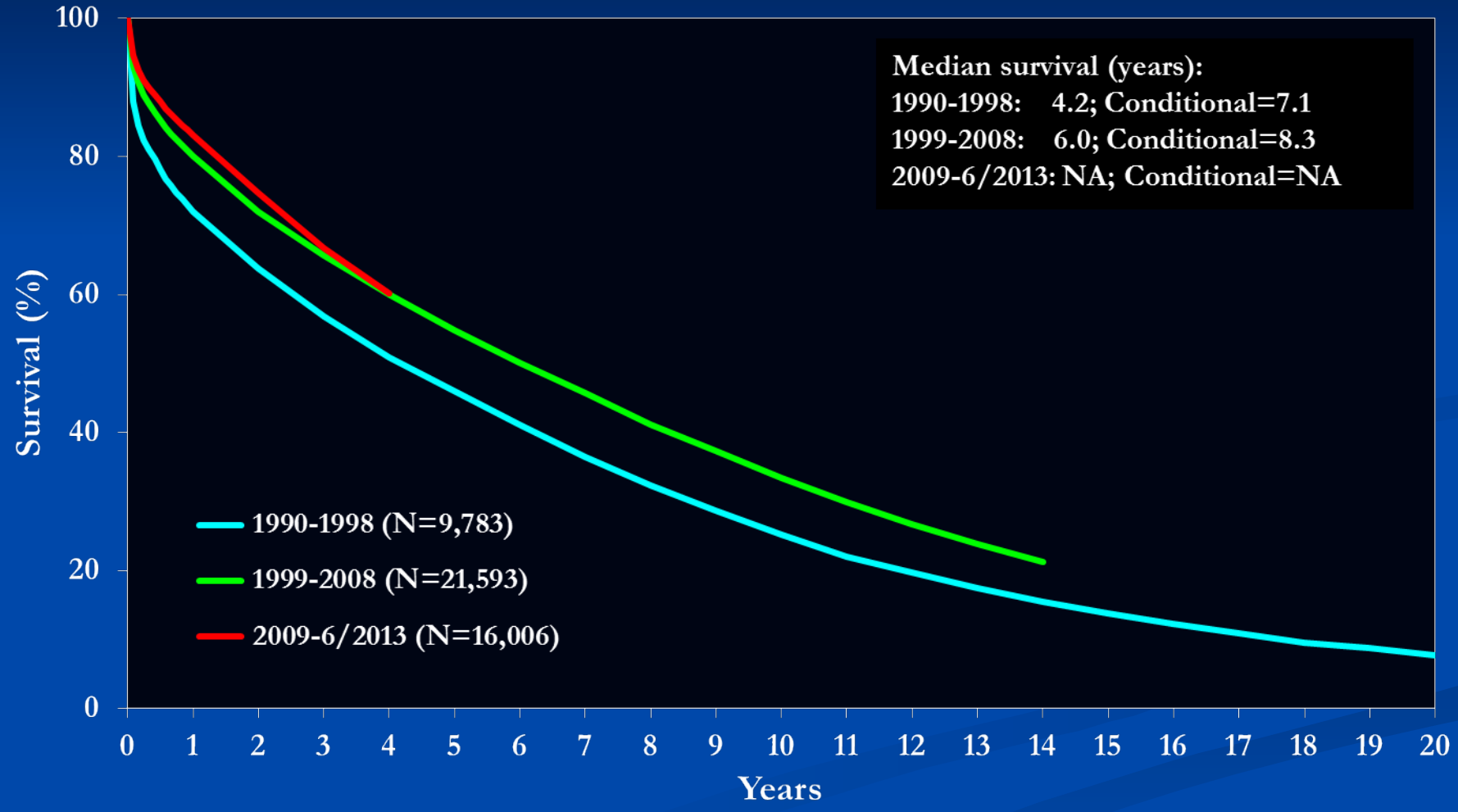
ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2015
JHLT. 2015 Oct; 34(10): 1264-1277

Adult Lung Transplants
Kaplan-Meier Survival by Transplant Type
(Transplants: January 1990 – June 2013)



Adapted from: JHLT. 2015 Oct; 34(10): 1264-1277

Adult Lung Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1990 – June 2013)

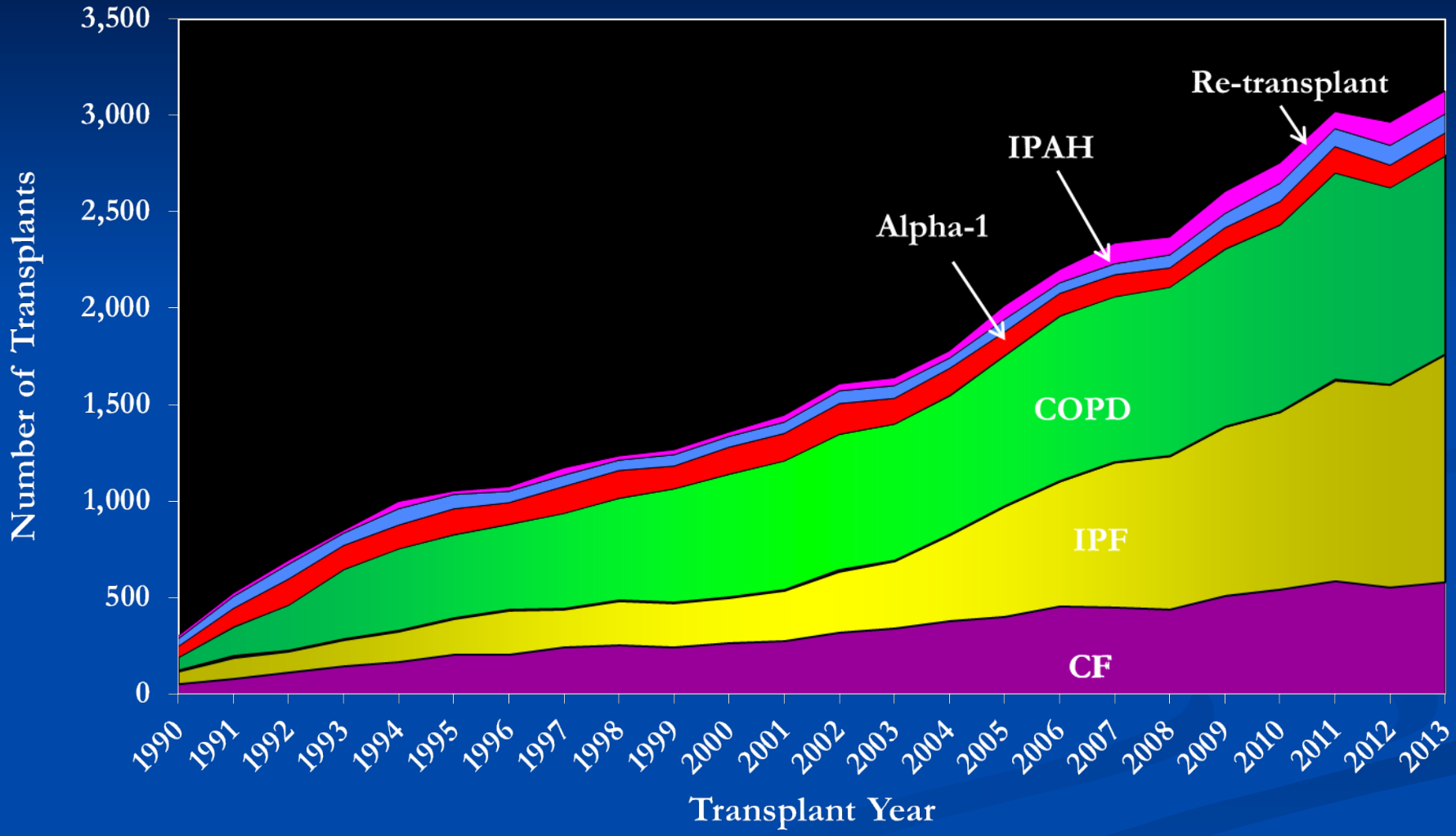


Adapted from: JHLT. 2015 Oct; 34(10): 1264-1277

Which of these diagnoses is contraindicated for lung transplantation?

- a) Hypersensitivity pneumonitis
- b) Pulmonary alveolar proteinosis
- c) Bronchoalveolar carcinoma
- d) Silicosis
- e) Scleroderma
- f) LAM
- g) None of the above

Adult Lung Transplants
Major Indications by Year (Number)



Adapted from: JHLT. 2015 Oct; 34(10): 1264-1277

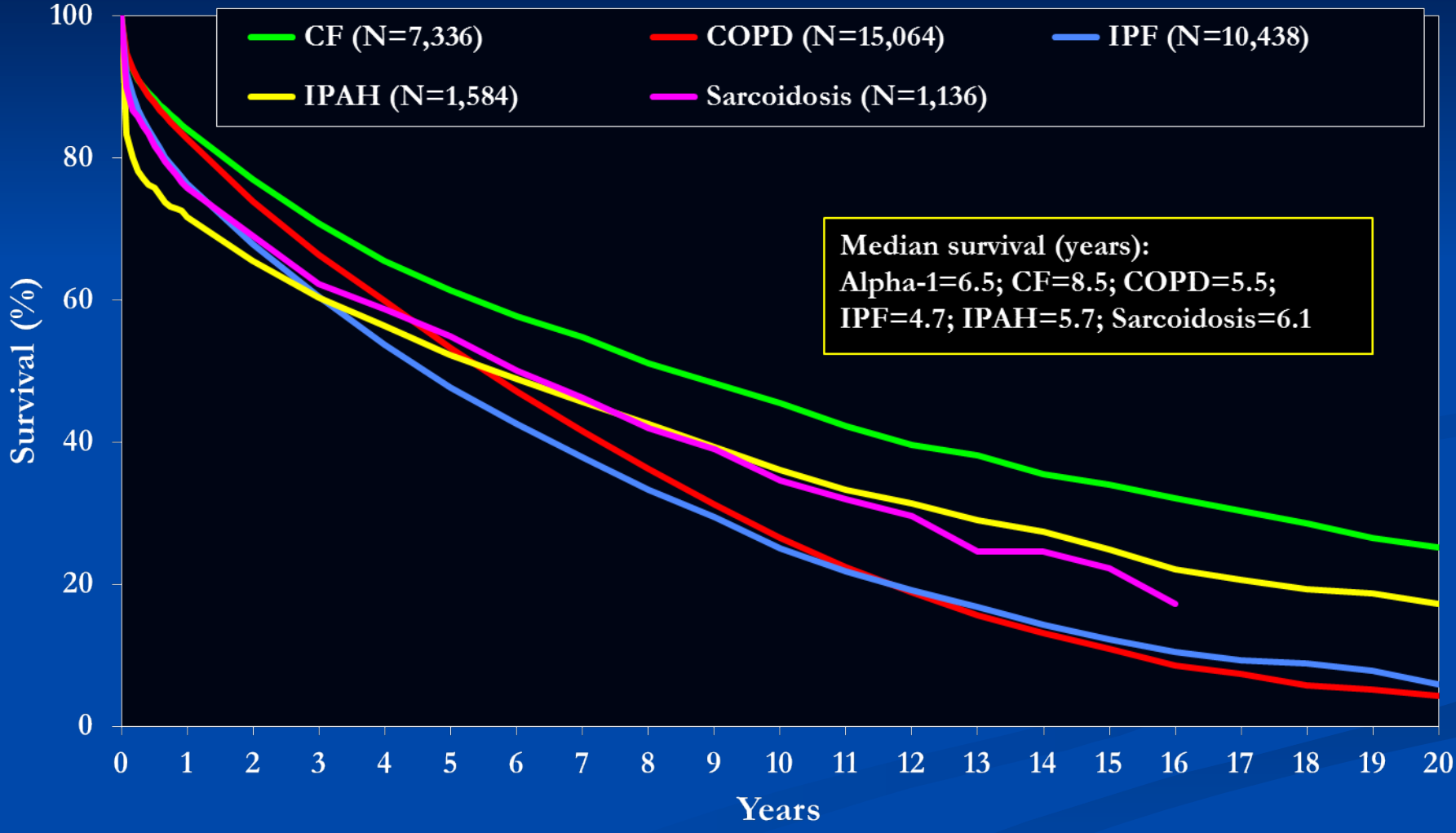
Adult Lung Transplants
Indications (Transplants: January 1995 – June 2014)

Diagnosis	SLT (N=16,226)	BLT (N=29,457)	TOTAL (N=45,683)
COPD/Emphysema	6,826 (42.1%)	7,856 (26.7%)	14,682 (32.1%)
Idiopathic Pulmonary Fibrosis	5,561 (34.3%)	5,442 (18.5%)	11,003 (24.1%)
Cystic Fibrosis	228 (1.4%)	7,191 (24.4%)	7,419 (16.2%)
Alpha-1	792 (4.9%)	1,667 (5.7%)	2,459 (5.4%)
Idiopathic Pulmonary Arterial Hypertension	91 (0.6%)	1,250 (4.2%)	1,341 (2.9%)
Pulmonary Fibrosis, Other	758 (4.7%)	1,125 (3.8%)	1,883 (4.1%)
Bronchiectasis	65 (0.4%)	1,167 (4.0%)	1,232 (2.7%)
Sarcoidosis	301 (1.9%)	857 (2.9%)	1,158 (2.5%)
Retransplant: Obliterative Bronchiolitis	338 (2.1%)	440 (1.5%)	778 (1.7%)
Connective Tissue Disease	200 (1.2%)	481 (1.6%)	681 (1.5%)
Other	1066 (6.6%)	1981 (6.6%)	3047 (13.2%)

Adapted from: JHLT. 2015 Oct; 34(10): 1264-1277

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

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



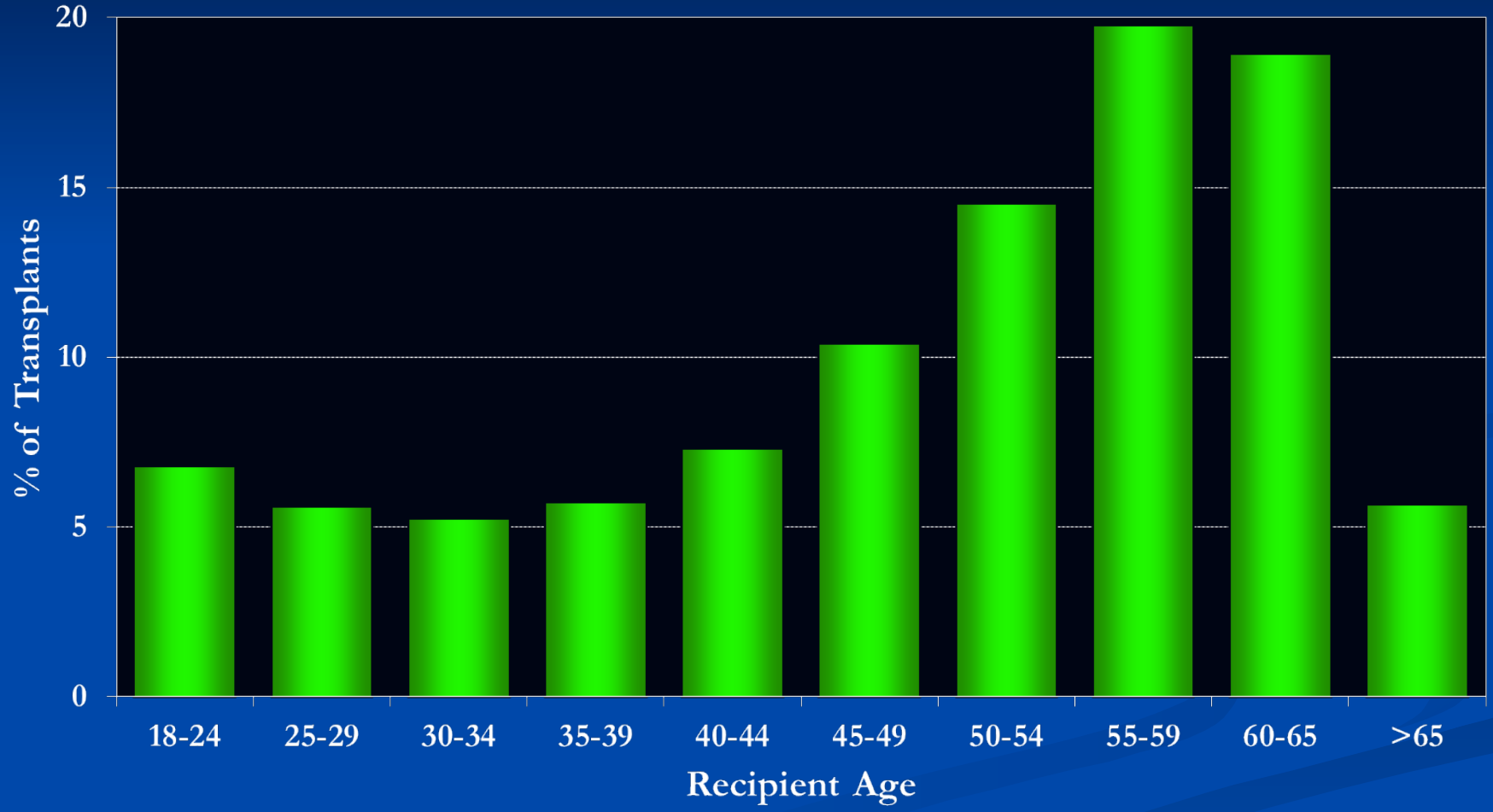
Adapted from: JHLT. 2015 Oct; 34(10): 1264-1277

Which of the following diseases can recur after lung transplantation?

- a) Bronchoalveolar carcinoma
- b) Pulmonary alveolar proteinosis
- c) Sarcoidosis
- d) LAM
- e) Diffuse pan bronchiolitis
- g) All of the above

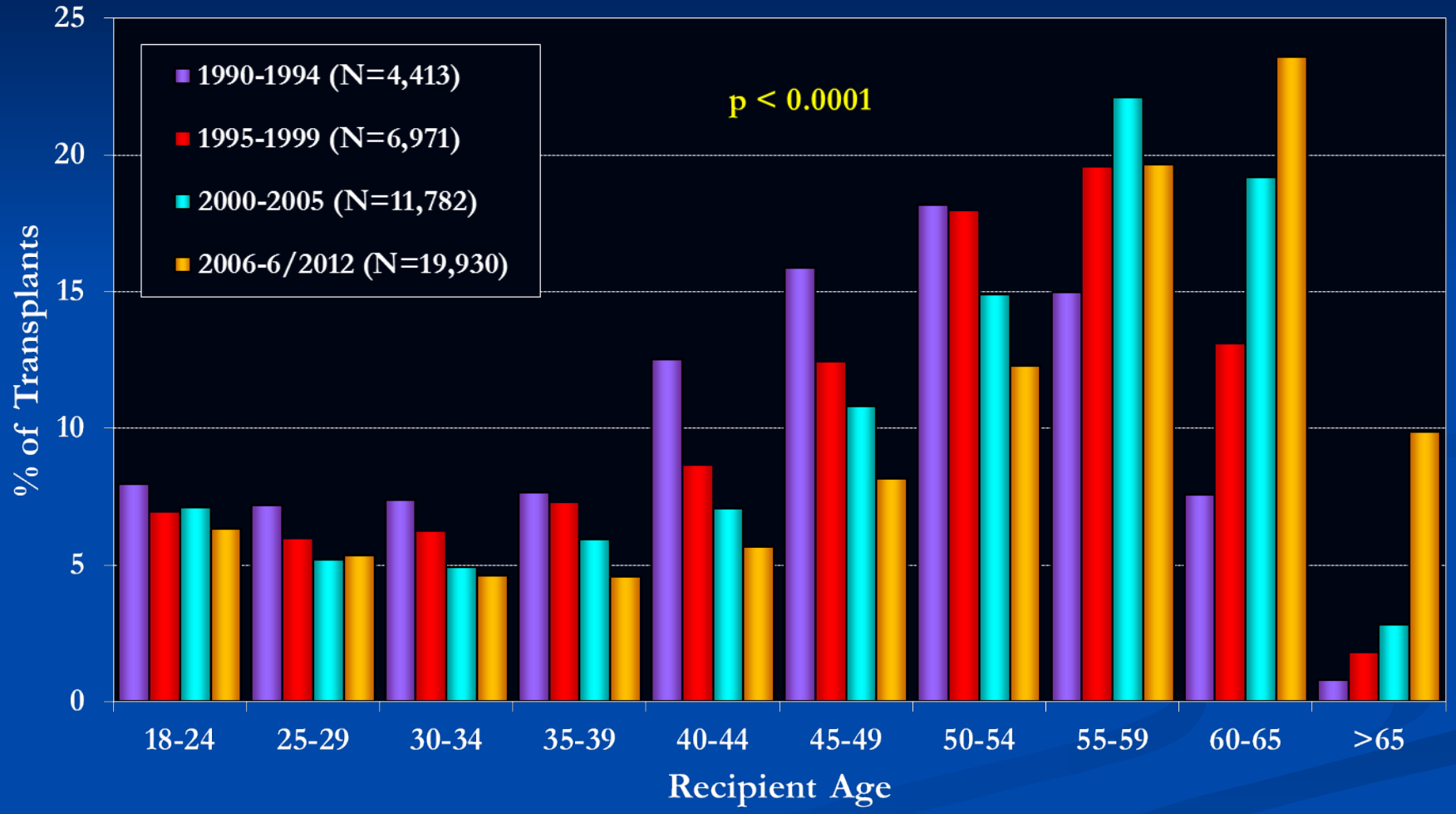
Adult Lung Transplants

Recipient Age Distribution (Transplants: January 1985 – June 2012)



Adapted from: JHLT. 2013 Oct; 32(10): 965-978

Adult Lung Transplants
Recipient Age Distribution by Era



Adapted from: JHLT. 2013 Oct; 32(10): 965-978

Which of these patients is NOT appropriate for lung transplantation?

- a) 68 yo female who is a Jehovah's Witness with COPD (FEV1 <25%) with osteoporosis.
- b) 22 yo male with CF colonized with Burkholderia cenocepacia with uncontrolled GERD.
- c) 60 yo female with IPF with single vessel CAD who quit smoking 4 mos ago.
- d) 35 yo female with PH previously on Phen-fen with BMI 34 and history of lymphoma in remission since 2004.

Contraindications for lung transplantation

ABSOLUTE

- Recent malignancy
- History of HIV, Hepatitis B or C with cirrhosis
- Active or recent cigarette smoking, drug abuse or alcohol abuse
- Severe psychiatric illness
- Active infection
- Noncompliance with medical care
- Absence of consistent social network
- Severe deconditioning

RELATIVE

- Age >70
- Obesity BMI>35
- Malnutrition BMI<16
- Presence of end organ damage
- Current use of corticosteroids >prednisone 10mg qday
- Prior thoracic surgery or pleurodeisis
- Invasive ventilation
- High level of preformed antibodies to HLA antigens

COPD

- BODE Index:

COPD

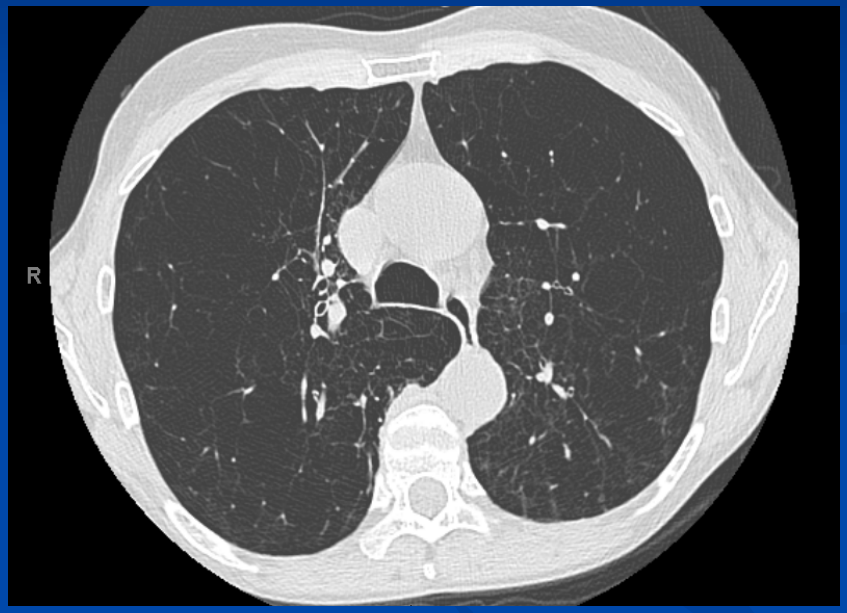
- BODE Index:

Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale‡	0–1	2	3	4
Body-mass index§	>21	≤21		

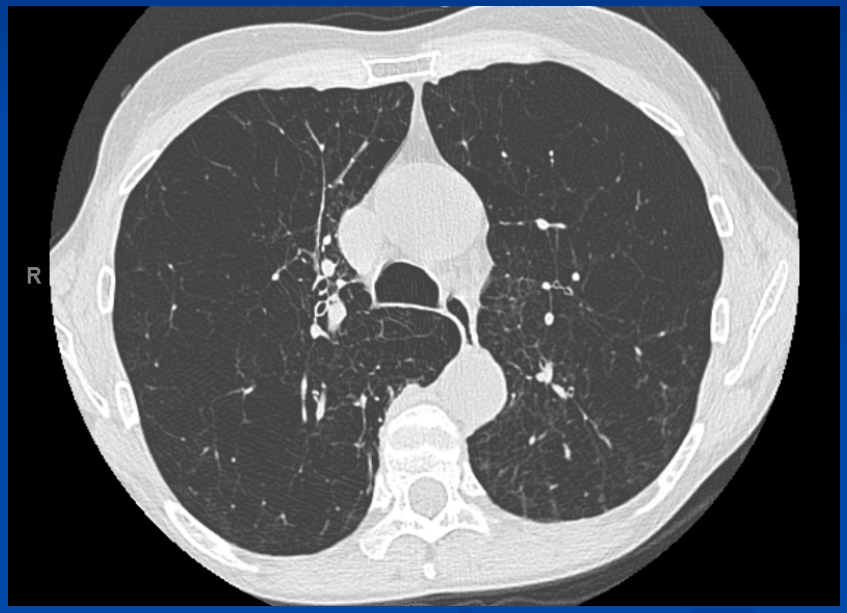
* The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV_1 denotes forced expiratory volume in one second.
† The FEV_1 categories are based on stages identified by the American Thoracic Society.
‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
§ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

COPD

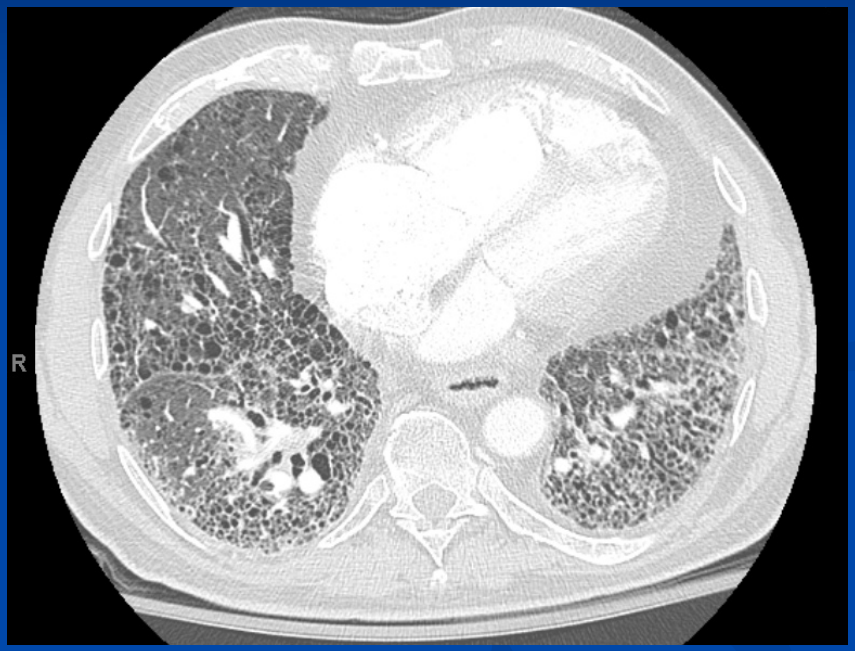


COPD

- BODE Index of 7-10 or:
- History of hospitalization of exacerbation with PCO2 >50mm Hg
- Pulmonary Hypertension or cor pulmonale
- FEV1 <20% and
  - DLCO <20% or
  - Homogenous distribution of emphysema

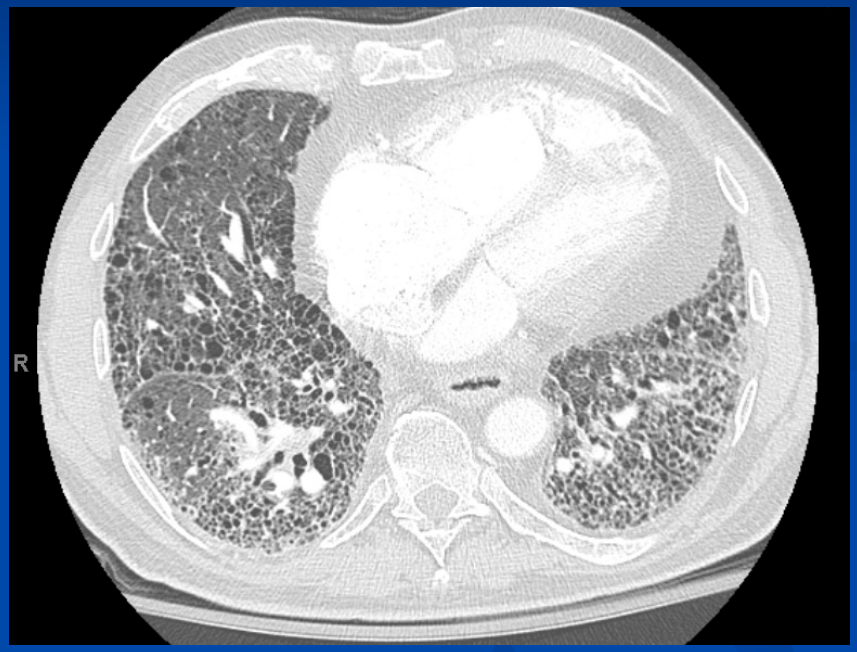


IPF/UIP



IPF/UIP

- DLCO <39% predicted
- FVC decrement of 10% over 6 mo. Period
- Desaturation <88% on 6-min walk
- Honeycombing on HRCT

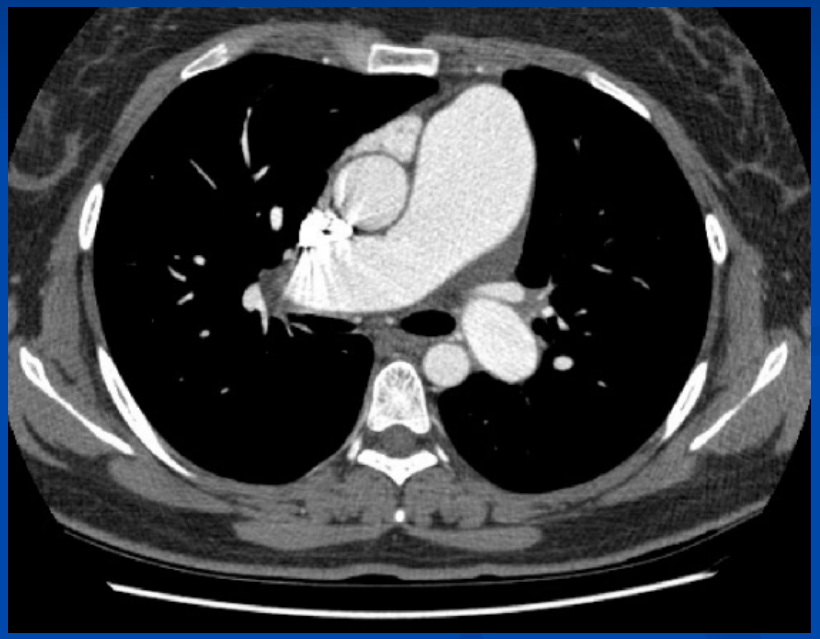


Cystic Fibrosis

Cystic Fibrosis

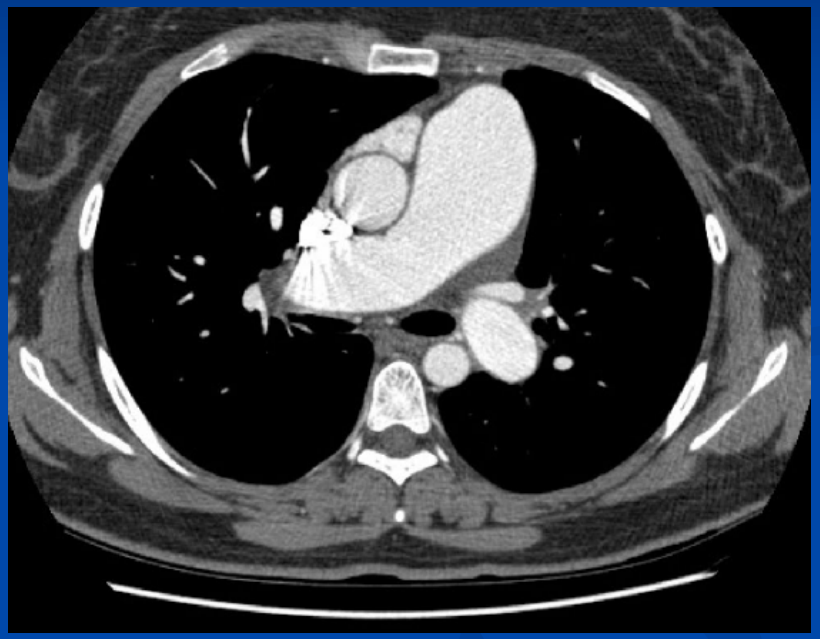
- FEV1 <30% or rapidly declining lung function
- Increasing oxygen requirements
- Hypercapnea
- Pulmonary hypertension

Pulmonary Hypertension



Pulmonary Hypertension

- NYHA Class III or IV
- Low (350m/1150ft) or declining 6-min walk
- Failing therapy with IV epoprostenol
- C.I. <2L/min/m2
- RA pressure >15 mm Hg



What pre-transplant factors does NOT affect 1 year mortality?

- a) Pre-transplant diagnosis
- b) Mechanical ventilation at the time of transplant
- c) Previous chest surgery
- d) Age
- e) Nutritional status
- f) Degree of hypoxia

Timing of listing

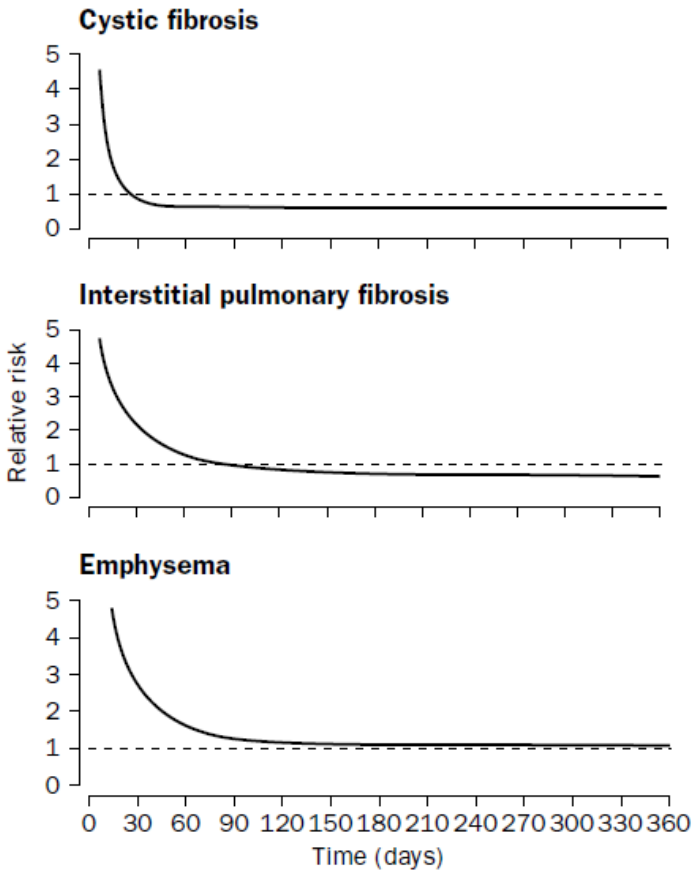


Figure 3: **Relative (transplantation/continued waiting) risk of death according to diagnosis**
Relative risk of 1·0 (broken line) indicates transplantation risk=waiting risk of mortality.

THE LANCET • Vol 351 • January 3, 1998

Influences on Mortality

TABLE 2. RECIPIENT FACTORS ASSOCIATED WITH INCREASED MORTALITY AT 1 AND 5 YEARS*

- Use of IV inotropes prior to transplantation
- Pretransplant mechanical ventilation
- Hospitalized at time of transplantation
- Prior sternotomy
- Older age (>55 y)

* Derived from multivariate analysis of the International Society of Heart and Lung Transplantation lung-transplant database (1)

Proc Am Thorac Soc Vol 6. pp 13–19, 2009

What study is not routinely obtained as part of the transplant evaluation?

- a) V/Q scan
- b) Previous microbiological data
- c) RUQ ultrasound
- d) Barium swallow
- e) DEXA scan

Evaluation for transplantation

- Complete history and physical examination
- Pulmonary function tests
- 6-minute walk
- CXR
- CT scan of chest
- V/Q scan
- Previous microbiological data
- Right and left cardiac catheterization
- Transthoracic echocardiogram
- Barium swallow
- Mammogram
- Colonoscopy
- DEXA scan
- Labs

Pre-Operative Testing: Labs

- CBC
- CMP
- PT/PTT/INR
- Prealbumin
- Thrombotic risk screen
- Arterial blood gas
- HLA Typing
- HLA antibody screen
- HIV
- Hepatitis B/C
- Serologies
  - CMV, EBV, HSV, VZV, Toxoplasmosis
- IgG
- Sputum Culture
- Urinalysis (cotinine)
- 24 hour urine collection

Evaluation for transplantation

- Transplant pulmonologist
- Transplant surgeon
- Nurse coordinator
- Social Worker
- Financial specialist
- Nutritionist
- Physical therapist/Pulmonary Rehabilitation
- Psychiatrist

Lung Allocation

- May 2005: Pts. assigned lung allocation score
  - expected number of days lived during the first year post-transplant
  - expected number of days lived during the first year post-transplant
- Post transplant survival measure – waitlist survival measure
- Score: 0-100

Chest. 2007 Nov;132(5):1646-51

Implications Post-LAS Model

- Lower median wait time: <5 months
  - Higher LAS = shorter wait time
- Less waitlist mortality
- Unchanged short term outcomes
- Mean LAS scores of transplanted patients increased
  - Older recipients
  - More patients with IPF
  - Higher baseline O2
  - More critically ill patients
    - Mechanical ventilation (8-10% of recipients on ventilator)

Which of these parameters is not included in the lung allocation score?

- a) diagnosis
- b) LV ejection fraction
- c) creatinine
- d) BMI
- e) %FVC

Lung Allocation Score

- Lung diagnosis
- Date of birth
- New York Heart Association Class
- Assisted ventilation
- Height and weight
- Diabetes
- Supplemental oxygen
- Percent predicted FVC
- Six minute walk distance
- Serum creatinine
- Pulmonary artery systolic pressure
- Mean pulmonary artery pressure

Lung Allocation

TABLE 1. FACTORS INVOLVED IN LUNG ALLOCATION SCORE CALCULATION

Factors Predicting Waitlist Survival (*Group*)	Factors Predicting Transplant Survival (*Group*)
Forced vital capacity	Forced vital capacity (B, D)
Pulmonary arterial diastolic pressure (A, C, D)	Pulmonary capillary wedge pressure (D)
Oxygen requirement at rest (A, C, D)	Mechanical ventilation
Age	Age
Body mass index	Creatinine
Diabetes mellitus, insulin-dependent	Functioanl Status
Functional status	Diagnosis
6 minute walk distance	
Mechanical ventilation	
Diagnosis by group (A, B, C, D)	

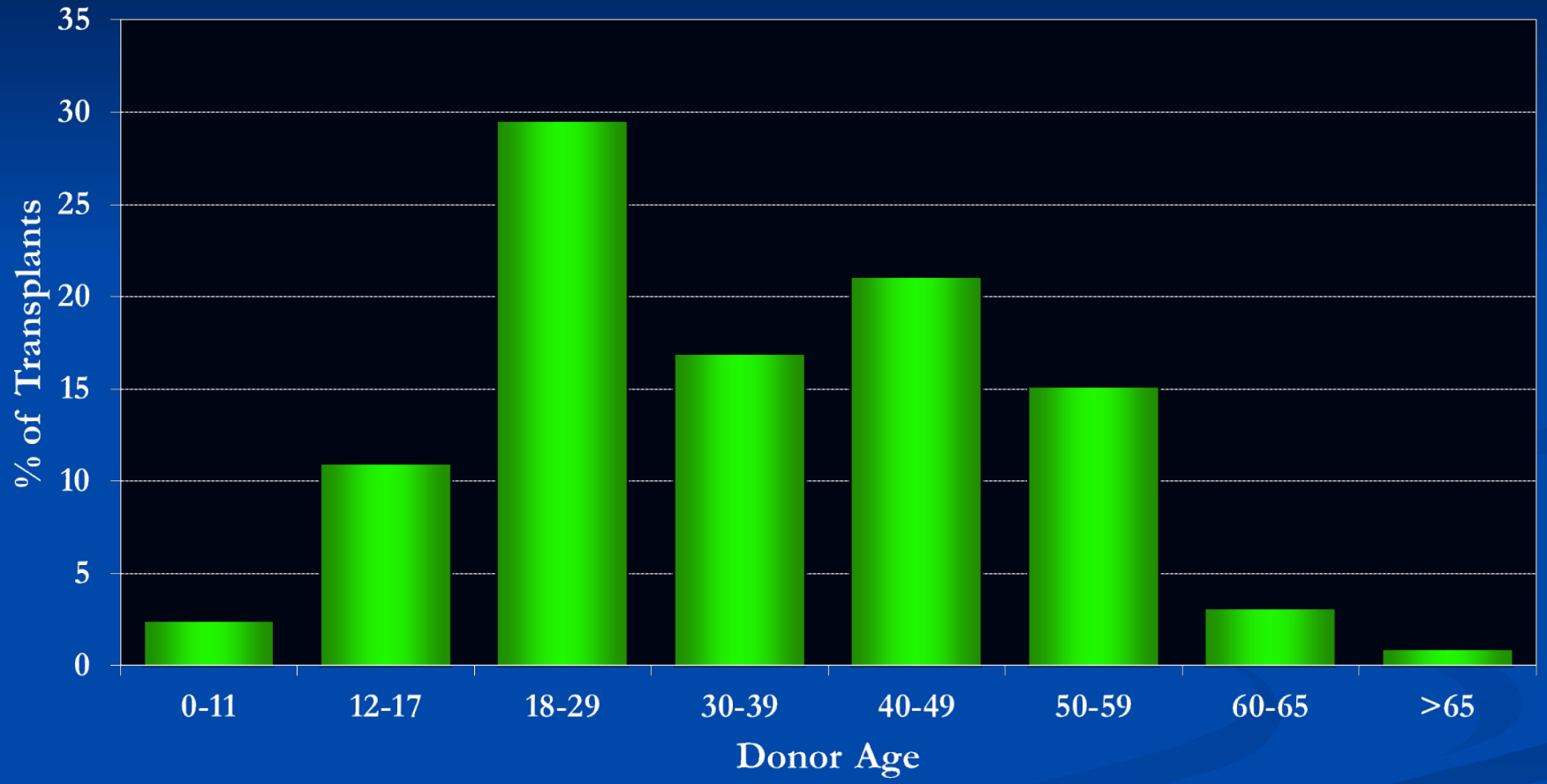
Where specified in table, the values entered affect the diagnosis groups as marked. Group A = mostly emphysema; Group B = pulmonary hypertension, idiopathic and congenital heart disease; Group C = septic lung disease (e.g., cystic fibrosis); Group D = interstitial lung disease (e.g., mostly idiopathic pulmonary fibrosis).

Proc Am Thorac Soc Vol 6. pp 13–19, 2009

Which of these patients is an acceptable donor ?

- a) 20 yo male with traumatic brain injury treated for VAP.
- b) 32 yo prison inmate with mild chest contusion and PaO2/FiO2 ratio 275
- c) 47 yo female with 18 pack year history of tobacco
- d) 52 yo male with history of colorectal CA 5 years ago
- e) 57 yo s/p cardiopulmonary arrest for massive PE

DONOR AGE DISTRIBUTION FOR LUNG TRANSPLANTS (1/1985-6/2011)



ISHLT

2012

J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

Donor Criteria

TABLE 1. STANDARD ("IDEAL") LUNG DONOR CRITERIA

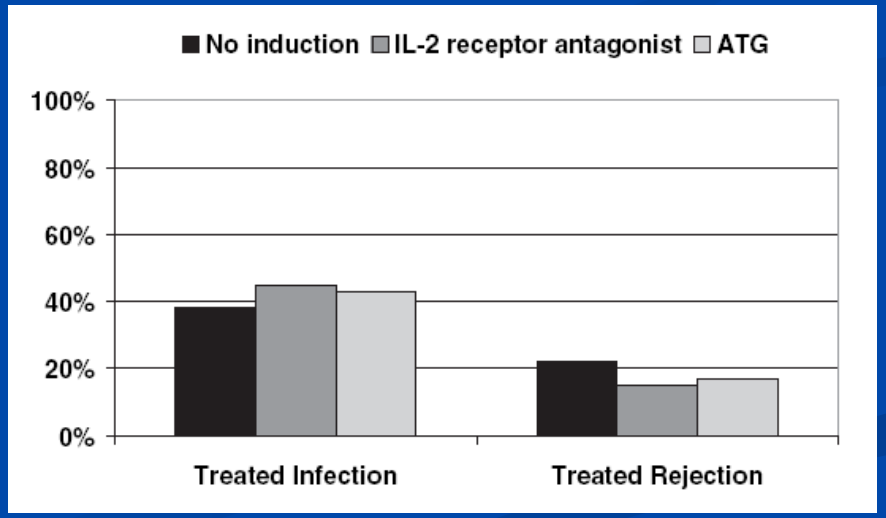
Age < 55 yr
Clear serial chest X-ray
Normal gas exchange (Pa_{O_2} > 300 mm Hg on FI_{O_2} = 1.0, PEEP 5 cm H_2O)
Absence of chest trauma
No evidence of aspiration or sepsis
Absence of purulent secretions at bronchoscopy
Absence of organisms on sputum gram stain
No history of primary pulmonary disease or active pulmonary infection
Tobacco history < 20 pack-years
ABO compatibility
No prior cardiopulmonary surgery
Appropriate size match with prospective recipient

Definition of abbreviation: PEEP = positive end-expiratory pressure.
Adapted by permission from Reference 15.

Proc Am Thorac Soc Vol 6. pp 28-38, 2009

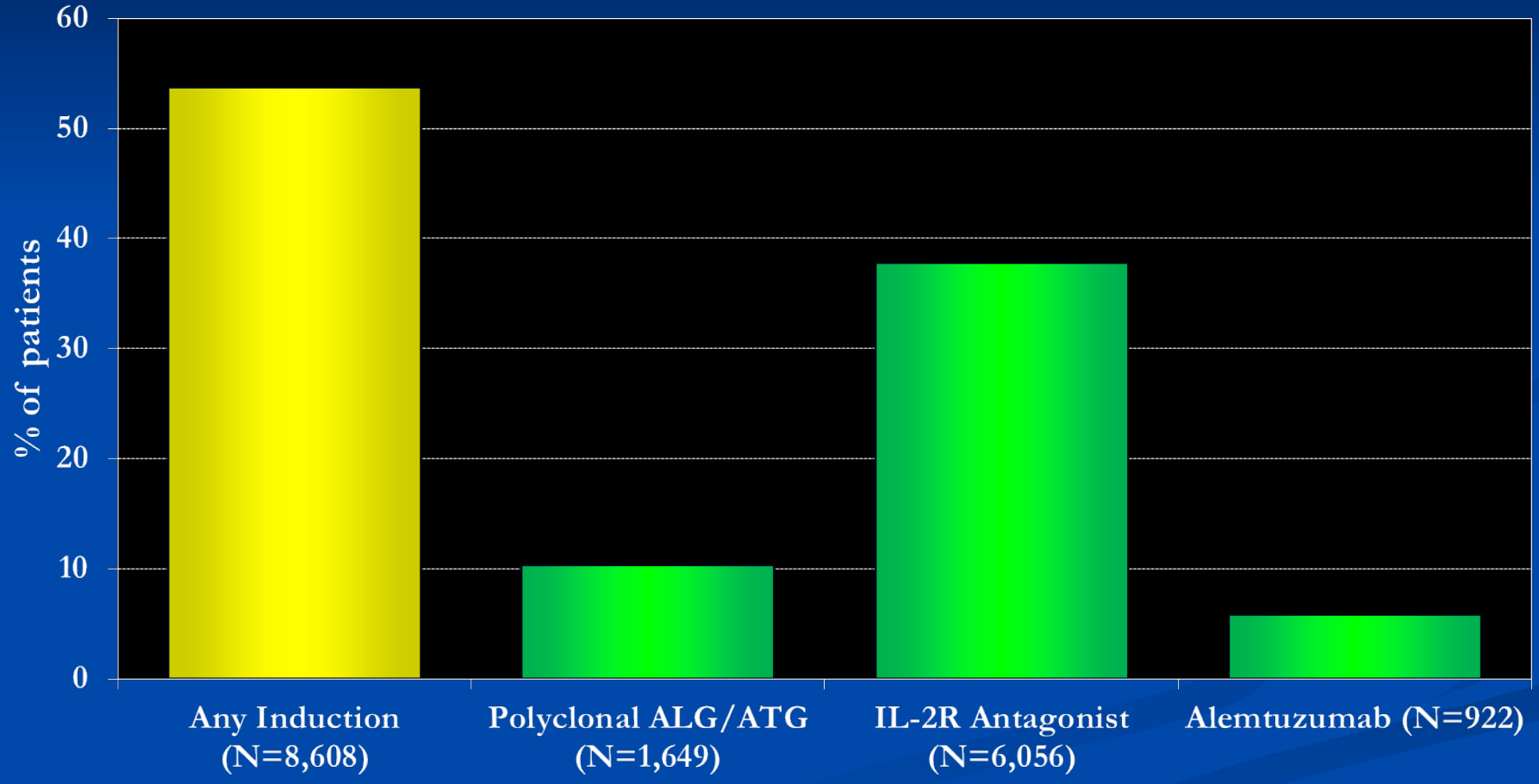
Immunosuppression: Induction Agents

- Decrease early alloreactivity
  - Reduce rejection episodes
  - Reduce development of chronic rejection
  - Improve overall survival



Clin Transplant 2008; 22:603-608

Adult Lung Transplants
Induction Immunosuppression
Analysis limited to patients receiving prednisone
(Transplants: January 2002 – June 2013)



Analysis is limited to patients who were alive at the time of the discharge

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

- There are NO immunosuppressive medications with FDA approval for lung transplantation

Immunosuppression: Maintenance Regimens

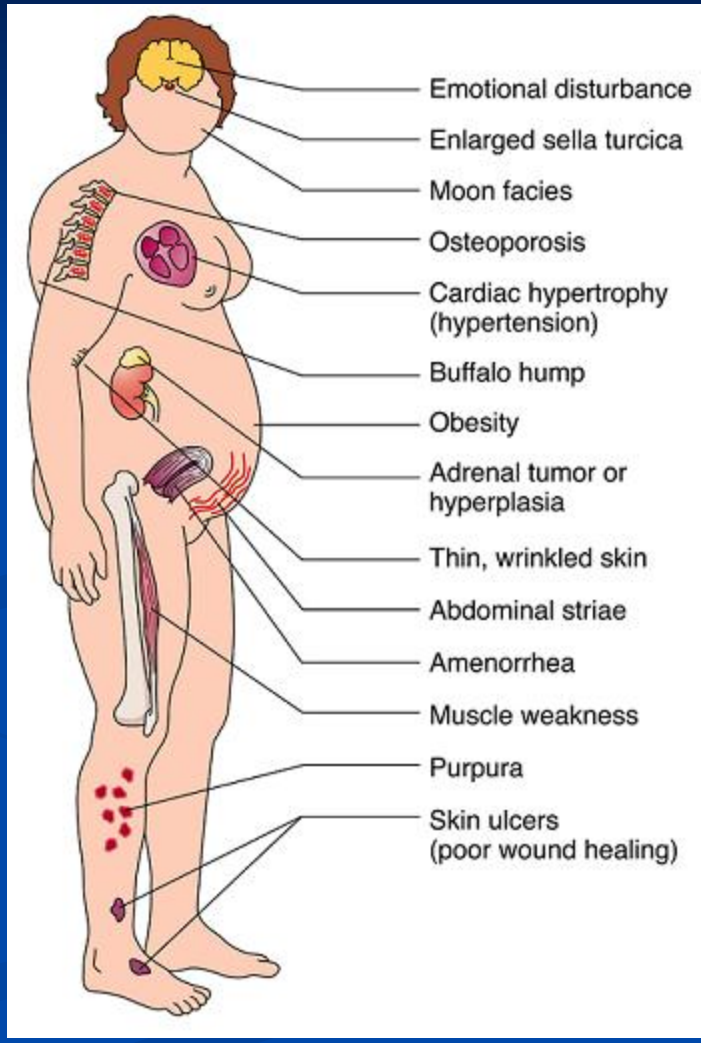
- Glucocorticoids
  - Prednisone
- Calcineurin inhibitors: decrease IL2 production
  - Tacrolimus
  - Cyclosporine
- Cell-cycle inhibitors
  - Azathioprine
  - Mycophenolate mofetil

Which of these medications is associated with tremors?

- a) Cyclosporine
- b) Tacrolimus
- c) Azathioprine
- d) Mycophenolate Mofetil
- e) Sirolimus

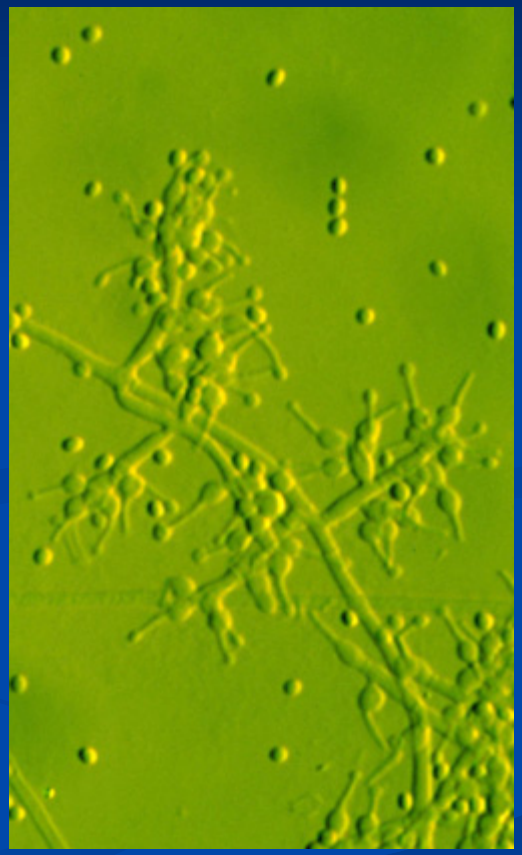
Glucocorticoids

- Used for maintenance and treatment of rejection
- Initially administered at high doses after transplantation and weaned to baseline
  - Methylprednisolone 500mg-1000mg IV qday
  - Prednisone 5-10mg qday
- Side effects: DM, HTN, PUD, osteoporosis, poor wound healing, acne, Cushingoid appearance



Calcineurin Inhibitors: Cyclosporine

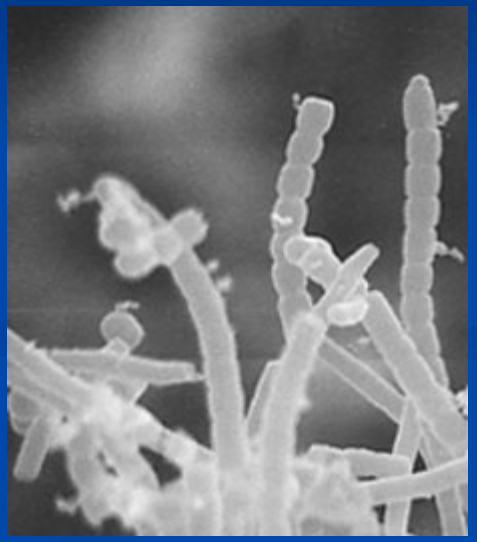
- Discovered in 1968; approved in renal transplantation in 1978
- Prevents activation and proliferation of CD4+ T cells through IL-2 pathway (calcineurin)
- Blood levels followed by trough
- Metabolized by cytochrome P450
- Causes renal dysfunction, HTN, hyperlipidemia
- Seizures (PRES), TTP/HUS



Tolypocladium inflatum

Calcineurin Inhibitors: Tacrolimus/FK506

- Antiproliferative agent with resultant decreased IL-2 mediated proliferation of T cells
- Administered orally, sublingually or IV
- Administer separate from fatty meals
- Follow trough level
- Cause renal dysfunction, HTN
- Neurologic complications: Headache, seizures, tremors



Streptomyces tsukubaensis

Which of these medications interacts with the metabolism of tacrolimus/cyclosporine?

- a) Diltiazem
- b) Voriconazole
- c) Rifampin
- d) Tenofovir
- e) Erythromycin

Cell-Cycle Inhibitors: Azathioprine

- Prodrug for active compound: 6-mercaptopurine
- Halts DNA replication and induces lymphocyte apoptosis
- Given oral or IV
- Caution with concomitant allopurinol
- Leukopenia, hepatotoxicity
- Thiopurine methyl transferase (TPMT): severe myelosuppression

Cell-Cycle Inhibitors: Mycophenolate Mofetil

- Converted to active component, mycophenolic acid
- Inhibits synthesis of guanine nucelotides
- Administered oral or IV
- Can obtain drug level
- Co-administration of antiacids/iron decease bioavailability
- Side effects: diarrhea, GI upset, leukopenia, bone marrow suppression
  - Enteric coated: Myfortic

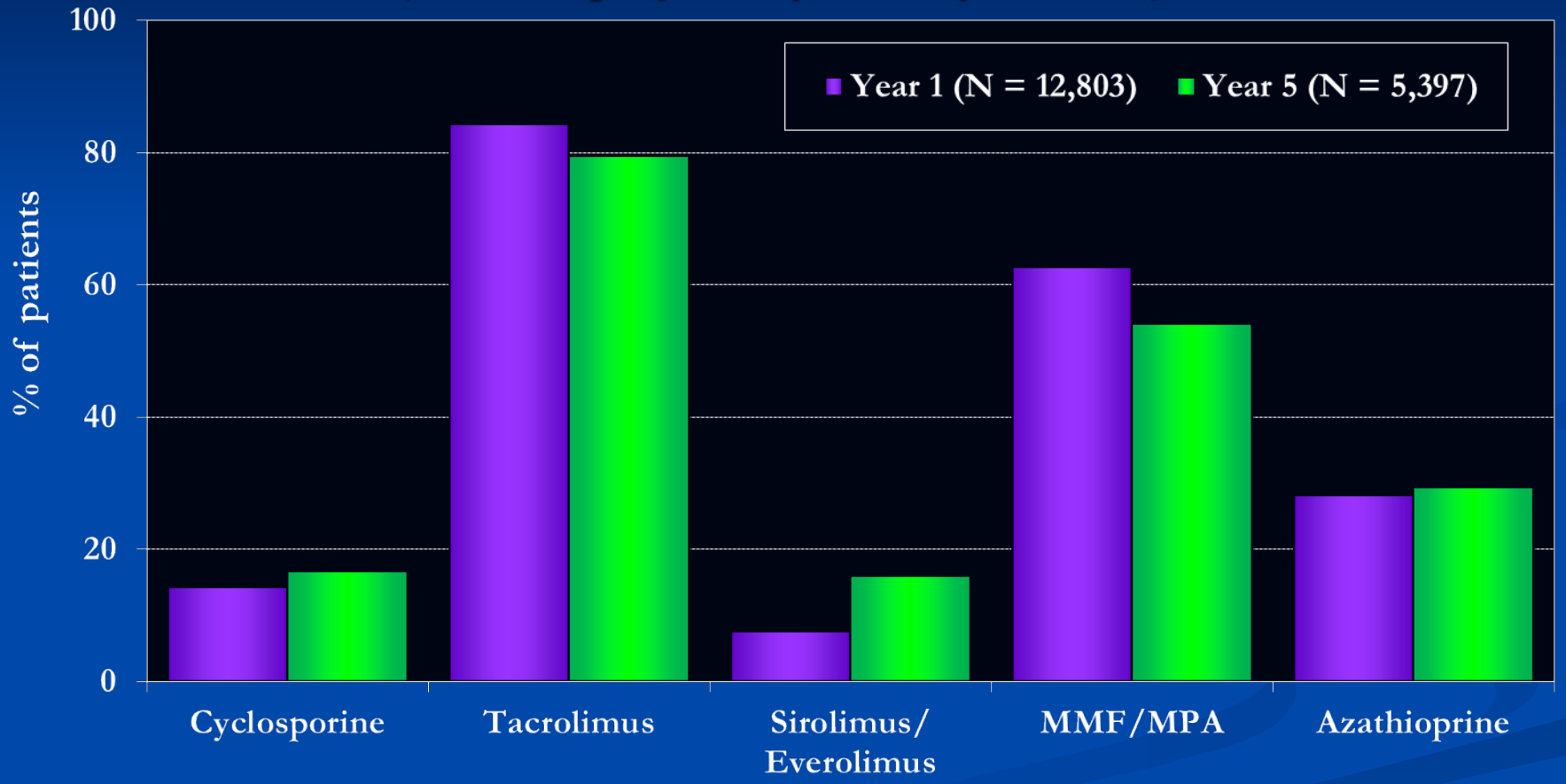
Sirolimus

- Binds to mammalian target of rapamycin (mTOR)
- Arrests T cells in late G1 phase of cell cycle
- Potent antifibroproliferative agent
  - Poor wound healing
- Used in place of azathioprine/MMF
- Monitor drug levels
- Side effects: HTN, myelosuppression, pulmonary toxicities

MAINTENANCE IMMUNOSUPPRESSION AFTER ALEMTUZUMAB (CAMPATH) INDUCTION

MONTHS	1-12	12-24	> 24 & CKD	NOTES:
Prednisone (mg/day)	**5** Begin AM post-op day 1	**5**	**5**	
Tacrolimus *¤ (blood level) 1st choice	**10-15** (10-12 hour trough)	**8-12**	**6-10**	Begin 0.5 mg PO bid. Give 1st dose 6 hours after arrival to ICU
Cyclosporine~¤ (usually Neoral) (blood level)	**200-300** (10-12 hour trough)	**200-250**	**100-200**	Use if intolerant to Tacrolimus
Cellcept ** (250 mg /tablet)	Begin 750 mg PO bid			Monitor neutropenia; Adjust dose accordingly
Myfortic ** (180 mg /tablet)	Begin 540 mg PO bid			Use if GI intolerance to Cellcept
		OTHER	MEDICATIONS	
Azathioprine ₸ (WBC > 3.5)	1.0 – 2 mg/kg/d			Start 50 mg/day, increase to goal after one week if WBC acceptable and tolerating
Sirolimus + (blood level)			4-12 ++ in combination with calcineurin inhibitors	Steady-state concentrations occur 5-7 days after dose change

Adult Lung Transplants
Maintenance Immunosuppression at Time of Follow-up
Analysis limited to patients receiving prednisone
(Follow-ups: January 2002 – June 2013)



NOTE: Different patients are analyzed in Year 1 and Year 5

Analysis is limited to patients who were alive at the time of the follow-up

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

Complications: Primary Graft Dysfunction

- Ischemia-reperfusion injury/Primary graft failure
- End result of multiple insults to graft
- Leading cause of morbidity/mortality in perioperative period
- Worse long-term function and increased chance of developing chronic rejection/bronchiolitis obliterans syndrome

Complications: Primary Graft Dysfunction

TABLE 1. INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION PRIMARY GRAFT DYSFUNCTION GRADING SCHEMA

Grade	$Pa_{O_2}/F_{I_{O_2}}$	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Proc Am Thorac Soc Vol 6. pp 39-46, 2009

What is the PGD grade?

- 45 yo female s/p DLTx for CF
- A/C Ventilation:
  - Vt 450, RR 16, PEEP 5 FIO2 1.0
- Abg: 7.32/58/197
- a) 0
- b) 1
- c) 2
- d) 3
- e) Bad…

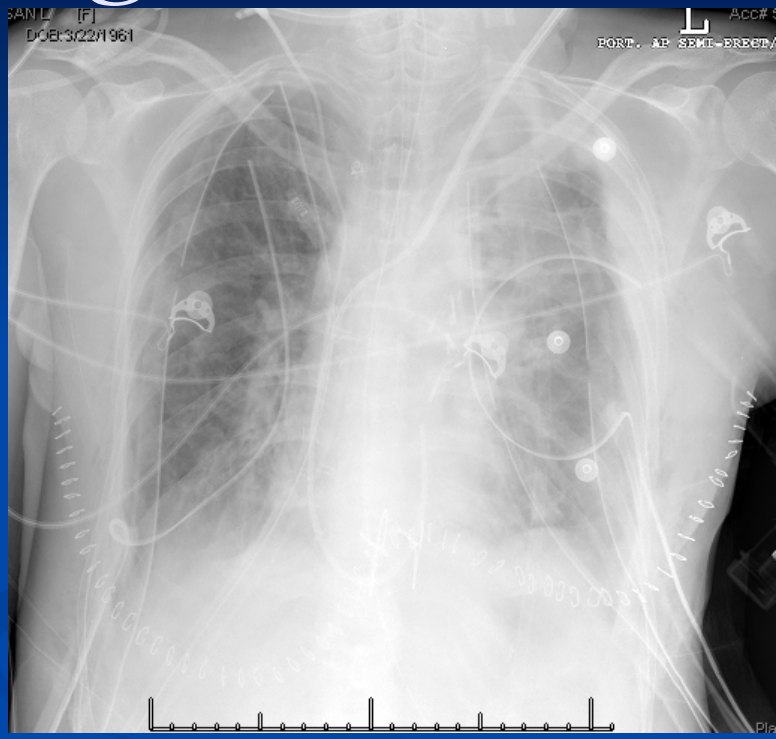

TABLE 1. INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION PRIMARY GRAFT DYSFUNCTION GRADING SCHEMA

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0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Complications: Primary Graft Dysfunction

TABLE 3. POSSIBLE PRIMARY GRAFT DYSFUNCTION RISK FACTORS

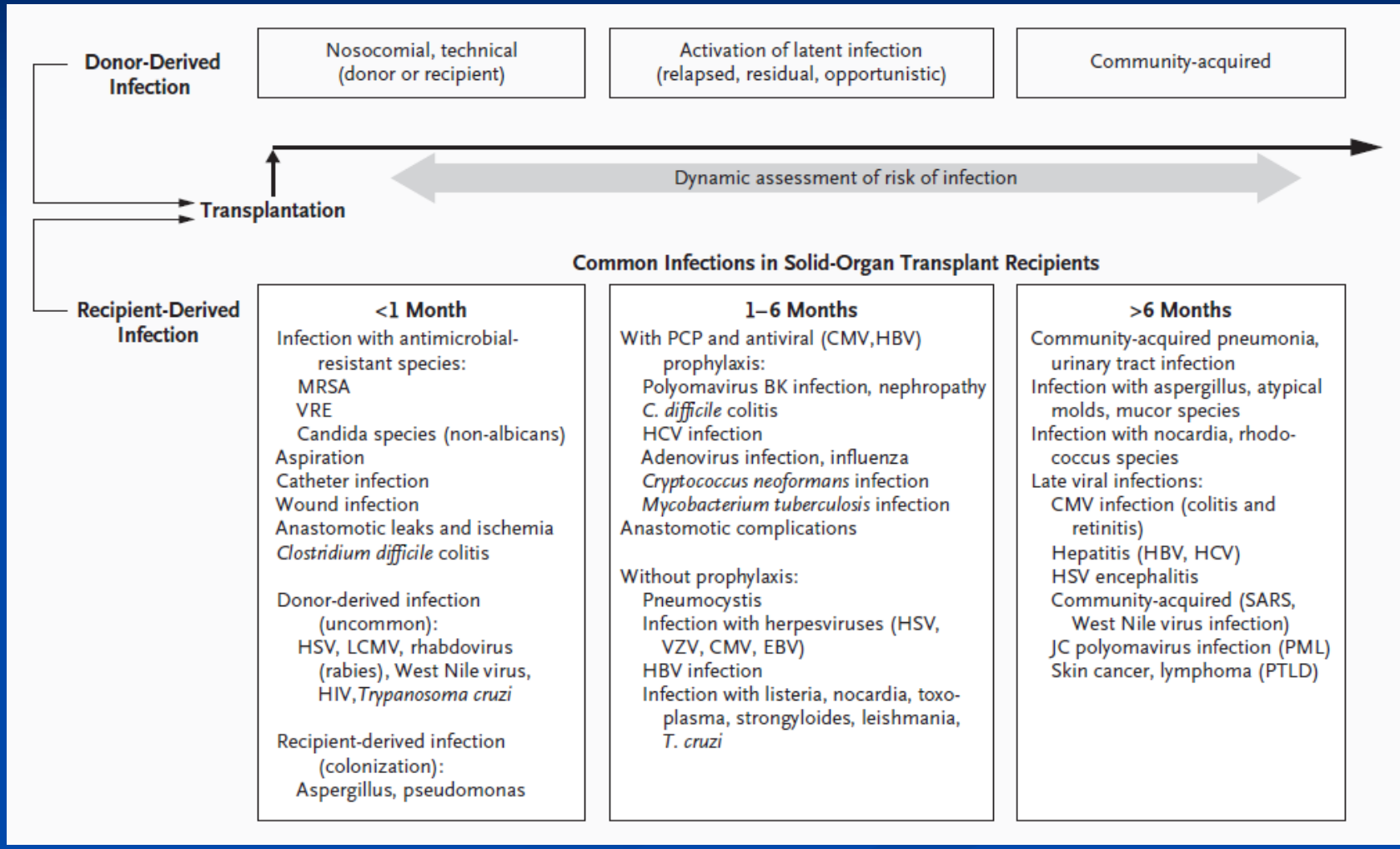
Category	Risk Factor for Primary Graft Dysfunction
Donor variables (inherent):	Age > 45 yr
	Age < 21 yr
	African-American race
	Female sex
	History of smoking
Donor variables (acquired):	Prolonged mechanical ventilation
	Aspiration
	Trauma
	Hemodynamic instability after brain death
Recipient variables:	Diagnosis of idiopathic pulmonary arterial hypertension
	Pulmonary arterial hypertension
	Diagnosis of diffuse parenchymal lung disease
Operative variables:	Use of cardiopulmonary bypass
	Blood product transfusion

Proc Am Thorac Soc Vol 6. pp 39-46, 2009

Complications: Infections

- Major cause of mortality during first year after transplant
- Increased susceptibility
  - Immunosuppressive medications, exposure to environment, dennervation and lack of ciliary movement and cough reflex
- Associated with chronic graft dysfunction/ rejection
- Incidence reduced from donor/recipient screening and antimicrobial prophylaxis

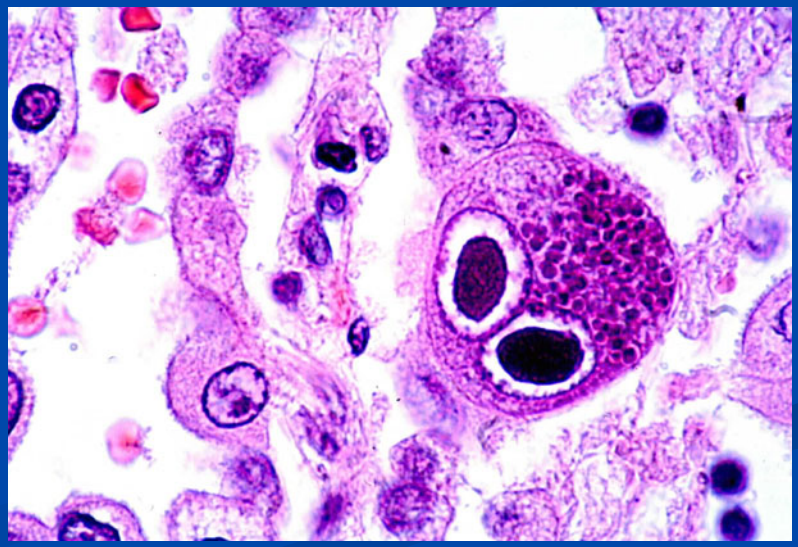
Timing of Infection after Transplantation



NEJM 357;25 pp 2601-2614, 2007

CMV

- Viral syndrome, CMV pneumonitis, Extra pulmonary disease
- CMV-seropositive donor transmits significant viral load to recipients
- CMV-seronegative recipients are at higher risk for primary infection



Which organ is less likely to be infected with CMV?

- a) Eye/retina
- b) Lung
- c) Liver
- d) Stomach
- e) Colon

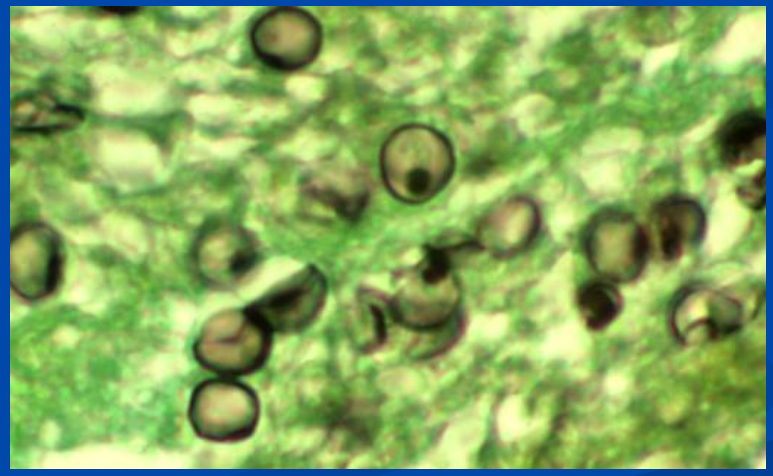
CMV

- Incidence 30-86%; reduced due to prophylaxis with Vanganciclovir
- Prophylaxis can result in anti-viral resistance

CMV Status	Dose				Duration
	GFR > 60	GFR 40-59	GFR 25-39	GFR 10-24	
D+/R-	900 mg qD	450mg qD	450mg qOD	450mg qMWF	Indefinite or until seroconversion
D-/R+ or D+/R+	450mg qD	450mg qOD	450mg qMWF	450mg qMTh	6 months
D-/R- or Herpes prophylaxis	450mg qD (consider valacyclovir as substitute to prophylax herpes infections)	450mg qOD	450mg qMWF	450mg qMTh	6 months

Pneumocystis

- Incidence reduced due to prophylaxis
  - Trimethoprim-sulfamethoxazole
  - Dapsone
  - Atovaquone/Mepron
  - Inhaled pentamidine
- Life long prophylaxis

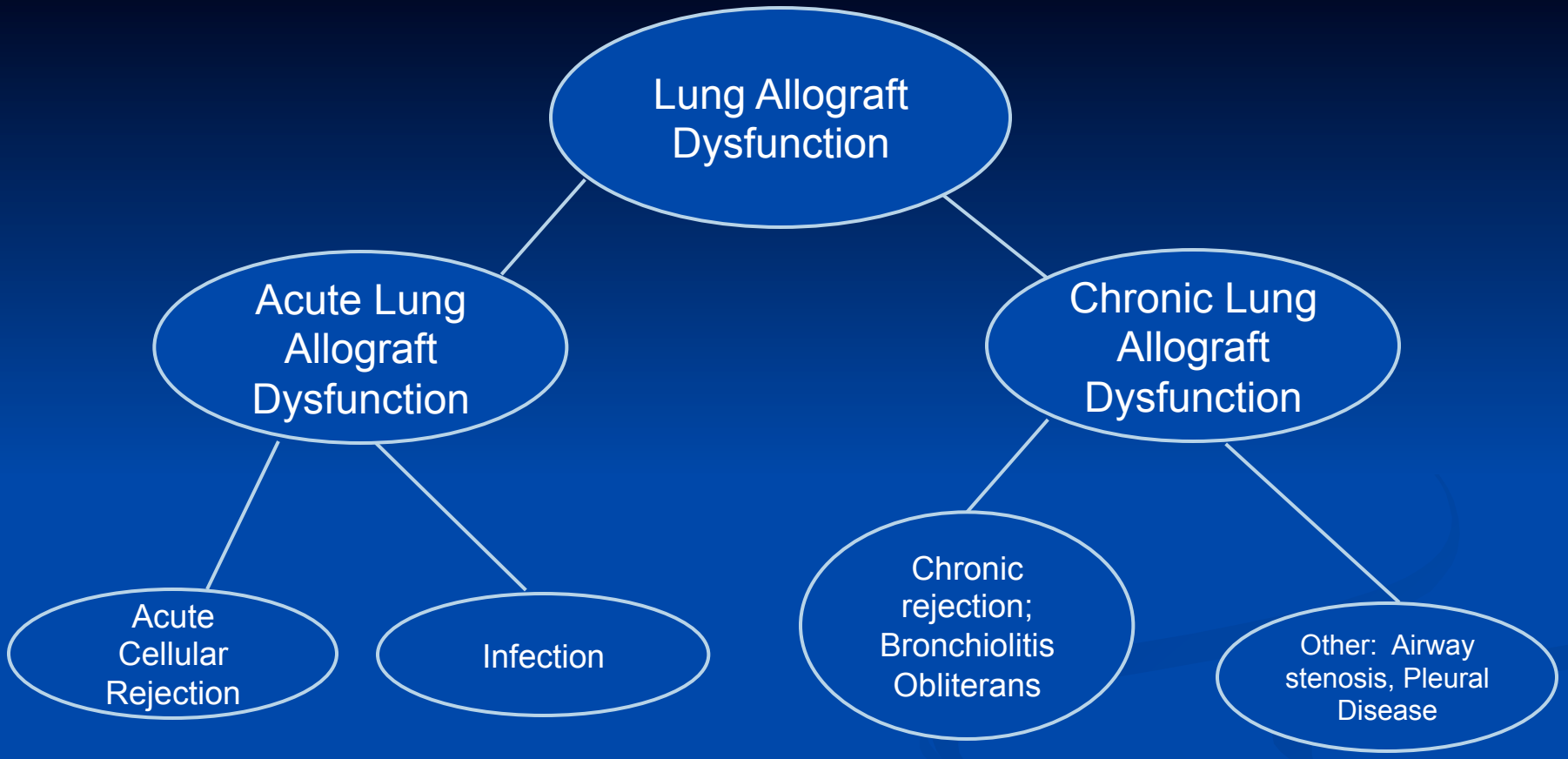


Fungal Infections

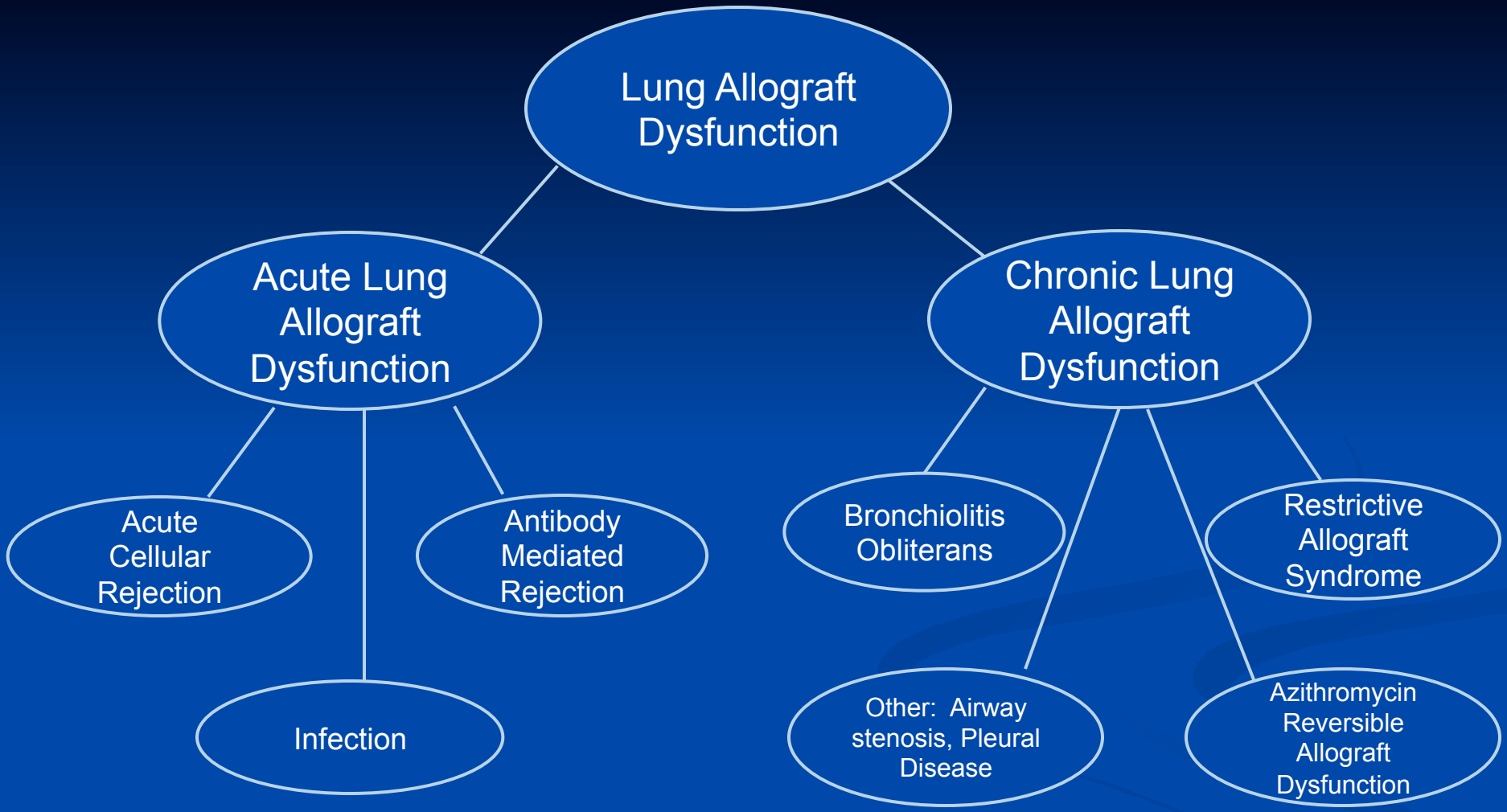
- Colonization, airway infections, dissemination
  - *Aspergillus* (Airway stent)
  - *Candida*
  - *Rhizopus*
  - *Rhizomucor*
  - *Mucor*
  - *Scedosporium*
  - *Fusarium*
- CT chest useful in distinguishing colonization form infection
- Prophylaxis
  - Reduces risk of invasive disease
  - Duration?

Multi-drug resistant Gram Negative Infections

- More common in cystic fibrosis/chronic rejection
- Acquired via colonization or nosocomially
- Burkholderia cepacia associated with poor transplant outcome
- Inhaled tobramycin

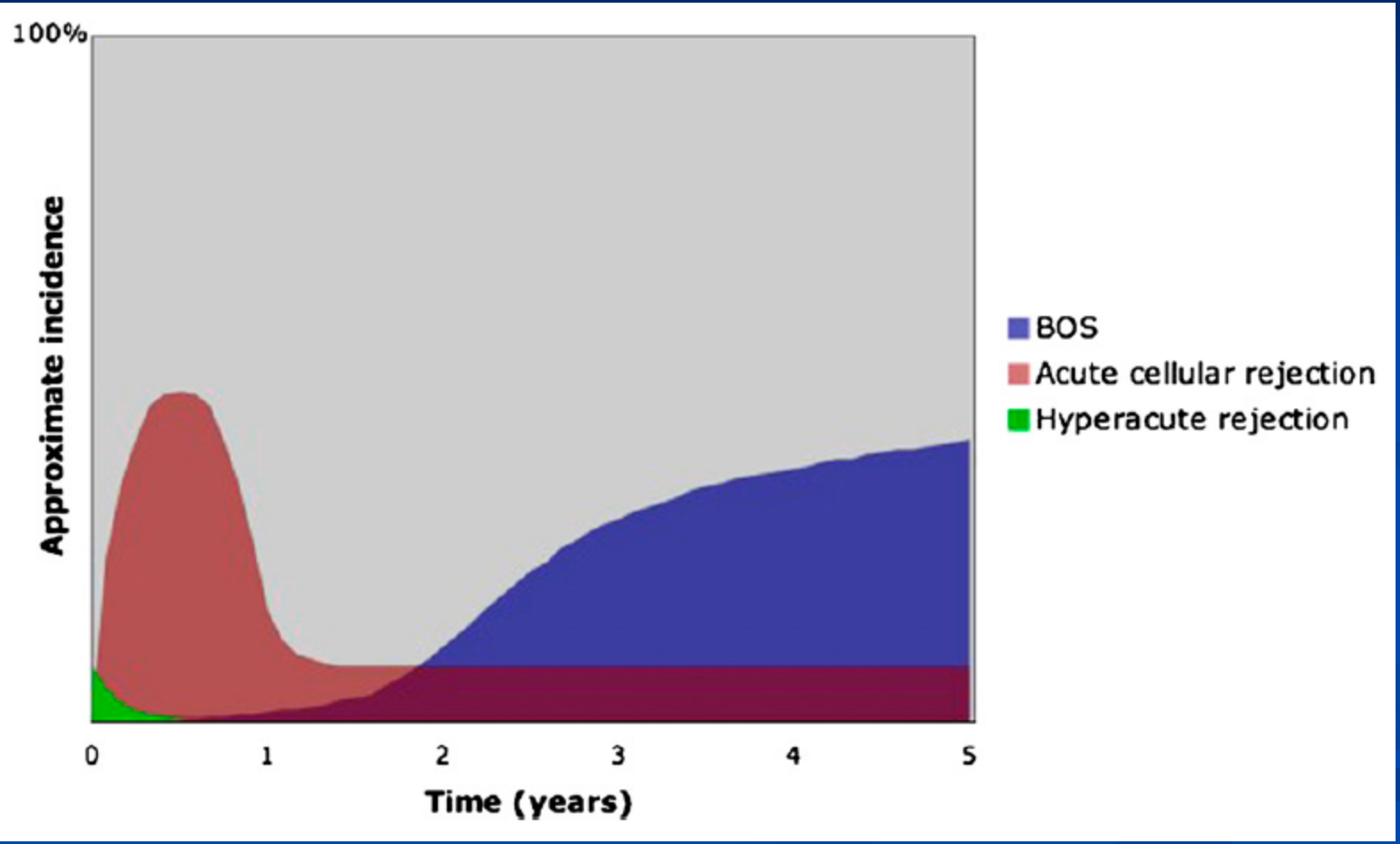


Early Classification of Lung Allograft Dysfunction



Current Classification of Lung Allograft Dysfunction

Timing of Rejection



Proc Am Thorac Soc Vol 6. pp 54-65, 2009

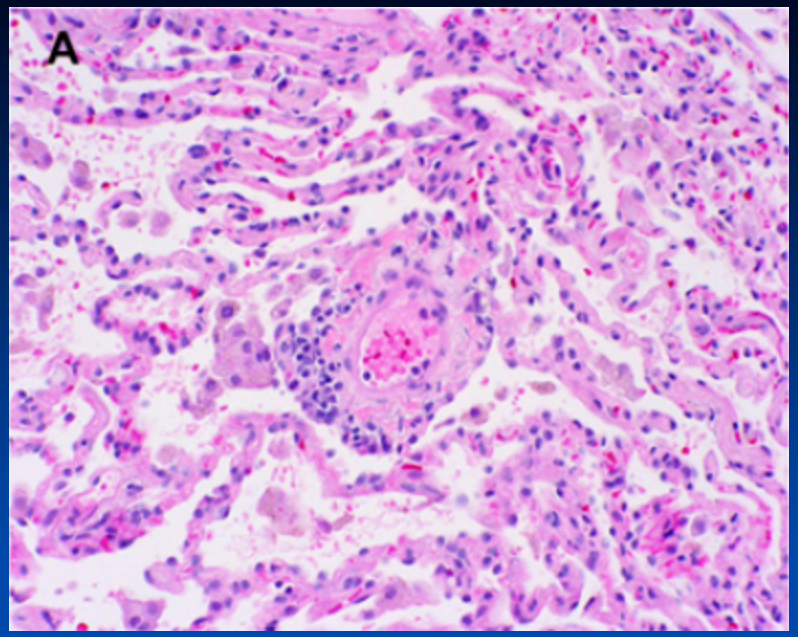
Complications: Acute Cellular Rejection

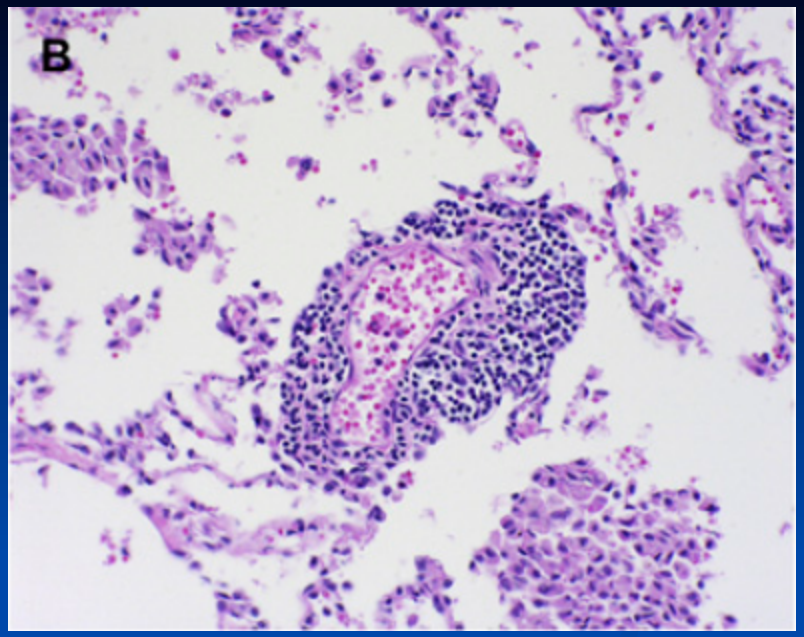
- Occurs in 90% of recipients
- Asymptomatic to severe hypoxemia and SOB
- Diagnosed by bronchoscopy and transbronchial biopsies
- Associated with development of chronic rejection
- Most episodes respond to high-dose steroids

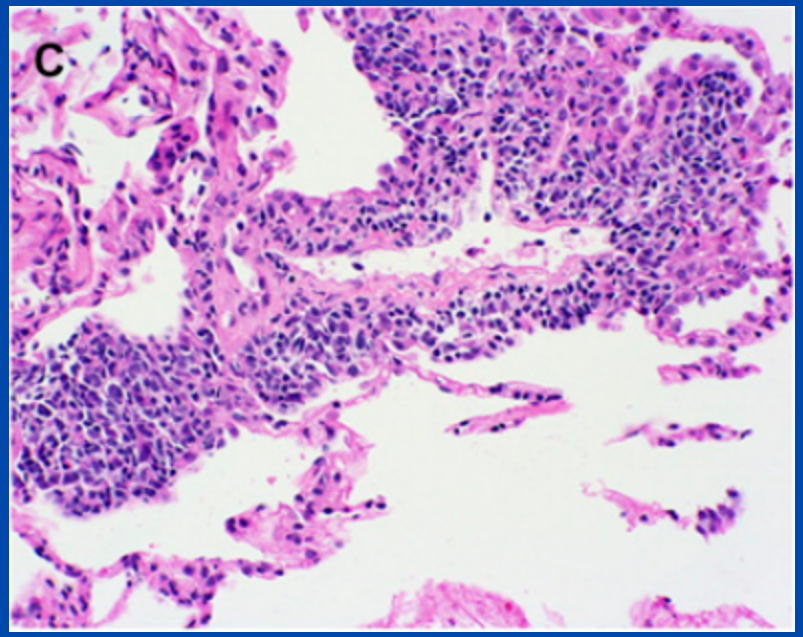
Pathologic Grading of Lung Rejection

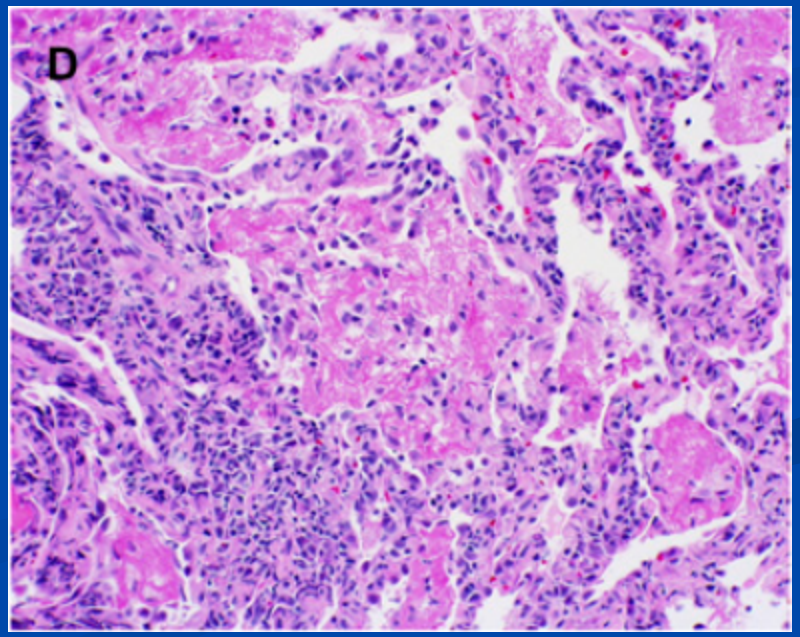
Category	Grade	Meaning	Appearance
A: acute rejection	0	None	Normal lung parenchyma
	1	Minimal	Inconspicuous small mononuclear perivascular infiltrates
	2	Mild	More frequent, more obvious, perivascular infiltrates, eosinophils may be present
	3	Moderate	Dense perivascular infiltrates, extension into interstitial space, can involve endothelialitis, eosinophils, and neutrophils
	4	Severe	Diffuse perivascular, interstitial, and air-space infiltrates with lung injury. Neutrophils may be present.
B: airway inflammation	0	None	No evidence of bronchiolar inflammation
	1R	Low grade	Infrequent, scattered or single layer mononuclear cells in bronchiolar submucosa
	2R	High grade	Larger infiltrates of larger and activated lymphocytes in bronchiolar submucosa. Can involve eosinophils and plasmacytoid cells.
	X	Ungradable	No bronchiolar tissue available
C: Chronic airway rejection – obliterative bronchiolitis	0	Absent	If present describes intraluminal airway obliteration with fibrous connective tissue
	1	Present	

Proc Am Thorac Soc Vol 6. pp 54-65, 2009









Proc Am Thorac Soc Vol 6. pp 54-65, 2009

Which of the following is NOT used to treat acute rejection?

- a) Anti-thymocyte globulin
- b) Methylprednisolone
- c) Rapamycin
- d) Alemtuzumab
- e) Photopheresis
- f) Prayer
- g) None of the above

Treatment of Rejection

ACR Grade 2 or symptomatic grade 1

- Prednisone 100 mg PO then decrease by 10 mg daily until back to baseline steroid maintenance dose.
- Bronchoscopy with biopsy 2 weeks after completion of taper.
- If no response, discuss with pulmonary transplant MD.

Symptomatic ACR grade 2 or grade 3-4

- Solumedrol 1 gram IV times 3 days (~15 mg/kg/day for weight <50 kg)
- Bronchoscopy with biopsy 2 weeks after treatment
- Start CMV and fungal prophylaxis unless CMV -/-
- Check CMV-PCR weekly for one month after steroid bolus
- If no response, discuss with pulmonary transplant MD.

Persistent or Refractory Rejection - Options

- Thymoglobulin (RATG)
- Alemtuzumab (Campath)
- Sirolimus (Rapamycin)
- Solu-medrol
- Photophoresis
- Total lymphocytic radiation

Which of the follow statements is true regarding chronic rejection?

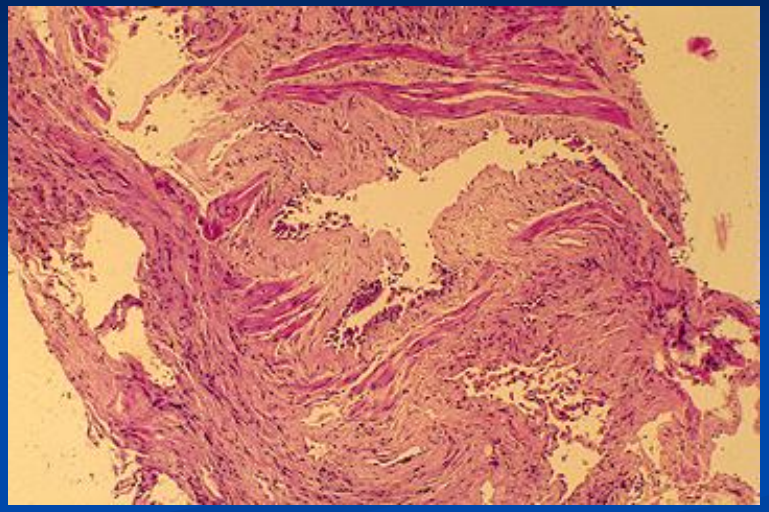
- a) Chronic rejection is the second most common cause of morbidity and mortality after the first two years after transplantation
- b) The only way to diagnose chronic rejection if by spirometric criteria.
- c) Chronic rejection begins insidiously with symptoms developing later in disease
- d) Bronchoscopic cultures in patients with known chronic rejection are almost always negative

Complications: Chronic Cellular Rejection

- Leading cause of morbidity and mortality
- Has both pathologic and clinical classifications
- Often begins insidiously with symptoms developing later in disease
- Permanent airway colonization with *Pseudomonas aeruginosa* and *Aspergillus fumigatus*
- Heterogeneous disease with both alloimune dependent and independent risk factors

Chronic Rejection

- Histologic:
  - Obliterative bronchiolitis



- Clinical:
  - Bronchiolitis obliterans syndrome (BOS)
    - FEV_1 below 80% peak value after transplant
    - BOS stages: 0-p, 1, 2, 3

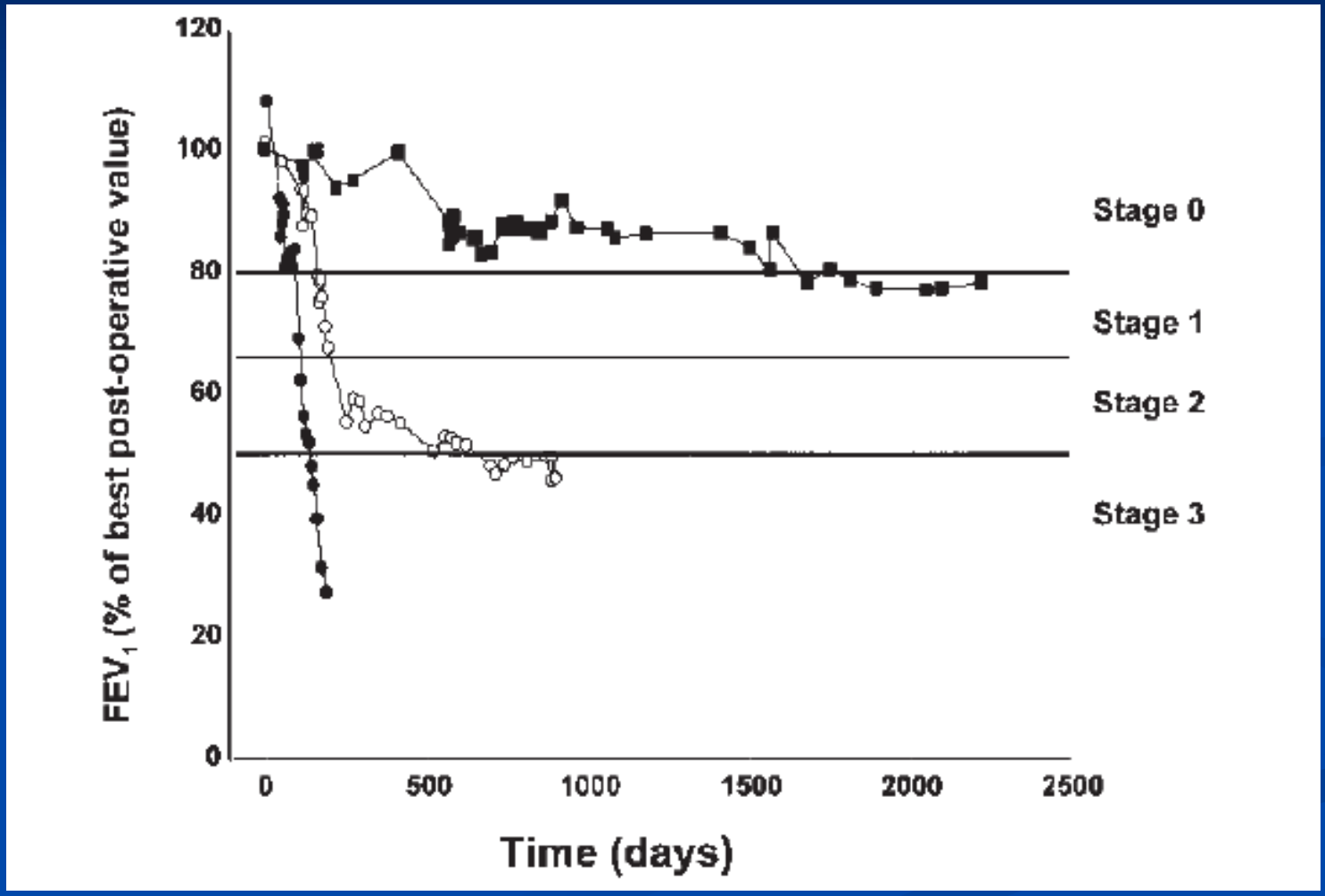
	PRE-BRONCHODILATOR		
	Actual	Pred.	%Pred.
SPIROMETRY			
FVC (L)	2.06	3.06	67
FEV1 (L)	0.86	2.68	32
FEV1/FVC (%)	42	88	47
FEF 25-75% (L/sec)	0.24	3.29	7
FEF 50% (L/sec)	0.28	4.59	6
FEF 75% (L/sec)	0.11	1.97	6
FEF Max (L/sec)	2.62	5.64	47
Expiratory Time (sec)	12.76		
FIF Max (L/sec)	2.51		

BOS classification

Original classification		Current proposition	
BOS 0	FEV_1 80% or more of baseline	BOS 0	$FEV_1 > 90\%$ of baseline and $FEF_{25-75} > 75\%$ of baseline
		BOS 0-p	FEV_1 81% to 90% of baseline and/or $FEF_{25-75} \leq 75\%$ of baseline
BOS 1	FEV_1 66% to 80% of baseline	BOS 1	FEV_1 66% to 80% of baseline
BOS 2	FEV_1 51% to 65% of baseline	BOS 2	FEV_1 51% to 65% of baseline
BOS 3	FEV_1 50% or less of baseline	BOS 3	FEV_1 50% or less of baseline

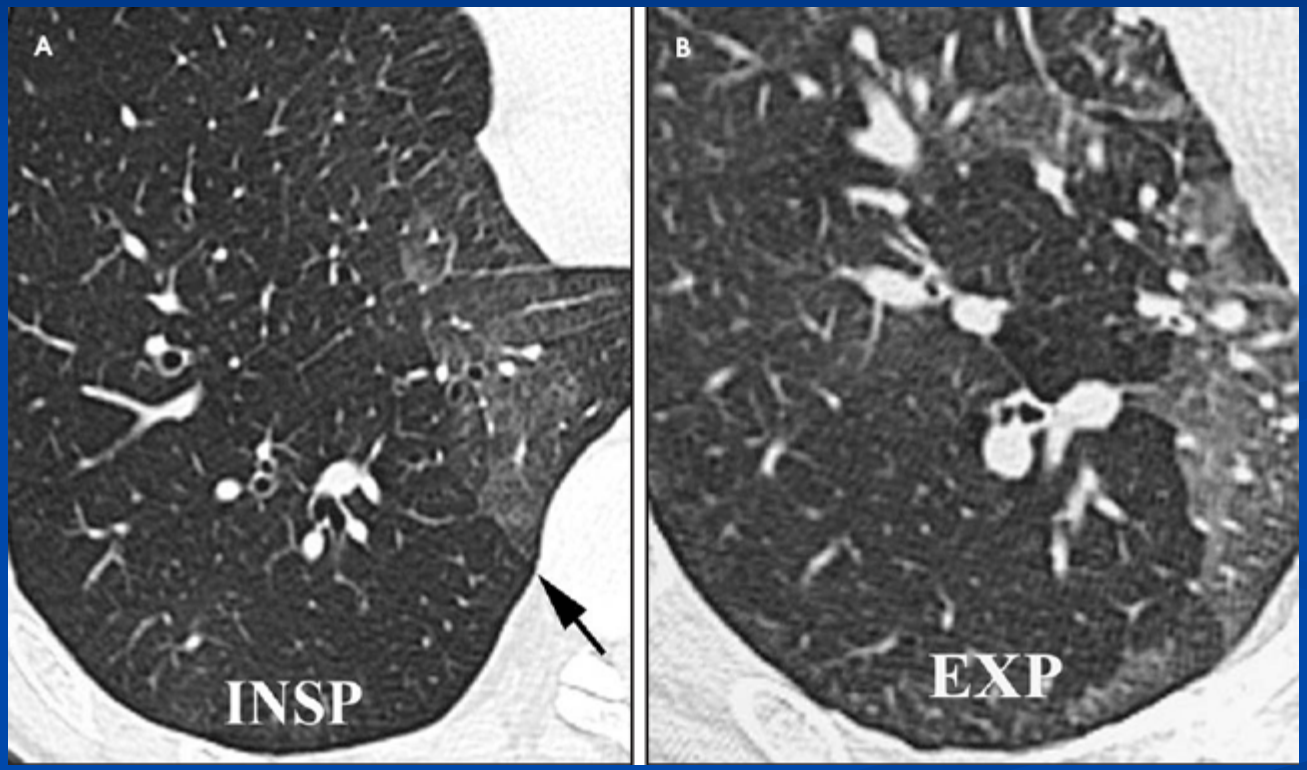
BOS, bronchiolitis obliterans syndrome; FEF_{25-75}, mid-expiratory flow rate; FEV_1, forced expiratory volume in 1 second.

Chronic Rejection



Semin Resp Critical Care 2006;27(5): 521-533

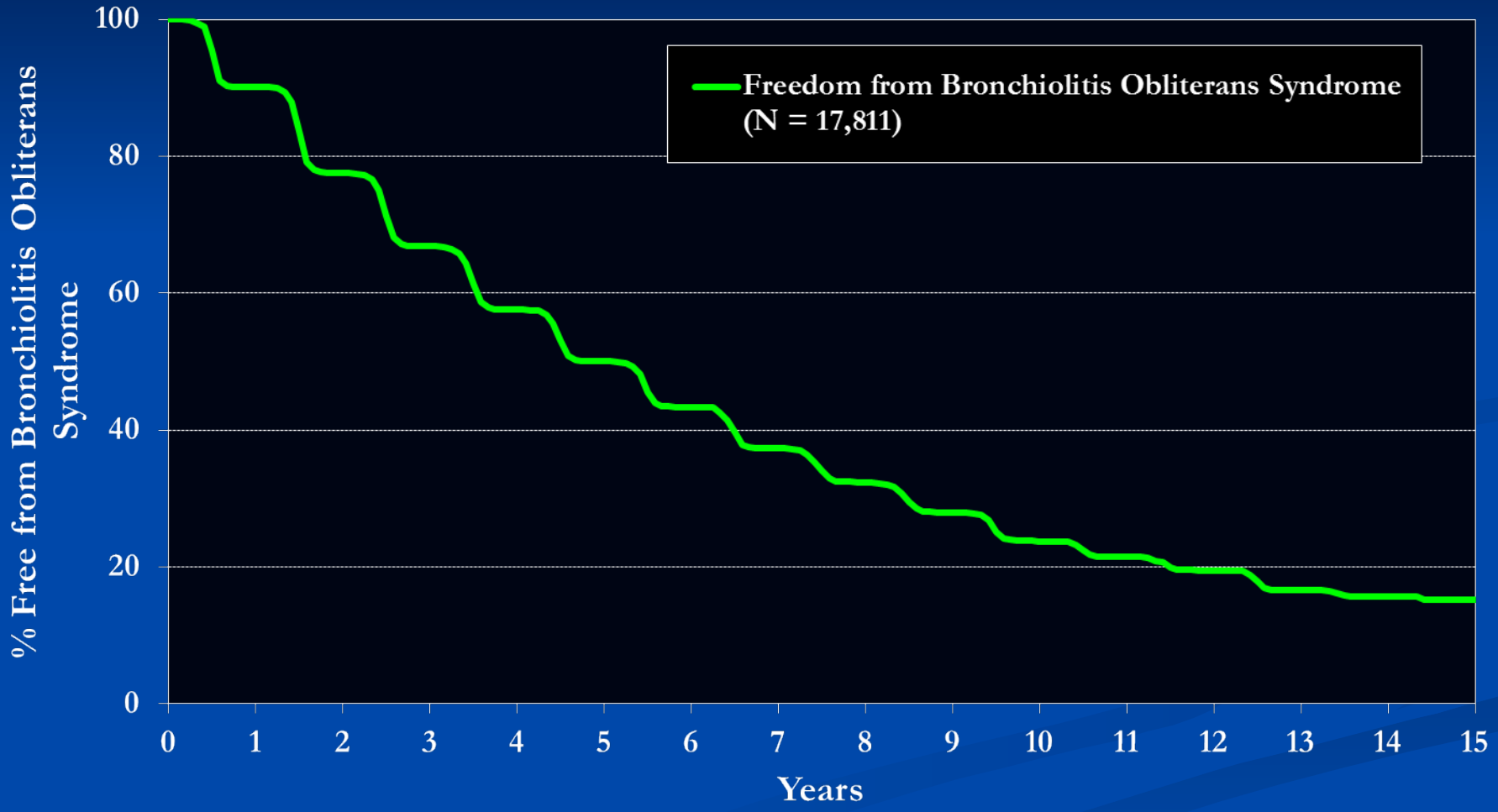
Air Trapping in Chronic Rejection



Adult Lung Transplants

Freedom from Bronchiolitis Obliterans Syndrome

Conditional on Survival to 14 days (Follow-ups: April 1994 – June 2013)



Risk Factors for Chronic Rejection

TABLE 2. MULTIVARIABLE COX PROPORTIONAL HAZARDS MODEL OF RISK FACTORS FOR BRONCHIOLITIS OBLITERANS SYNDROME STAGE 1

Variable	RR	95% CI	*P* Value
Acute rejection grade : A_2	1.54	1.1–2.1	0.011
Lymphocytic bronchiolitis grade : B_2	1.61	1.1–2.3	0.008
CARV infection	1.53	0.9–2.6	0.119
PGD Grade:			
PGD 0 (reference)	1.00		
PGD 1	1.68	1.03–2.7	0.037
PGD 2	2.04	1.2–3.4	0.007
PGD 3	2.61	1.5–4.5	<0.0005

Definition of abbreviations: CARV = community-acquired respiratory virus; CI = confidence interval; PGD = primary graft dysfunction; RR = relative risk.

Adapted by permission from Reference 10.

Proc Am Thorac Soc Vol 6. pp 39-46, 2009

Treatment of Chronic Rejection

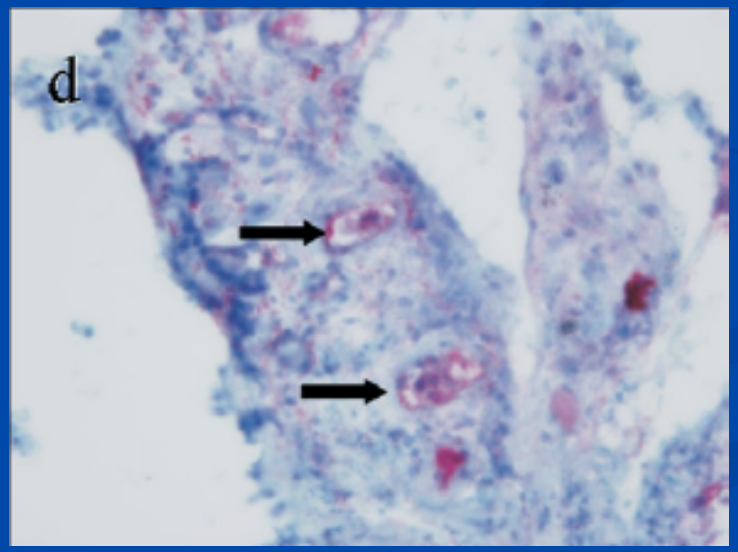
- High dose corticosteroids
- Conversion of current immunosuppressive regimen
- Sirolimus
- Antilymphocyte therapy
  - Antithymocyte globulin
- Azithromycin
- Total lymph node irradiation
- Photopheresis
- Re-transplantation

Humoral Rejection

- Recognized clinical entity in renal/heart transplant
- Recognition of allo-antigens by recipient antibodies
- Detection of HLA antibodies is a risk factor for chronic rejection
  - Screen at routine intervals and when clinically indicated

Humoral Rejection

Stage	Circulating antibody[b]	C4d deposition	Tissue pathology	Graft dysfunction
I: Latent humoral response	+	–	–	–
II: Silent humoral reaction	+	+	–	–
III: Sub-clinical humoral rejection	+	+	+	–
IV: Humoral rejection	+	+	+	+



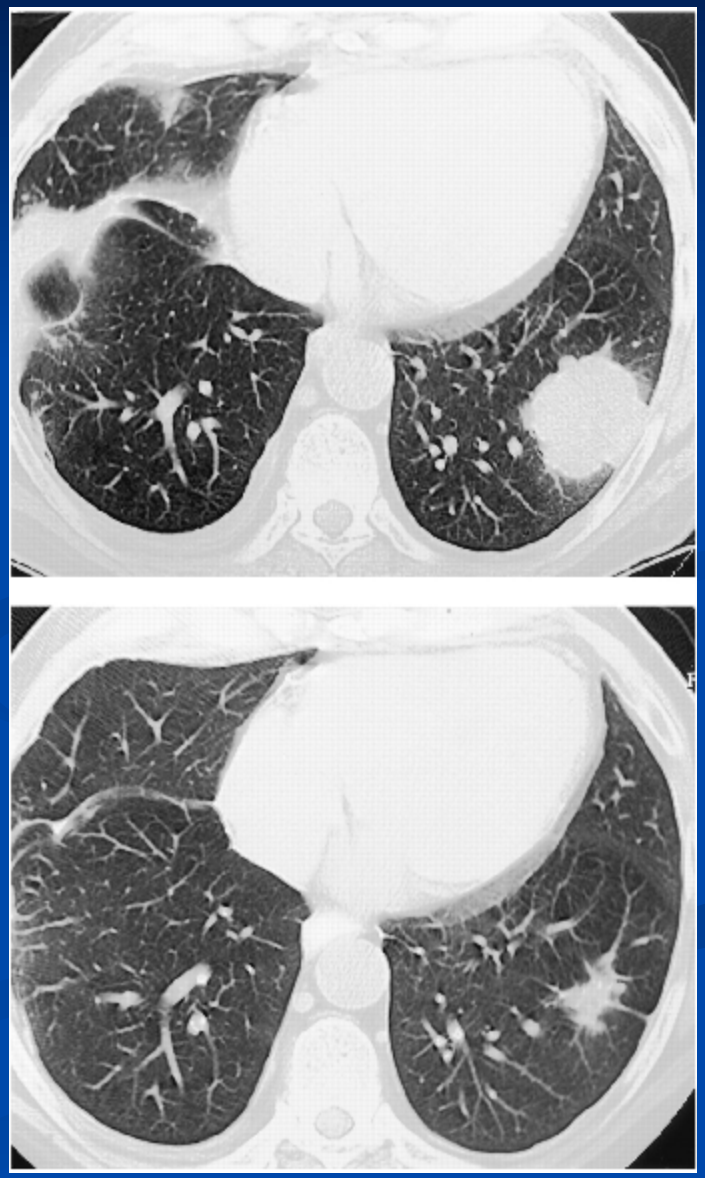
J Heart Lung Transplant 2009;28(1): 96-100

Humoral Rejection: Treatment

- IVIG
  - Causes B cell apoptosis and blocks binding of donor-reactive antibodies
- Rituximab: anti-CD20 monoclonal antibody
  - Results in B cell depletion
- Plasmapheresis
  - Removes antibody from circulation
  - Reserve for severe episodes of rejection

Post-transplant Lymphoproliferative Disease

- Incidence of 1.3 to 20%
- Usually occurs in first year after transplant
- Reactivation of EBV
- B-cell involvement
- Involves thorax and abdomen
- Rituximab ± systemic chemotherapy/XRT



Which type of malignancy is the most prevalent in lung transplantation?

- a) PTLD
- b) Non-small cell lung cancer
- c) Colo-rectal cancer
- d) Skin cancer
- e) Renal cell carcinoma

Medical Complications

- Diabetes mellitus
- Hypertension
- Hyperlipidemia
- Renal dysfunction
- Osteoporosis
- Cytopenias
- Avascular necrosis of femoral head
- GERD
- Tremors
- Malignancies

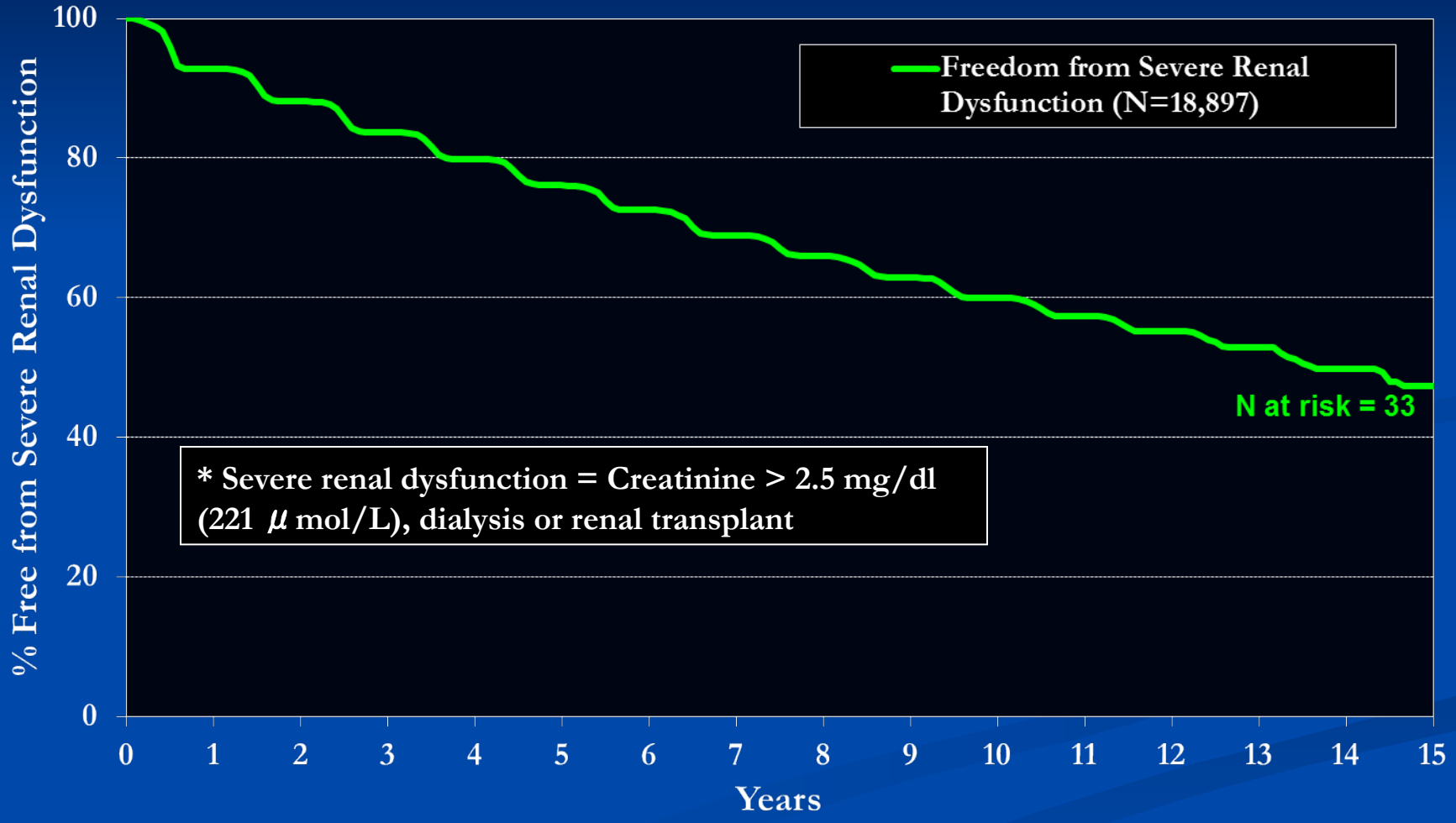
Adult Lung Transplants
Cumulative Morbidity Rates in Survivors within 1 and 5 Years Post Transplant (Follow-ups: April 1994 – June 2014)

Outcome	Within 1 Year	Total number with known response	Within 5 Years	Total number with known response
Hypertension	**51.7%**	**(N=17,813)**	**80.7%**	**(N=5,293)**
Renal Dysfunction	**22.5%**	**(N=20,551)**	**53.3%**	**(N=7,056)**
Abnormal Creatinine ≤ 2.5 mg/dl	*15.7%*		*35.3%*	
Creatinine > 2.5 mg/dl	*5.0%*		*14.3%*	
Chronic Dialysis	*1.7%*		*3.0%*	
Renal Transplant	*0.1%*		*0.8%*	
Hyperlipidemia	**26.2%**	**(N=18,510)**	**57.9%**	**(N=5,643)**
Diabetes	**23.0%**	**(N=20,502)**	**39.5%**	**(N=6,941)**
Bronchiolitis Obliterans Syndrome	**9.3%**	**(N=19,348)**	**41.1%**	**(N=5,987)**

Adapted from: JHLT. 2015 Oct; 34(10): 1264-1277

JHLT. 2015 Oct; 34(10): 1264-1277

Adult Lung Transplants
Freedom from Severe Renal Dysfunction*
(Follow-ups: April 1994 – June 2013)



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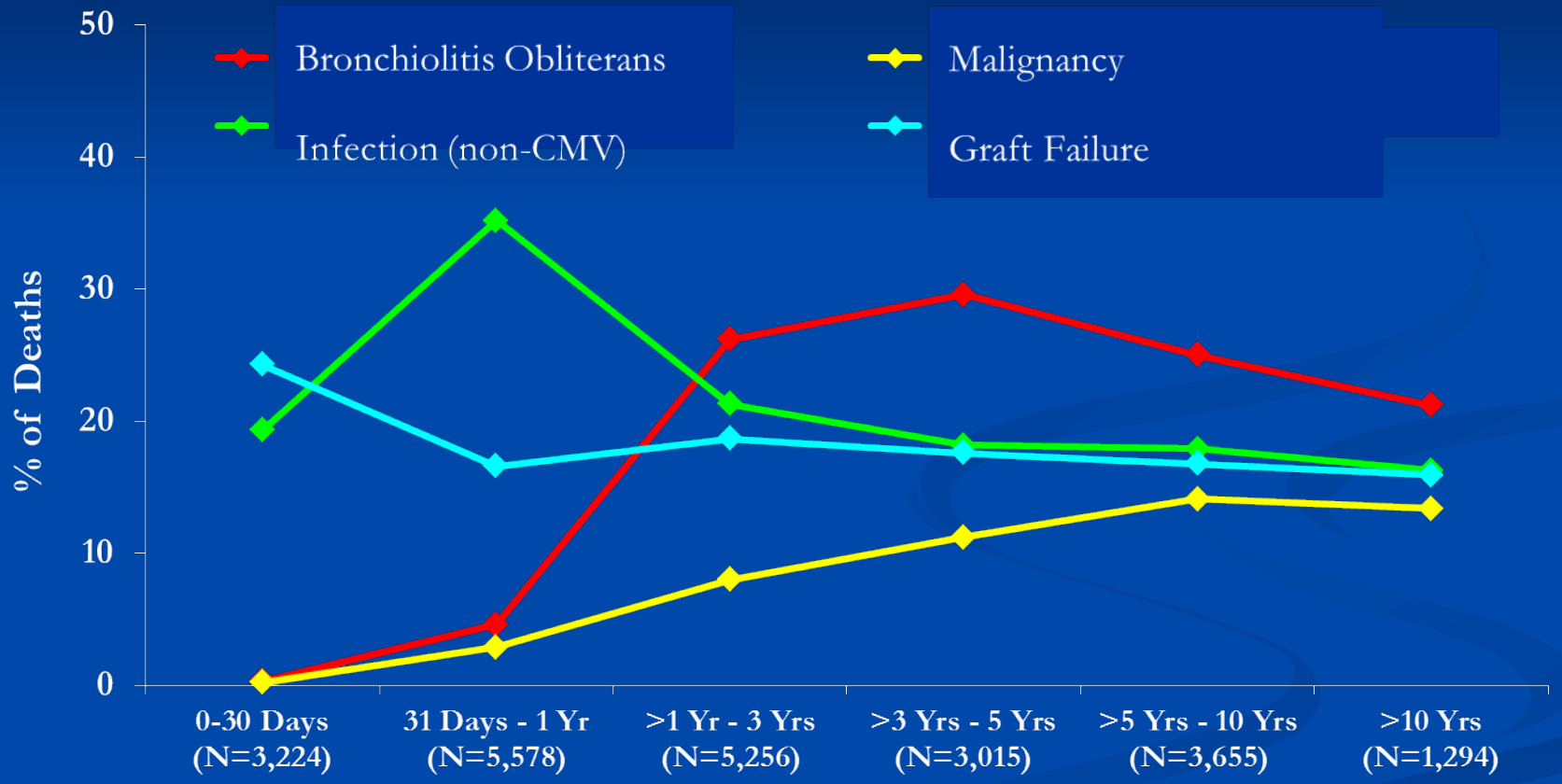
JHLT. 2014 Oct; 33(10): 1009-1024

Factors Affecting Survival



Adapted by ISHLT Registry 2015

Adult Lung Transplants
Cumulative Post Transplant Malignancy Rates in Survivors(Follow-ups: April 1994 – June 2013)

Malignancy/Type		1-Year Survivors	5-Year Survivors	10-Year Survivors
No Malignancy		18,644 (96.4%)	5,600 (84.3%)	1,049 (72.2%)
Malignancy (all types combined)		701 (3.6%)	1,042 (15.7%)	403 (27.8%)
*Malignancy Type**	*Skin*	*237*	*724*	*284*
	Lymphoma	*261*	*101*	*43*
	Other	*176*	*263*	*113*
	Type Not Reported	*27*	*9*	*0*

Other malignancies reported include: adenocarcinoma (2; 2; 1), bladder (2; 1; 0), lung (2; 4; 0), breast (1; 5; 2); prostate (0; 5; 1), cervical (1; 1; 0); liver (1; 1; 1); colon (1; 1; 0). Numbers in parentheses represent the number of reported cases within each time period.

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

Adult Lung Transplants
Cause of Death (Deaths: January 1992 – June 2013)

Cause of Death	0-30 Days (N = 2,905)	31 Days - 1 Year (N = 5,098)	>1 Year - 3 Years (N = 4,797)	>3 Years - 5 Years (N = 2,746)	>5 Years – 10 Years (N = 3,263)	>10 Years (N = 1,092)
Bronchiolitis	8 (0.3%)	233 (4.6%)	1,230 (25.6%)	804 (29.3%)	806 (24.7%)	219 (20.1%)
Acute Rejection	96 (3.3%)	93 (1.8%)	75 (1.6%)	17 (0.6%)	18 (0.6%)	2 (0.2%)
Lymphoma	1 (0.0%)	114 (2.2%)	84 (1.8%)	42 (1.5%)	60 (1.8%)	35 (3.2%)
Malignancy, Non-Lymphoma	5 (0.2%)	144 (2.8%)	380 (7.9%)	300 (10.9%)	448 (13.7%)	135 (12.4%)
CMV	0	116 (2.3%)	48 (1.0%)	7 (0.3%)	4 (0.1%)	1 (0.1%)
Infection, Non-CMV	550 (18.9%)	1,803 (35.4%)	1,041 (21.7%)	506 (18.4%)	586 (18.0%)	182 (16.7%)
Graft Failure	702 (24.2%)	844 (16.6%)	906 (18.9%)	493 (18.0%)	558 (17.1%)	181 (16.6%)
Cardiovascular	329 (11.3%)	257 (5.0%)	210 (4.4%)	138 (5.0%)	182 (5.6%)	83 (7.6%)
Technical	330 (11.4%)	180 (3.5%)	45 (0.9%)	14 (0.5%)	28 (0.9%)	8 (0.7%)
Other	884 (30.4%)	1,314 (25.8%)	778 (16.2%)	425 (15.5%)	573 (17.6%)	246 (22.5%)

Percentages represent % of deaths in the respective time period

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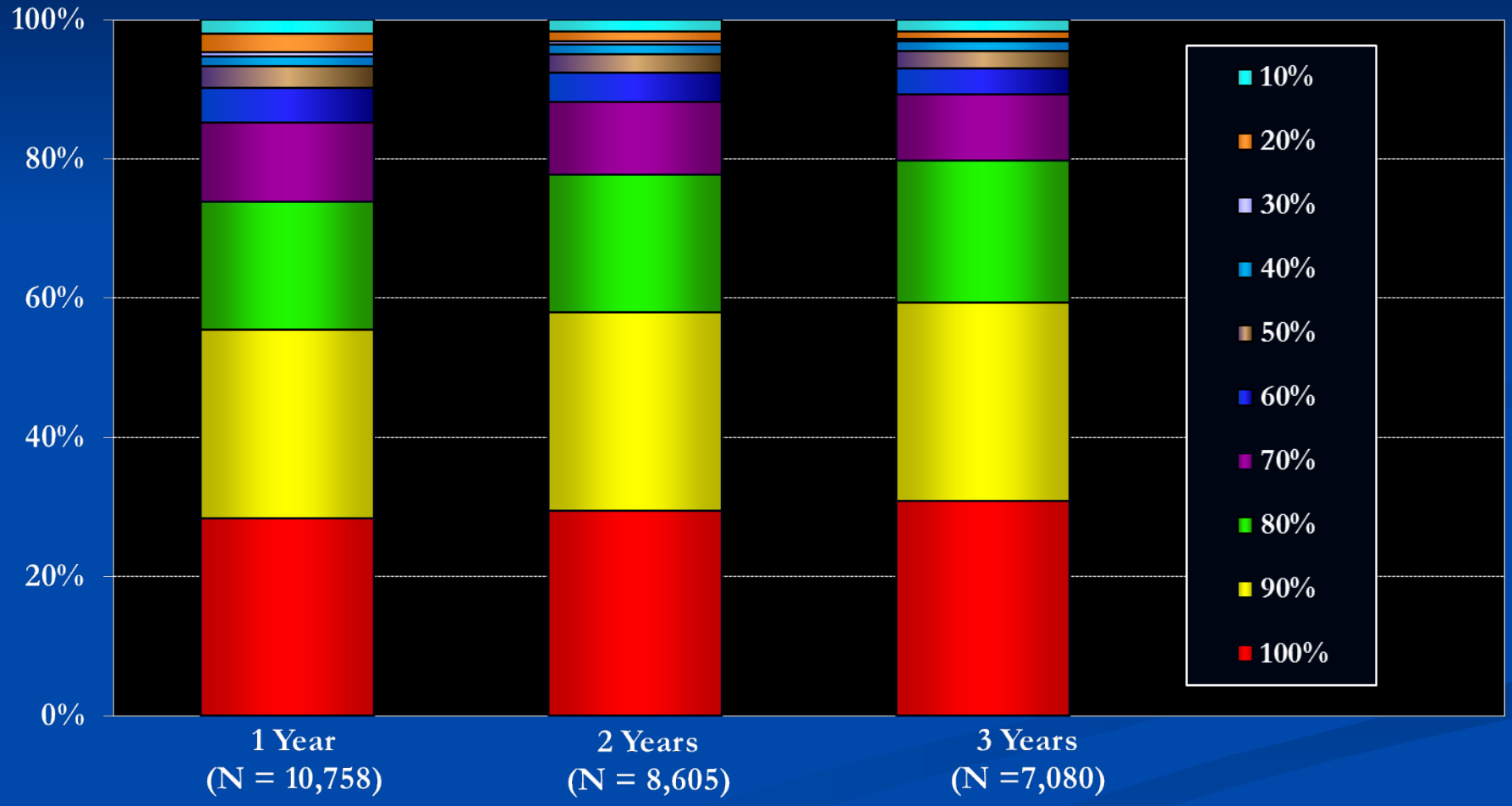
Adult Lung Transplants
Functional Status of Surviving Recipients
(Follow-ups: March 2005 – June 2013)



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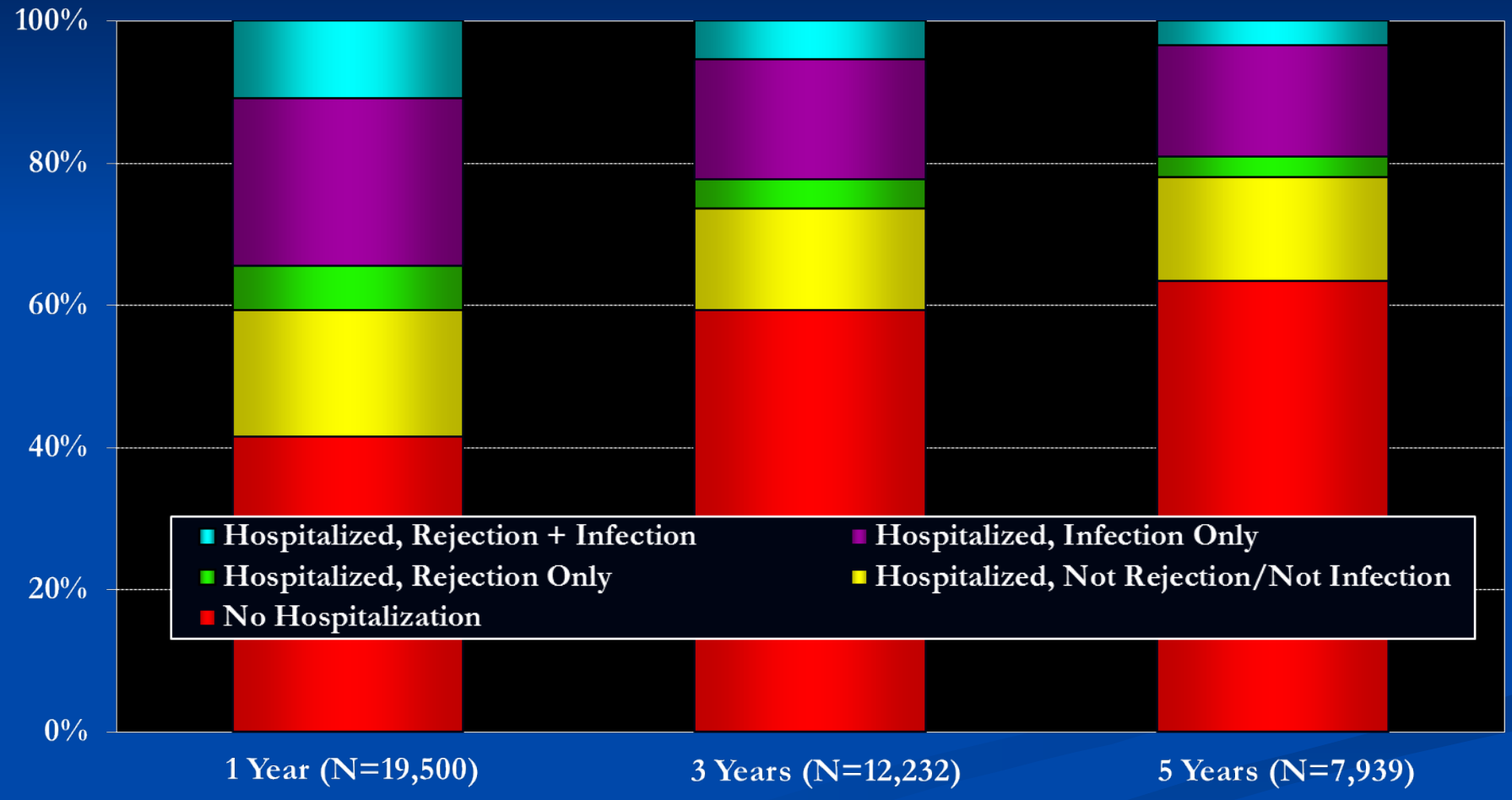
JHLT. 2014 Oct; 33(10): 1009-1024

Adult Lung Transplants
Rehospitalization Post Transplant of Surviving Recipients
(Follow-ups: April 1994 – June 2013)



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Adult Lung Transplants
Employment Status of Surviving Recipients
(Follow-ups: April 1994 – June 2013)