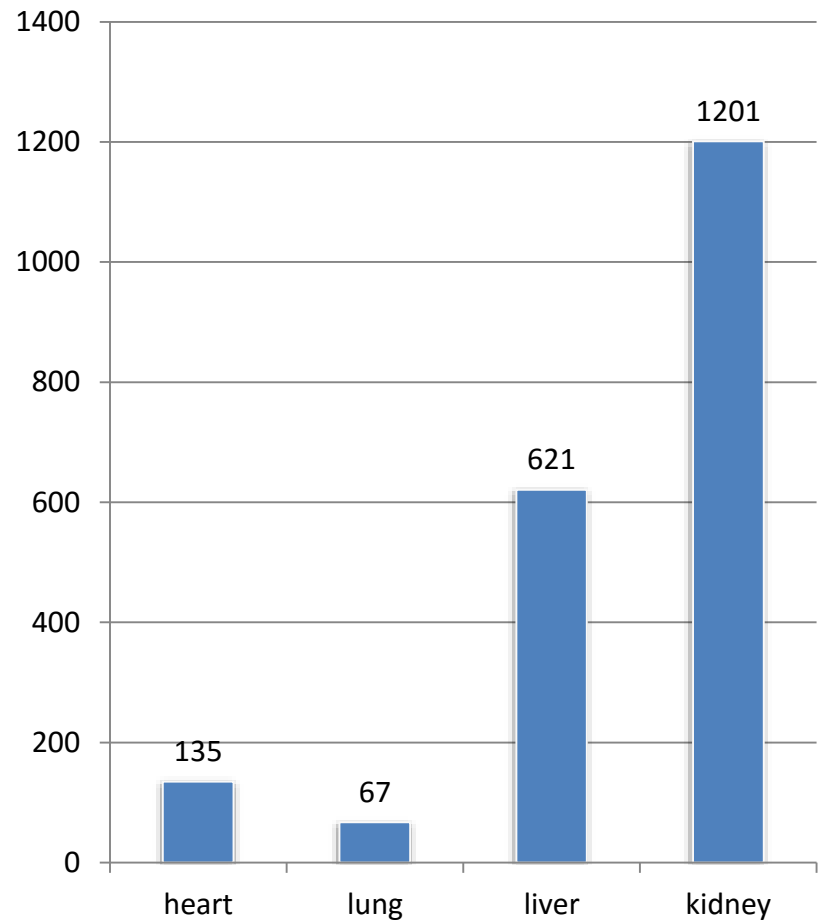


# CARE OF LUNG TRANSPLANT RECEPIENTS: Challenges unique to developing countries

Dr Milind Baldi

# LT in India

- Number of lung transplantation procedures done in India till July 2015
- Tamil Nadu: 67
- Karnataka: 0
- Kerala: 0



# Numbers...

- China\* : 244 (till 2013)
- Iran#: 63 (till 2014)
- Brazil ^^: ~ 700 (till Apr 2015)

\*[Transplant Proc.](#) 2013 Jan-Feb;45(1):349-55

# [Exp Clin Transplant.](#) 2014 Mar;12 Suppl 1:38-41

^^ [Einstein \(Sao Paulo\).](#) 2015 Apr-Jun;13(2):297-304

# Literature review

## Case Report

### Single Lung Transplantation in India: An Initial Experience

Raja Saravanan Elumalai<sup>1</sup>, Ganesh Somasundaram<sup>1</sup>, Kirthivasan Vaidyanathan<sup>1</sup>,  
Rajesh Venkatraman<sup>2</sup>, Madhusankar Nainar<sup>2</sup> and Vijil Rahulan<sup>3</sup>

Departments of Cardiac Anaesthesiology<sup>1</sup>, Cardiothoracic Surgery<sup>2</sup> and Pulmonology and Critical Care<sup>3</sup>, Global Hospital and Health City, Chennai, India

## *Review Article*

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### Lung transplantation in India: A possible treatment option

KALPAJ R. PAREKH, PRASAD S. ADUSUMILLI, G. ALEXANDER PATTERSON

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# Extrapolation from...

- Other Solid organ transplant complications in developing countries &
- Lung transplant related complications in developed countries.

# Complications

- PGD
- Infectious complications
- CAD
- Airway complications
- Malignancy
- Non infectious, non malignant long term complications

# Primary Graft Dysfunction

## Pathology

- DAD

## Pathophysiology

- Ischemia Reperfusion Injury

## Clinically

- Decreased oxygenation

## Radiology

- Diffuse pulmonary infiltrates

## Treatment

- Largely supportive

# Primary Graft Dysfunction

- acute lung injury
- within the first 72 hours.
- pulmonary edema with diffuse alveolar damage
- progressive hypoxemia and
- radiographic pulmonary infiltrates without other identifiable causes.



# Various names

- ischemia-reperfusion injury,
- re-implantation response and edema,
- reperfusion edema,
- non-cardiogenic pulmonary edema,
- early graft dysfunction,
- primary graft failure, and
- post-transplant ARDS;

# ISHLT, 2005

**Table 1**  
**ISHLT PGD grading schema**

<b>Grade</b>	<b>Pao<sub>2</sub>/Fio<sub>2</sub></b>	<b>Radiographic Infiltrates Consistent with Pulmonary Edema</b>
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Time points for assessment: T (0 to within 6 hours of reperfusion, 24, 48, and 72 hours).

- Several modifications (exclusions) have been proposed since then.

# PGD

- The reported incidence of PGD ranges from 10% to 25%, with 30-day mortality close to 50%
- Prediction models:
  - » normal BMI,
  - » COPD/CF, and
  - » absent or mild pulmonary hypertension

Category	Risk factors for PGD
Donor inherent variables	Age>45yo, Age<21yo African American race Female gender <b>History of smoking &gt;20py, &gt;10py, current, any</b>
Donor acquired variables	Prolonged mechanical ventilation Aspiration Head trauma Hemodynamic instability after brain death
Recipient variables	<b>Obesity Body mass index&gt;25</b> Female gender <b>Diagnosis of idiopathic pulmonary hypertension</b> Diagnosis of secondary pulmonary hypertension Diagnosis of idiopathic pulmonary fibrosis <b>Diagnosis of sarcoidosis</b> <b>Elevated pulmonary arterial pressure at time of surgery</b>
Operative variables	<b>Single lung transplantation</b> Prolonged ischemic time <b>Use of cardiopulmonary bypass</b> <b>Blood products transfusion &gt;1L</b> <b>High FiO<sub>2</sub> &gt;=0.4 at reperfusion</b> Use of intra-cellular (hyperkalemic) type (Euro-Collins) preservation solution

# Preventive Interventions

- 1) optimizing selection, matching, and management of donors and recipients preoperatively;
- 2) improving lung preservation and storage techniques; and
- 3) improving lung implantation and reperfusion techniques

# Treatment

- Therapy for established PGD after diagnosis remains generally **supportive**, and is influenced by those applied in patients with ARDS, including
  - lung-protective ventilation strategies,
  - avoidance of excess fluid administration,
  - iNO or prostacycline, and
  - extracorporeal membrane oxygenation support (ECMO)

# Pulmonary infections following lung transplantation

- Survival for lung transplant recipients continues to lag behind that of other solid organ transplant recipients
- a median survival (“half-life”) of 5.5 years.
- **First year after transplantation** : Graft failure and non-cytomegalovirus (non-CMV) infection
- **After first year**: the most common identifiable causes for mortality are bronchiolitis obliterans syndrome (BOS) and non-CMV infection.

# Higher than other solid organ transplant ...

- **Immunosuppression**
- preoperative microorganism colonization
- transmission of infectious agents from the donor
- blunted cough mechanism due to denervation
- impaired mucociliary clearance
- poor lymphatic drainage
- ischemic large airways in the immediate postoperative period and
- constant exposure to the environment



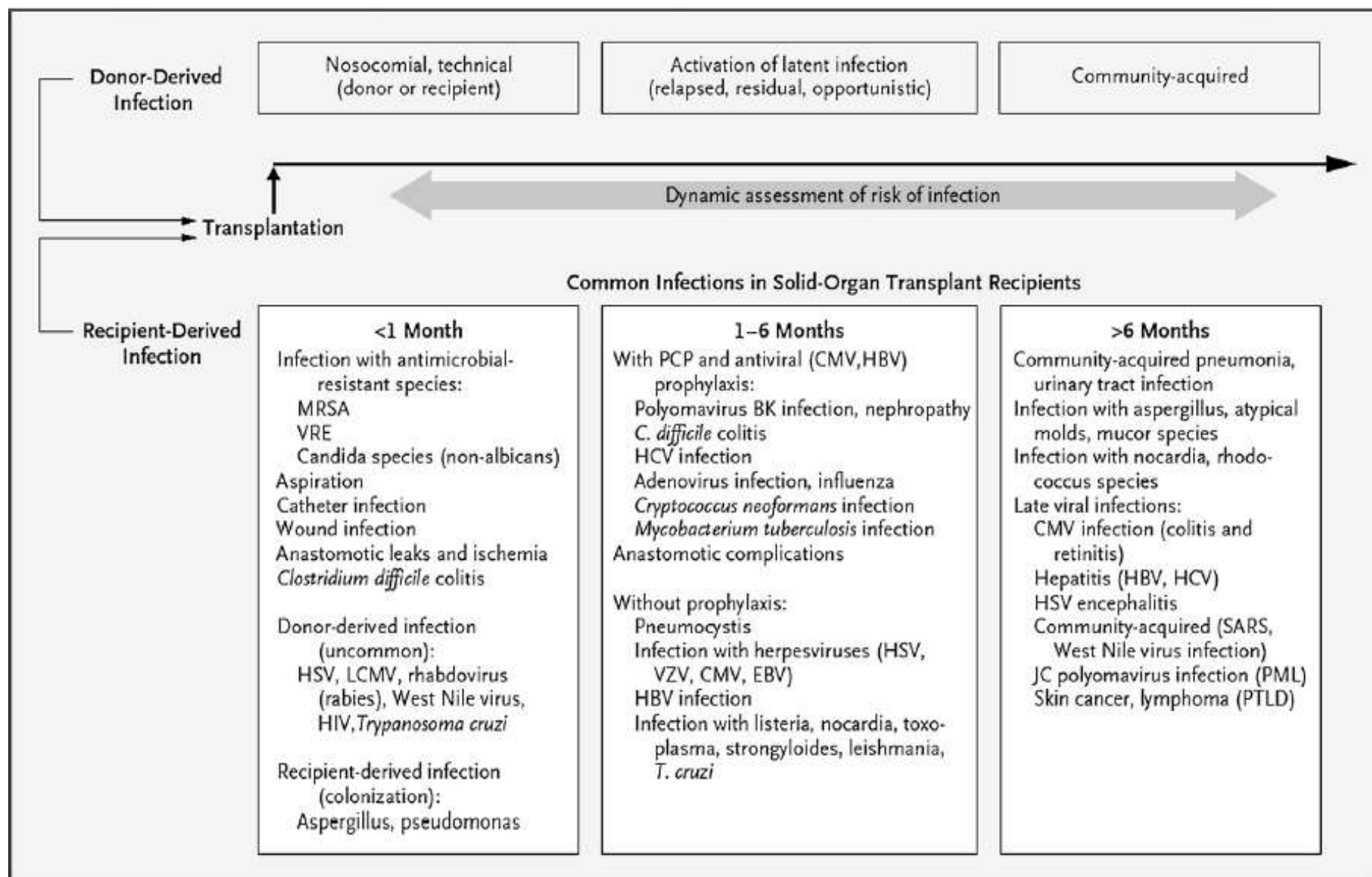
# Adult Lung Retransplants

## Cause of Death (Deaths: January 1992 – June 2013)

Cause of Death	0-30 Days (N = 226)	31 Days - 1 Year (N = 306)	>1 Year - 3 Years (N = 215)	>3 Years - 5 Years (N = 80)	>5 Years – 10 Years (N = 88)	>10 Years (N = 18)
Bronchiolitis	4 (1.8%)	26 (8.5%)	78 (36.3%)	30 (37.5%)	22 (25.0%)	6 (33.3%)
Acute Rejection	6 (2.7%)	8 (2.6%)	0	0	0	0
Lymphoma	0	4 (1.3%)	4 (1.9%)	2 (2.5%)	3 (3.4%)	0
Malignancy, Non-Lymphoma	0	3 (1.0%)	11 (5.1%)	5 (6.3%)	6 (6.8%)	2 (11.1%)
CMV	0	5 (1.6%)	3 (1.4%)	0	0	0
Infection, Non-CMV	39 (17.3%)	102 (33.3%)	39 (18.1%)	16 (20.0%)	13 (14.8%)	0
Graft Failure	56 (24.8%)	49 (16.0%)	45 (20.9%)	15 (18.8%)	20 (22.7%)	2 (11.1%)
Cardiovascular	24 (10.6%)	16 (5.2%)	10 (4.7%)	2 (2.5%)	3 (3.4%)	1 (5.6%)
Technical	31 (13.7%)	7 (2.3%)	1 (0.5%)	0	1 (1.1%)	1 (5.6%)
Other	66 (29.2%)	86 (28.1%)	24 (11.2%)	10 (12.5%)	20 (22.7%)	6 (33.3%)

# BOS

- Chronic allograft rejection is the major life-limiting complication after lung transplantation.
- Pulmonary infections with viruses, including CMV; gram-negative bacilli, especially *Pseudomonas aeruginosa*; and *Aspergillus* species have all been associated with an increased risk of BOS



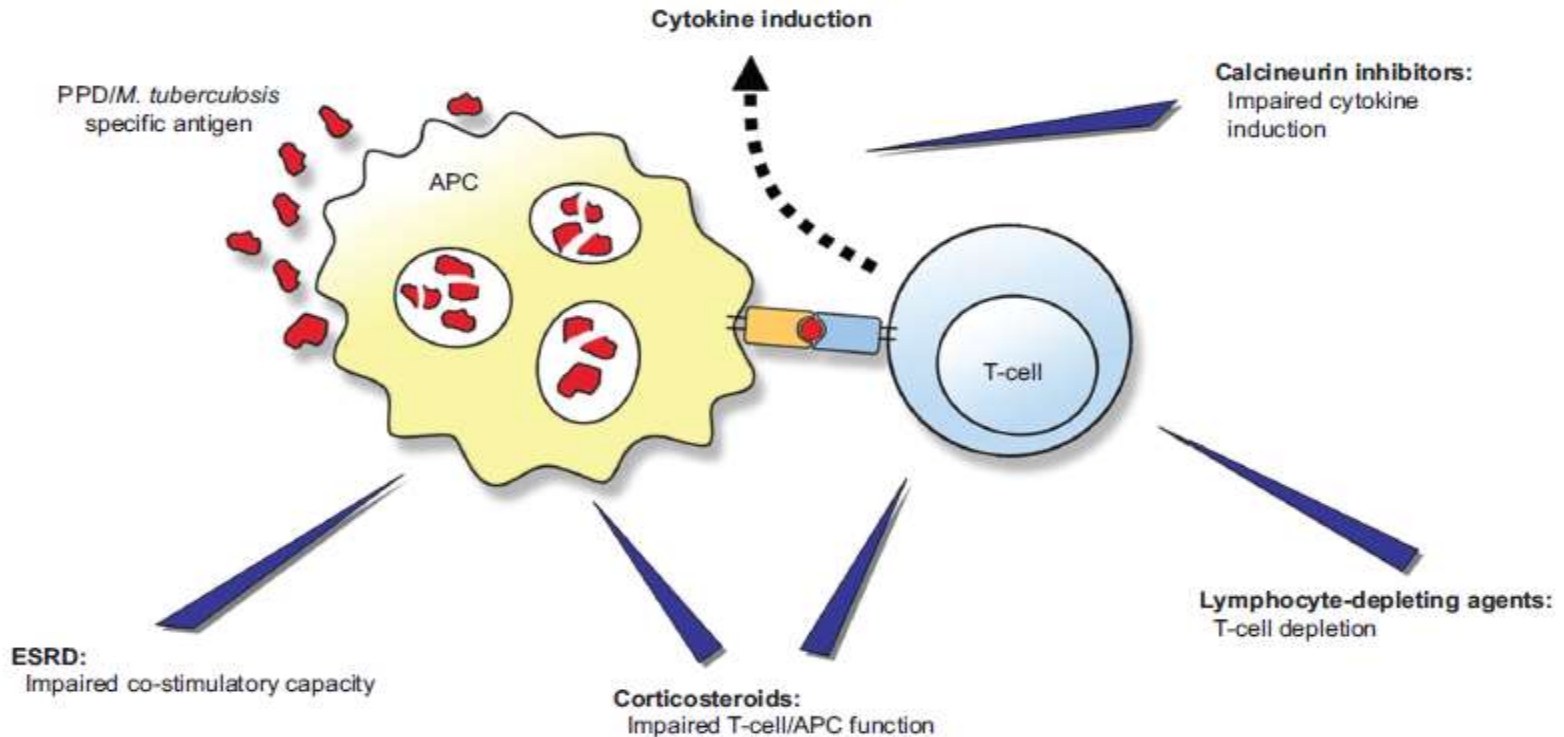
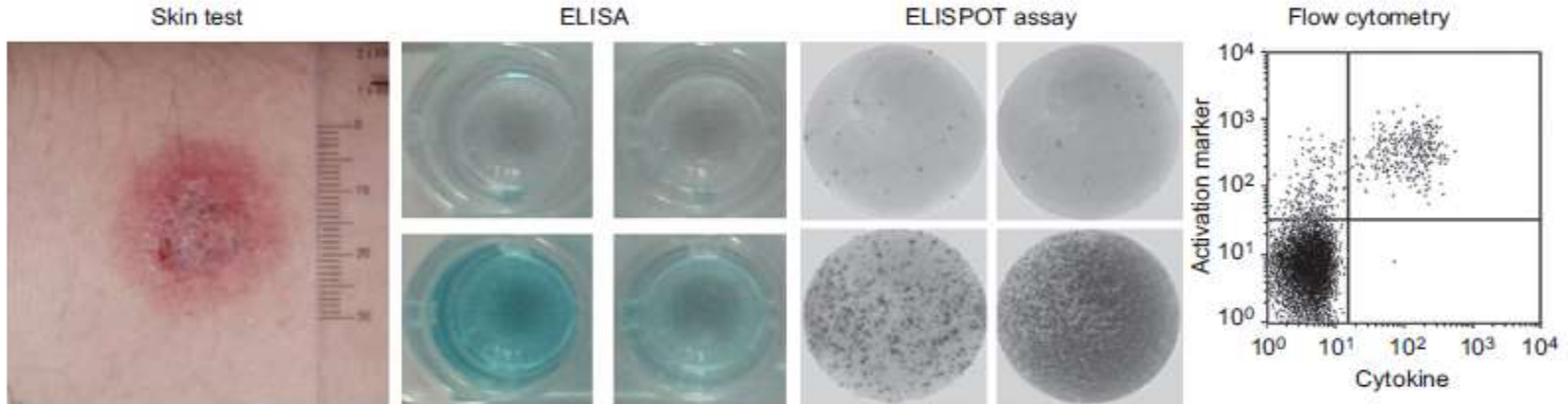
# Diagnosis of LTBI

- Interferon-gamma Release Assay Agreement With Tuberculin Skin Test in Pre transplant Screening for Latent Tuberculosis in High-prevalence Country
- There was a fair agreement between IGRAs and TST in the study ( $\kappa = 0.31$ )
- assessment of cellular immunity response in end-stage renal disease patients be a priority before reliance on IGRAs

# Diagnosis of LTBI

- Utility of QuantiFERON-TB Assay for Prediction of Tuberculosis Development in Kidney Transplant Patients in an Intermediate Tuberculosis-Burden Country
- The QFT test did not predict subsequent short-term TB development. Furthermore, a long-term and larger-scale study is needed to confirm our results

# Diagnosis of LTBI



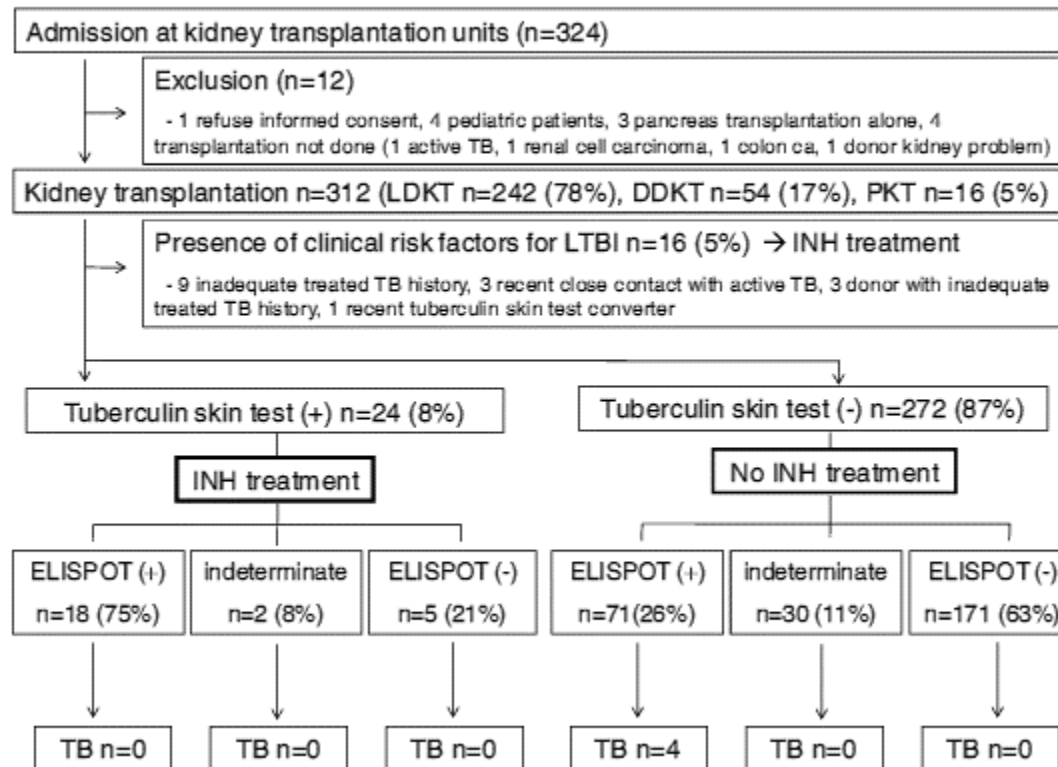
- A TST reaction of  $\geq 5$  mm of induration is considered positive (in transplant recipients)\*
- When compared to TST, IGRAs have some operational advantages that are particularly relevant in immunocompromised patients

- While screening of living donors is achievable, testing of deceased donors is challenging, as TST is not feasible and the performance of in vitro assays have not yet been assessed.
- When screening recipients, the decrease in test sensitivity with increasing immunosuppression has important practical consequences,
  - as screening should be carried out before administration of immunosuppressive drugs to ensure sensitivity and
  - to allow sufficient time to initiate chemoprophylaxis.



- The limited number of studies so far indicates that its value may be higher in low-prevalence countries as compared to highly endemic regions.

## Predictive Value of ELISPOT



- Further longitudinal studies are needed to estimate the risk for progression to post-transplant TB after IGRA- and TSTbased screening

# **Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis**

- Conducted in countries that have high prevalence of TB (India and Pakistan)
- Prophylactic administration of isoniazid reduced the risk of developing TB posttransplant
- there was no significant effect on all-cause mortality
- substantial risk of liver damage

- We found **limited evidence** of **suboptimal quality** to support that anti-TB prophylaxis using isoniazid for kidney transplant recipients during the first sixth months to one year post-transplant reduced the risk of developing TB

# Transplant and Tuberculosis

- 511 cases reported worldwide
- 5-15% in India (renal transplant patients)
- Immunosuppression: Cyclosporine and Azathioprine ( 47%)
- Time of onset: 9 months
- Mode of acquisition: MC: reactivation of old TB, donor transmitted in 4%

# Epidemiology

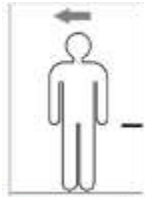
TB in transplant recipients is

- more frequent compared to the general population (estimates state 20–74 times as frequent in SOT recipients )
- often fatal (up to 31% in SOT recipients),

Nation	Risk post transplant	Organ assessed	Reference
Korea	Incidence: 2.1%	Kidney	The IJTLD, Volume 16, Number 2, 1 February 2012, pp. 248-254(7)
Taiwan	Hazard ratio: 2.25	Liver	<a href="#">Am J Transplant.</a> 2015 Apr 14. doi: 10.1111/ajt.13235
China	Incidence : 1.1%	Liver	<a href="#">Transplant Proc.</a> 2014 May;46(4):1032-5
China	Incidence: 3.2%	Kidney	<a href="#">Transplant Proc.</a> 2014 May;46(4):1032-5
China	Incidence: 2.8%	Heart	<a href="#">Transplant Proc.</a> 2014 May;46(4):1032-5
<b>India</b>	<b>Incidence: 2.3%</b>	<b>Liver</b>	<a href="#">Liver Transpl.</a> 2014 Aug;20(8):960-6
China	Incidence: 2.4%	Liver and Kidney	BMC Infect Dis. 2014; 14: 387.
China	Incidence : 3.2%	kidney	<a href="#">Transplant Proc.</a> 2014;46(2):588-91
Tunisia	Incidence: 3.2%	Kidney	<a href="#">Biomed Res Int.</a> 2013;2013:347103

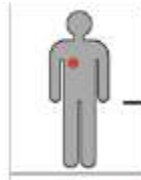


- The risk is highest in lung transplant recipients
- A history of a positive TST or radiographic evidence of past TB is associated with earlier onset of disease
- Hallmark symptoms of TB, are not present universally in transplant patients eg. Fever in 64% of recipients
- a wide range of radiographic manifestations

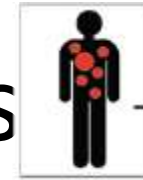


Healthy

# Tb in scenarios



LTBI

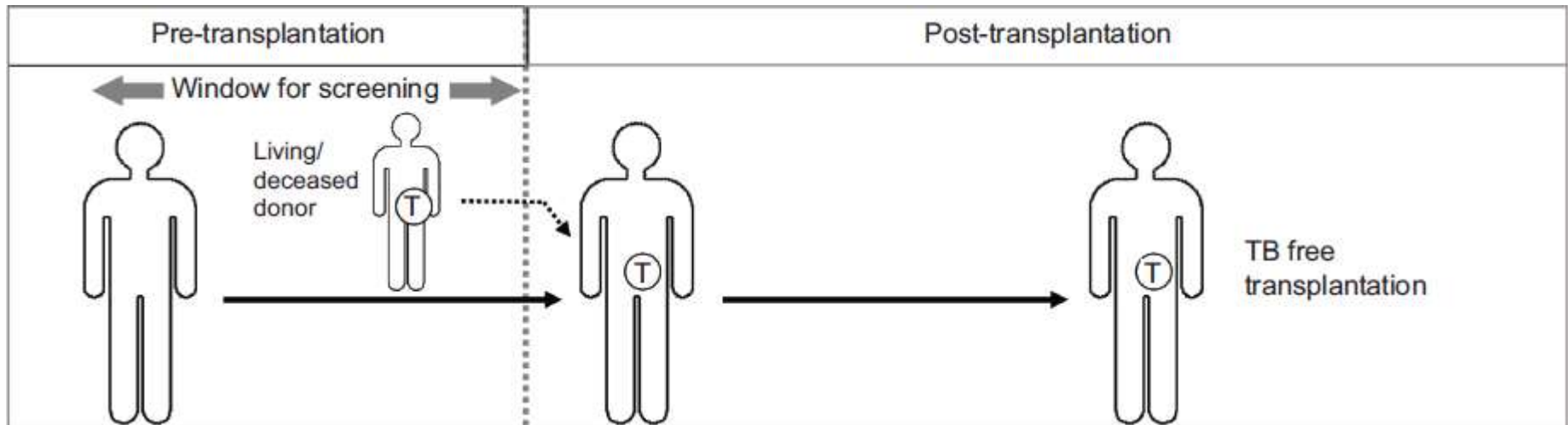


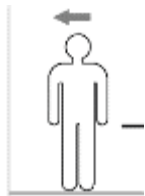
Active TB

● Latent infection with *M. tuberculosis*

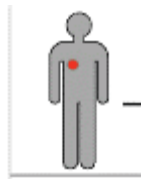
● Active TB

Ⓣ Transplanted graft

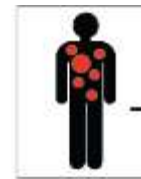




Healthy



LTBI



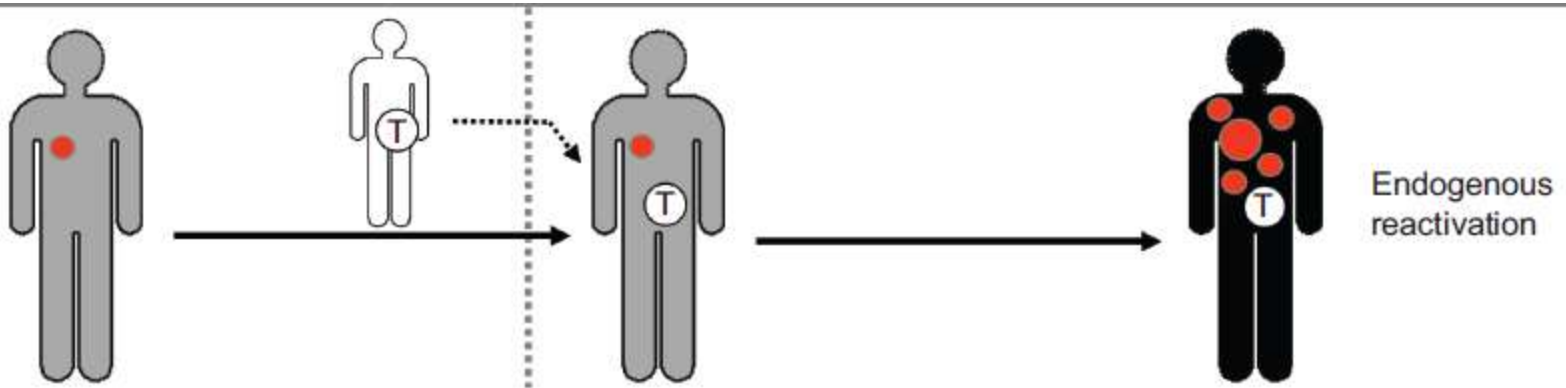
Active TB

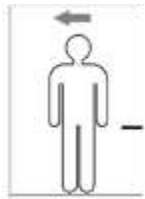
● Latent infection with *M. tuberculosis*

● Active TB

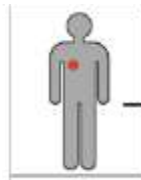
Ⓣ Transplanted graft

a)

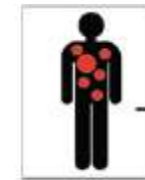




Healthy



LTBI



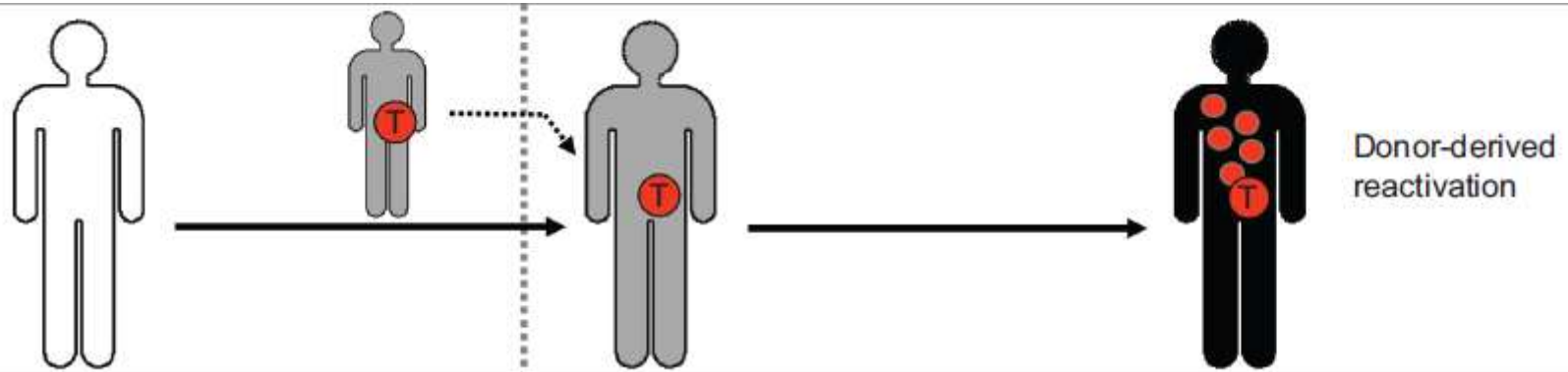
Active TB

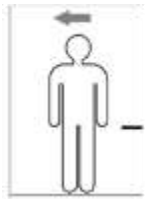
● Latent infection with *M. tuberculosis*

● Active TB

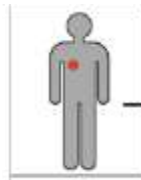
Ⓣ Transplanted graft

b)





Healthy



LTBI



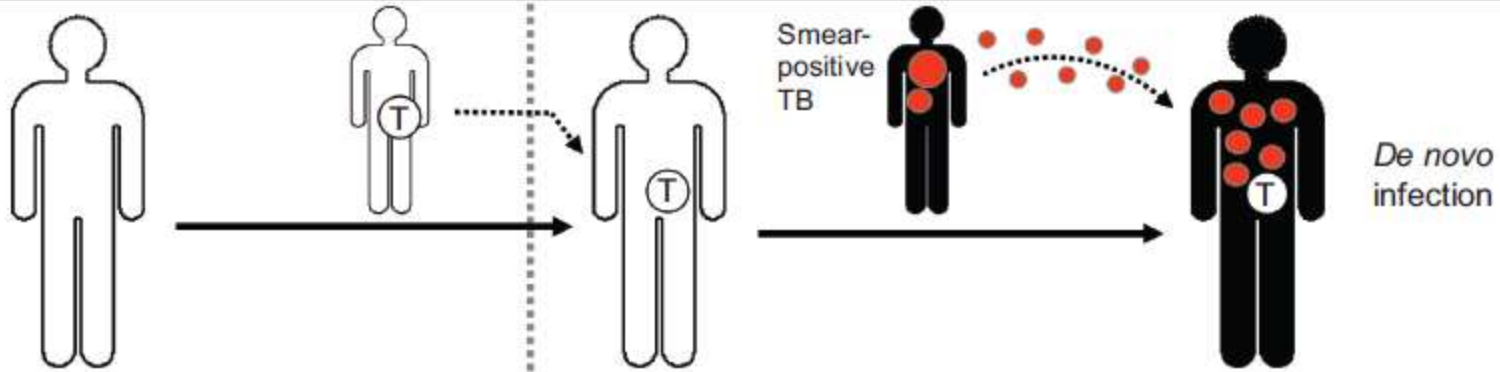
Active TB

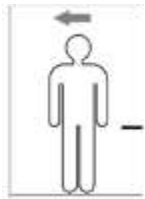
● Latent infection with *M. tuberculosis*

● Active TB

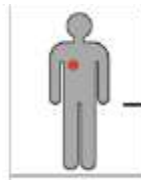
Ⓣ Transplanted graft

c)





Healthy



LTBI



Active TB

● Latent infection with *M. tuberculosis*

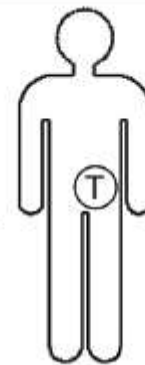
● Active TB

Ⓣ Transplanted graft

d)



TB treatment



Pre-transplant  
active TB

# PREVENTION OF TB IN Tx

- Effective pre-transplant screening for LTBI may prevent significant morbidity and mortality post-transplant .
- Apart from TST- or IGRA-positive individuals after targeted screening, treatment of SOT recipients may also be indicated due to a high-risk pretransplant exposure history (even with negative TST or IGRA)
  - residence in an endemic TB region during the early posttransplant period,
  - specific *M. tuberculosis* exposure post-transplant, or
  - with a donor history of untreated or incompletely treated LTBI or TB.

# PREVENTION OF TB IN Tx

- **Preventive chemotherapy:** used to denote treatment of LTBI among individuals identified as having a positive immune response to M. tuberculosis antigens.
- **Chemoprophylaxis:** is used here to denote primary chemoprophylaxis to prevent TB among individuals with risk factors but without a positive immune response to M. tuberculosis antigens (either negative test or not tested).



# PREVENTION OF TB IN Tx

- Risk-adapted pretransplant screening is therefore essential, for:
  - An opportunity for preventive chemotherapy in patients with LTBI, and
  - to raise the index of suspicion of active disease in those patients at high risk.
- In cases where the pre-transplant screening may be falsely negative, as with anergy to TST or an indeterminate IGRA, specialised imaging may be employed in selected patients.

# PREVENTION OF TB IN Tx

- Treatment of LTBI:
- “Treatment of LTBI is likely to be beneficial in persons with reversible risk factors that increase the chance of developing active TB”
- Active infection should be ruled out first

# PREVENTION OF TB IN Tx

- Treatment of LTBI
- Isoniazid:
  - 9-12 months
  - most commonly used .
    - But, hepatotoxicity,
    - poor compliance because of long duration,
    - presence of high primary resistance to the drug.
- Rifampin and pyrazinamide :
  - 2 months, but
    - liver injury is higher
- Isoniazid and Rifampacin:
  - 3 months
  - equivalent to standard therapy with isoniazid
  - Can be extended if intense immunosuppression or high risk

# PREVENTION OF TB IN Tx

- Treatment of LTBI
- Timing of therapy ?
- ? Pre transplant: lowers the risk of drug interactions.
- ? Post transplant: immunosuppression has started and the risk of reactivation TB is higher

# TREATMENT OF ACTIVE TB IN TRANSPLANT RECIPIENTS

- Different from general population in two ways:
  1. as rifamycins interact with immunosuppressive drugs of the calcineurin inhibitor family (cyclosporine and tacrolimus), rapamycin and corticosteroids, **rifamycin-sparing treatment regimens** are preferred

If a rifamycin is used, the risk of rejection may be increased due to lowered levels of calcineurin inhibitors; consequently, **levels of cyclosporine or tacrolimus** should be carefully monitored and doses should be adapted (**3–5-fold increase**)

- 2. adverse anti-TB drug events are more frequent. Consequently, one or more first-line drugs cannot be used and thus the recommended **duration of therapy** is generally longer than in the general population.

	ISONIAZID	RIFAMPICIN	STREPTOMYCIN	FLUROQUINOL ONE
<b>STEROIDS</b>	↑ steroid levels	↓ steroid levels and efficacy	None	↑ tendon related side effects
<b>CYCLOSPORIN A</b>	None	↓ Cyclosporin levels, use alt. or monitor levels	↑ risk of nephrotoxicity, avoid or monitor	↑ Cyclosporin levels
<b>TACROLIMUS</b>	None	↓ Tacrolimus levels, monitor levels or use alternative	↑ risk of nephrotoxicity, avoid or monitor	None
<b>SIROLIMUS / RAPAMYCIN</b>	None	↓ Sirolimus levels, monitor levels or use alt.	None	None
<b>MMF</b>	None	↓ MMF levels, use alt. or monitor levels	None	↓ MMF levels

No interaction with Pyrazinamide and Ethambutol

# CMV

- Despite 3 months of CMV-directed viral prophylaxis, 10% of postlung transplant pneumonias reported were caused by CMV (n= 236)
- maximum risk in Lung transplant
  - More intense immunosuppression
  - Huge viral load
  - Max risk in D+/R- combination



# CMV

- Measurement of **CMV-specific CMI** as a predictor of the development of CMV viremia and disease after the completion of primary prophylaxis.
- Commercially available CD81 CMV-specific interferon  $\gamma$  release assay to test serial CMV-specific CMI in SOT recipients during a 3-month posttransplant CMV prophylaxis period.
- Postprophylaxis CMV disease occurred in 22.9% of patients with no detectable CMV-specific CMI, versus 5.3% in patients with a positive QuantiFERON-CMV result, suggesting a possible role in predicting late-onset CMV disease.

# CMV

- There are 2 generally accepted strategies for CMV prophylaxis in solid-organ transplantation:
  - universal prophylaxis (administration of antivirals to all at-risk individuals) and
  - preemptive therapy (administration of antivirals only to individuals with demonstrable viral replication).
- Significant uncertainty remains regarding the appropriate duration of prophylaxis.
- Recent trials have suggested that extending prophylaxis to 1 year or longer after transplant may reduce CMV-related complications
- Reinitiation of CMV prophylaxis should be considered during the treatment of acute rejection if antilymphocyte antibody therapy or high-dose steroids are used.

# CMV

- For CMV tissue-invasive disease, oral valganciclovir 900 mg every 12 hours (adjusted for renal function) is noninferior to intravenous ganciclovir in a mixed population of SOT recipients.
- Treatment should be continued for a minimum of 2 to 3 weeks and until the cessation of viral replication has been verified and any CMV attributable symptoms have resolved.
- Secondary prophylaxis with lower-dose valganciclovir (900 mg daily adjusted for renal function) can be considered for high-risk patients after completion of CMV treatment, especially those in whom reduction of immunosuppression is not possible.

# CMV

- This systematic review found that the antiviral agents improve outcomes for solid organ transplant recipients far beyond the primary indication for use.
- In addition to reducing the risk of CMV disease by 60%, these agents reduced all-cause mortality by 40%, predominantly due to
  - reduced mortality from CMV disease,
  - reducing clinical disease caused by herpes simplex and herpes zoster
  - bacterial infections, and
  - protozoal infections.
- These benefits occurred in both CMV positive recipients and CMV negative recipients of CMV positive organs

# CARVs

- In a significant percentage of patients, symptomatic or asymptomatic **viral infection** is a trigger for acute rejection and obliterative bronchiolitis/BOS
- Effective antiviral therapies for most CARVs are not available, with the notable exception of influenza virus and perhaps RSV, thus appropriate infection control strategies including **hand hygiene** and **droplet precautions** are mandatory to prevent the spread of disease

# CARVs

- Influenza
- All transplant recipients and their household contacts should receive **yearly influenza vaccination** with inactivated influenza vaccine for the prevention of disease.
- Suspected cases of influenza should be treated ideally within 48 hours of symptom onset, but symptomatic recipients should be treated regardless of the duration of symptoms.

# CARVs

- RSV
- **Supportive care** with the reduction of immunosuppression if possible is universally recommended
- Oral **ribavirin** appears to be an effective, well-tolerated alternative to IV or inhaled ribavirin; provides considerable cost savings and reduces length of hospital stay

Am J Transplant 2009;9(Suppl 4):S166–72

[J Heart Lung Transplant.](#) 2015 Jul;34(7)

# Gram negative Bacterial Infections

- Bacterial pathogens : most common cause of pneumonia after lung transplantation,
- gram-negative bacteria responsible for the bulk of disease.
- a positive donor Gram stain does not lead to poorer posttransplant outcomes if **targeted, aggressive antimicrobial prophylaxis** is given initially.



- No difference in the incidence of posttransplant pneumonia at 30 days or duration of mechanical ventilation between recipients of donor lungs with positive or negative Gram stains in patients treated with standard postoperative antibiotic prophylaxis (vancomycin plus a third-generation cephalosporin for 7 days)

Microorganism	n (%)	Incidence (Number of episodes per 1.000 LT recipients/year)
BACTERIA	47 (82.7)	398
Gram-negative bacilli:	34 (59.9)	288
<i>Pseudomonas aeruginosa</i>	14 (24.6)	118.6
<i>Acinetobacter baumannii</i>	8 (14)	67.8
<i>Escherichia coli</i>	3 (5.3)	25.4
<i>Klebsiella pneumoniae</i>	3 (5.3)	25.4
<i>Stenotrophomonas maltophilia</i>	3 (5.3)	25.4
<i>Pseudomonas putida</i>	1 (1,8)	8.4
<i>Serratia marcescens</i>	1 (1,8)	8.4
<i>Burkholderia cepacia</i>	1 (1,8)	8.4
Gram-positive cocci:	8 (14)	67.8
<i>Staphylococcus aureus</i>	8 (14)	67.8
<i>Nocardia</i> sp.	2 (3,5)	16.8
Mycobacteria	3 (5,3)	25.4
<i>M. tuberculosis</i>	2 (3,5)	16.8
<i>M. avium</i>	1 (1,8)	8.4
FUNGI	8 (14)	67.8
<i>Aspergillus fumigatus</i>	4 (7)	33.8
<i>Aspergillus niger</i>	1 (1,8)	8.4
<i>Scedosporium prolificans</i>	1 (1,8)	8.4
<i>Acremonium</i> sp.	1 (1,8)	8.4
<i>Mucor</i> sp.	1 (1,8)	8.4
VIRUS	6 (10,4)	50.8
Cytomegalovirus	6 (10,4)	50.8
TOTAL	57 (107)*	

*American Journal of Transplantation* 2007; 7:  
1989–1996

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Mycobacteria	3 (5.3)	25.4	18%
<i>M. tuberculosis</i>	2 (3.5)	16.8	
<i>M. avium</i>	1 (1.8)	8.4	
FUNGI	8 (14)	67.8	
<i>Aspergillus fumigatus</i>	4 (7)	33.9	10%
<i>Aspergillus niger</i>	1 (1.8)	8.4	
<i>Scedosporium prolificans</i>	1 (1.8)	8.4	
<i>Acremonium</i> sp.	1 (1.8)	8.4	
<i>Mucor</i> sp.	1 (1.8)	8.4	
VIRUS	6 (10.4)	50.8	
Cytomegalovirus	6 (10.4)	50.8	15%
TOTAL	57 (107)*		

# Fungal Infections

Fungal infections have a **bimodal** presentation:

- early onset, in relation to difficult postsurgeries and prior colonizations, and
- late onset, primarily in relation to chronic rejection and terminal renal insufficiency
- Fungal infections occur in 15–35% of patients after lung transplantation
- overall mortality of 80%

# Transplant Associated Infection No. Surveillance Network (TRANSNET)

IFI type	Kidney (n = 332)	Liver (n = 378)	Pancreas (n = 128)	Lung (n = 248)	Heart (n = 99)	Small bowel (n = 22)
Candidiasis	164 (49)	255 (68)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other mold	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0.0)
Unspecified mold	7 (2.1)	8 (2.1)	0 (0.0)	7 (2.8)	2 (2.0)	0 (0.0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0.0)	0 (0.0)	1 (5)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0.0)	1 (5)

Peter G. Pappas et al. Clin Infect Dis. 2010;50:1101-1111

# Aspergillus

- **pretransplant airway colonization** was once considered as a risk factor for IA, but subsequent studies have not found the same.
- **Galactomannan assay** : approved in hematopoietic stem cell transplant population, approved for use as a twice weekly
- LT recipients: mixed results, BAL better sensitivity and specificity than serum

# Aspergillus

- Prophylaxis:

Majority of centers aim to target Aspergillus and Candida infection.

Monotherapy with either voriconazole or inhaled amphotericin B mostly variable time periods (40% 3-6 months; 30%  $\geq 12$  months)

TDM (itraconazole/voriconazole) was used in 86% of centers.

# Aspergillus

- Prophylaxis:
- A uniform approach on the optimal agent, dose, frequency, route of administration, type and duration of antifungal prophylaxis in LTx recipients, has not been established.
- Despite the lack of RCTs, the majority of existing studies suggested that antifungal prophylaxis can reduce the incidence and risk of IA among LTx recipients, with tolerable ADRs.



# Aspergillus

- Treatment:
  - Voriconazole for Aspergillus tracheobronchitis
  - along with reduction of immunosuppression,
  - with attention paid to drug interactions with calcineurin inhibitors and to
  - potential side effects including hepatotoxicity and visual hallucinations.
  - Duration of treatment is guided by bronchoscopic surveillance.

# Aspergillus

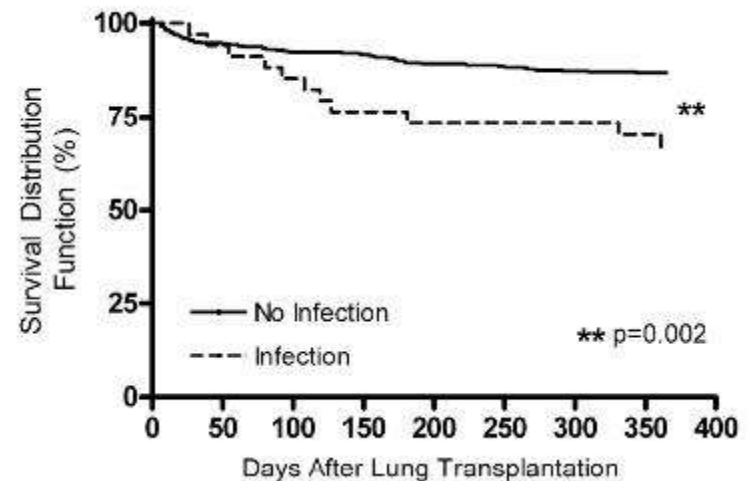
- Treatment
  - Treatment of IA also relies on voriconazole
  - Reduction of immunosuppression is again an important component of treatment.
  - Surgical intervention
  - Interferon gamma immunotherapy studied in renal transplant recipient

# Candida

- Risk Factors
  - prolonged stays in the intensive care unit,
  - Prolonged indwelling catheters and
  - broad-spectrum antibiotic therapy and
  - parenteral nutrition, and
  - heavy growth of Candida from the donor lung
- Culture remains the gold standard for the diagnosis of candidal infections
- given the increasing use of azole prophylaxis (both fluconazole and voriconazole) in lung transplant patients experts recommend empiric therapy with an echinocandin or liposomal amphotericin B

# Early Pleural Space Infection Following Lung Transplantation

- Pleural effusions requiring drainage occurred in 27% of recipients (124/455)
- pleural space infection occurred in 27% (34/124)
- MC infectious etiology: Fungal (60%)
- *Candida albicans* was the predominant organism



### Some common prophylaxis regimens in the lung transplant recipient

Infection	Viruses/Organisms	Common Prophylaxis Regimens
Viral	Herpes simplex virus CMV	<p>Acyclovir, 200 mg, po twice daily indefinitely</p> <p>High risk (D<sup>+</sup>/R<sup>-</sup>)</p> <p>Valganciclovir, 900 mg, po daily for 6–12 mo</p> <p>Medium Risk (D<sup>+</sup>/R<sup>+</sup>, D<sup>-</sup>/R<sup>+</sup>)</p> <ol style="list-style-type: none"> <li>1. Weekly CMV polymerase chain reaction, treat when test result is positive</li> <li>2. Valganciclovir, 900 mg, po daily for 3–12 mo</li> </ol>
<i>Pneumocystis jiroveci</i> pneumonia	<i>Pneumocystis jiroveci</i>	<p>Trimethoprim/sulfamethoxazole, 160/800 mg, po 3 times weekly indefinitely</p> <p>Alternatives for sulfa intolerant, all continued indefinitely</p> <ol style="list-style-type: none"> <li>1. Atovaquone, 1500 mg, po daily</li> <li>2. Pentamidine, 300 mg, inhaled monthly</li> <li>3. Dapsone, 100 mg, po daily</li> </ol>
Fungal	<i>C albicans</i>  <i>Aspergillus</i> species	<p>Until corticosteroid dose weaned postoperatively or 3 mo</p> <ol style="list-style-type: none"> <li>1. Nystatin, 5 mL, po 4 times daily</li> <li>2. Fluconazole, 100 mg, po daily</li> </ol> <p>When colonized preoperatively or immediately postoperatively, continued until cultures negative</p> <ol style="list-style-type: none"> <li>1. Voriconazole, 200 mg, po twice daily</li> <li>2. Itraconazole, 200 mg, po twice daily</li> <li>3. Amphotericin, 20–40 mg, inhaled daily</li> </ol>

# Immunosuppression

- One of the factors that has led to significant improvements in post transplant survival in the current era of solid organ transplantation
- targeting multiple pathways
- Unfortunately, these agents have not been as effective in lung transplantation where graft rejection remains a major obstacle to long-term survival

# Conventional approaches

- Some variability
- **Maintenance regimens** typically involve administration of three distinct classes of immunosuppressive agents:
- Calcineurin inhibitors (eg, cyclosporine, tacrolimus),
- Antiproliferative agents (eg, azathioprine, mycophenolate mofetil , sirolimus),
- Corticosteroids

# Induction therapy

- In addition, approximately 60% of lung recipients receive **induction therapy** to augment immunosuppression in the early posttransplant period
- a potent immunosuppressive agent
  - to reduce risk of acute rejection
  - permit more gradual initiation of maintenance immunosuppression.
- specifically target T-lymphocytes



- high quality studies comparing one regimen to another are also absent.
- Transplant center practices regarding induction therapy are based largely on retrospective studies, registry reports, and small prospective single-center investigations as well as institutional experiences and expert opinion.

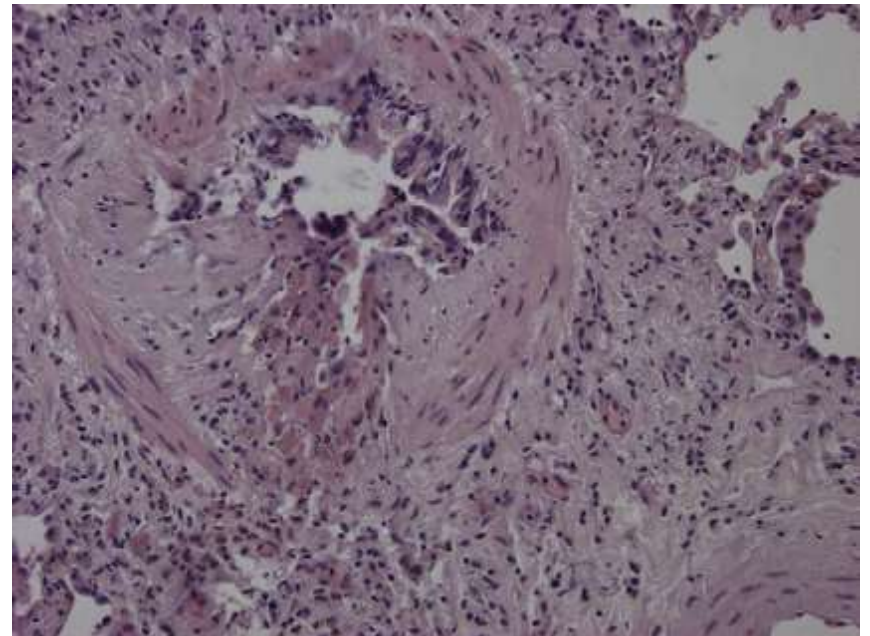
- retrospective study of almost 4000 lung transplant recipients in the ISHLT
- registry transplanted between January 2000 and March 2004, induction therapy with either an IL-2R antagonist or polyclonal ATG remained independently associated with **improved survival at 4 years** (IL2R antagonist, 64%; ATG, 60%; no induction, 57%).
- There was also a significantly **higher rate of infection** in both induction therapy groups compared with patients who did not receive induction therapy

# To induce or not to induce...?

- *United Network for Organ Sharing* registry from 2001 to 2012 for adult
- deceased donor lung transplants who received no induction (**NONE**) or the contemporary agents of basiliximab, alemtuzumab, thymoglobulin, antilymphocyte globulin, or antithymocyte globulin (**INDUCED**).
- Amongst the 23 951 lung transplants performed with **12 858** meeting the inclusion criteria; 5713 (44%) were INDUCED.
- Being INDUCED significantly increased overall survival ( $p < 0.0001$ ).
- Median INDUCED survival was 71.3 months (confidence interval [CI]: 65.7–75.5) as compared with 63.2 months (CI: 60.1–65.9).
- There was less rejection in INDUCED patients (37%), as compared to NONE (42%;  $p < 0.0001$ ).

# Chronic Allograft Dysfunction

- first described in 1984
- Lung biopsy:  
intraluminal polyps of  
fibromyxoid granulation  
tissue, which tends to  
obliterate the lumen of  
terminal bronchioles,  
and dense submucosal  
eosinophilic fibrous  
scars



- The small airway lesions have a patchy distribution,
- can hardly be demonstrated by TBB
- As a result, in order to establish the diagnosis of BO without the need for open lung biopsy, in 1993, the ISHLT proposed a clinical definition based on pulmonary function criteria.

# Updated classification

**Table 1**  
Bronchiolitis obliterans syndrome classification system

1993 Classification		2002 Classification	
	FEV <sub>1</sub> 80% or more of baseline	FEV <sub>1</sub> >90% of baseline <i>and</i> FEF <sub>25-75</sub> >75% of baseline	BOS 0
		FEV <sub>1</sub> 81% to 90% of baseline <i>and/or</i> FEF <sub>25-75</sub> = or <75% of baseline	BOS 0-p
BOS 1	FEV <sub>1</sub> 66% to 80% of baseline	FEV <sub>1</sub> 66% to 80% of baseline	BOS 1
BOS 2	FEV <sub>1</sub> 51% to 65% of baseline	FEV <sub>1</sub> 51% to 65% of baseline	BOS 2
BOS 3	FEV <sub>1</sub> 50% or less of baseline	FEV <sub>1</sub> 50% or less of baseline	BOS 3

# Conditions to be satisfied for a patient to be classified in the staging system

- (1) the functional loss to be present for at least 3 weeks
- (2) the loss had to include a decrease in both FEV1 and FEV1/vital capacity ratio, and
- (3) confounding conditions that may produce a decrease in FEV1 should be excluded
  - eg, infection,
  - acute rejection,
  - anastomotic complications,
  - disease recurrence, and
  - progression of disease in native lung is needed to be excluded.

# Adult Lung Transplants

Cumulative Morbidity Rates in Survivors within 1 Year Post Transplant (Follow-ups: April 1994 – June 2013)

Outcome	Follow-ups: April 1994 – June 2003		Follow-ups: July 2003– June 2013	
	Within 1 Year	Total number with <u>known response</u>	Within 1 Year	Total number with <u>known response</u>
Hypertension	50.8%	(N = 5,982)	52.3%	(N = 10,503)
Renal Dysfunction	26.1%	(N = 5,991)	21.6%	(N = 12,890)
Abnormal Creatinine $\leq$ 2.5 mg/dl	15.8%		16.1%	
Creatinine > 2.5 mg/dl	8.3%		3.8%	
Chronic Dialysis	2.0%		1.7%	
Renal Transplant	0.0%		0.1%	
Hyperlipidemia	16.3%	(N = 6,264)	31.3%	(N = 10,937)
Diabetes	20.1%	(N = 5,959)	25.6%	(N = 12,856)
Bronchiolitis Obliterans Syndrome	9.4%	(N = 5,592)	9.4%	(N = 12,169)



# Adult Lung Transplants

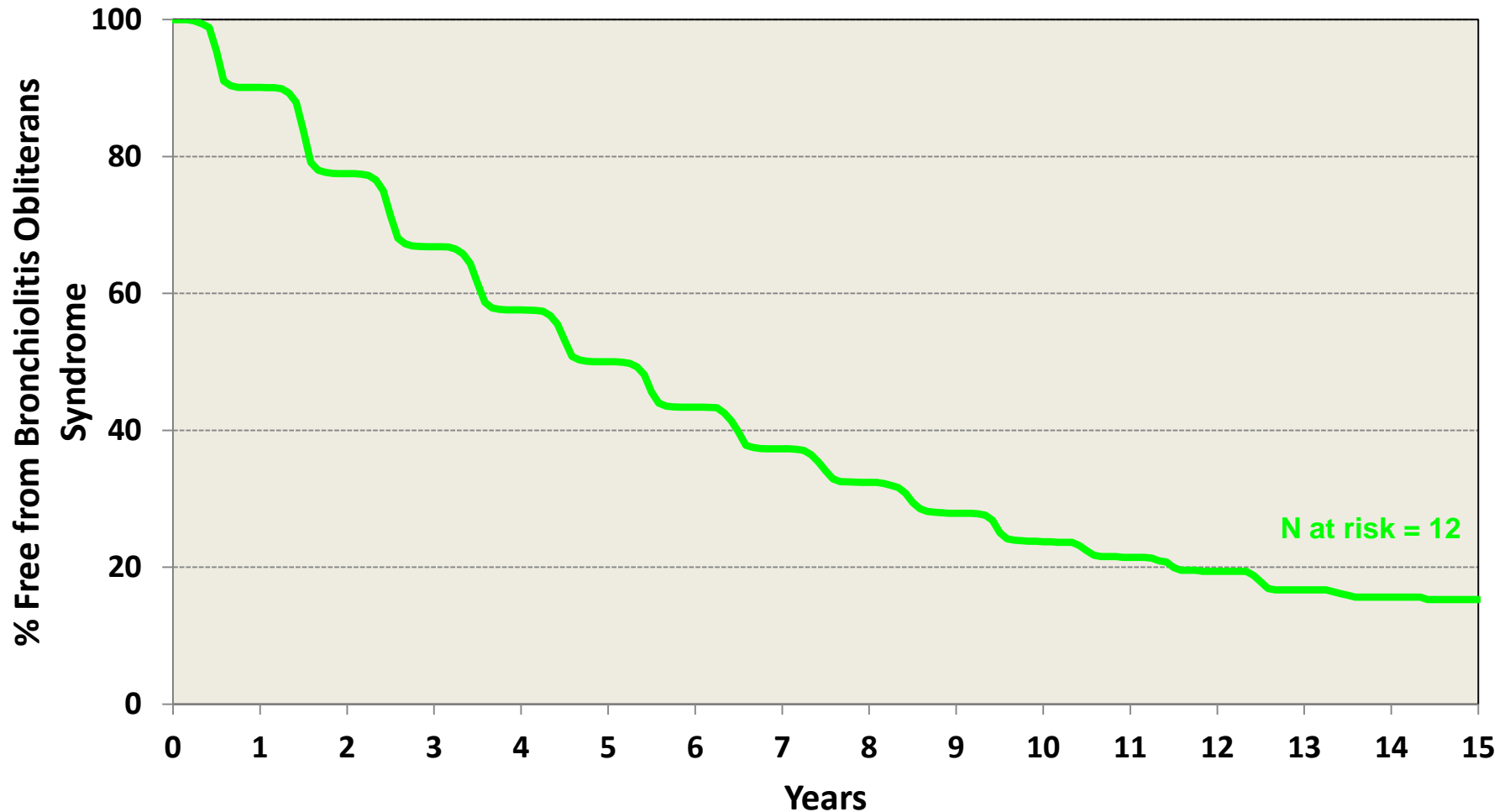
## Cumulative Morbidity Rates in Survivors within 10 Years Post-Transplant (Follow-ups: April 1994 – June 2013)

Outcome	Within <u>10 Years</u>	Total number with <u>known response</u>
Renal Dysfunction	73.5%	(N = 1,270)
Abnormal Creatinine $\leq$ 2.5 mg/dl	41.1%	
Creatinine > 2.5 mg/dl	19.4%	
Chronic Dialysis	7.8%	
Renal Transplant	5.3%	
Bronchiolitis Obliterans Syndrome	63.4%	(N = 946)

# Adult Lung Transplants

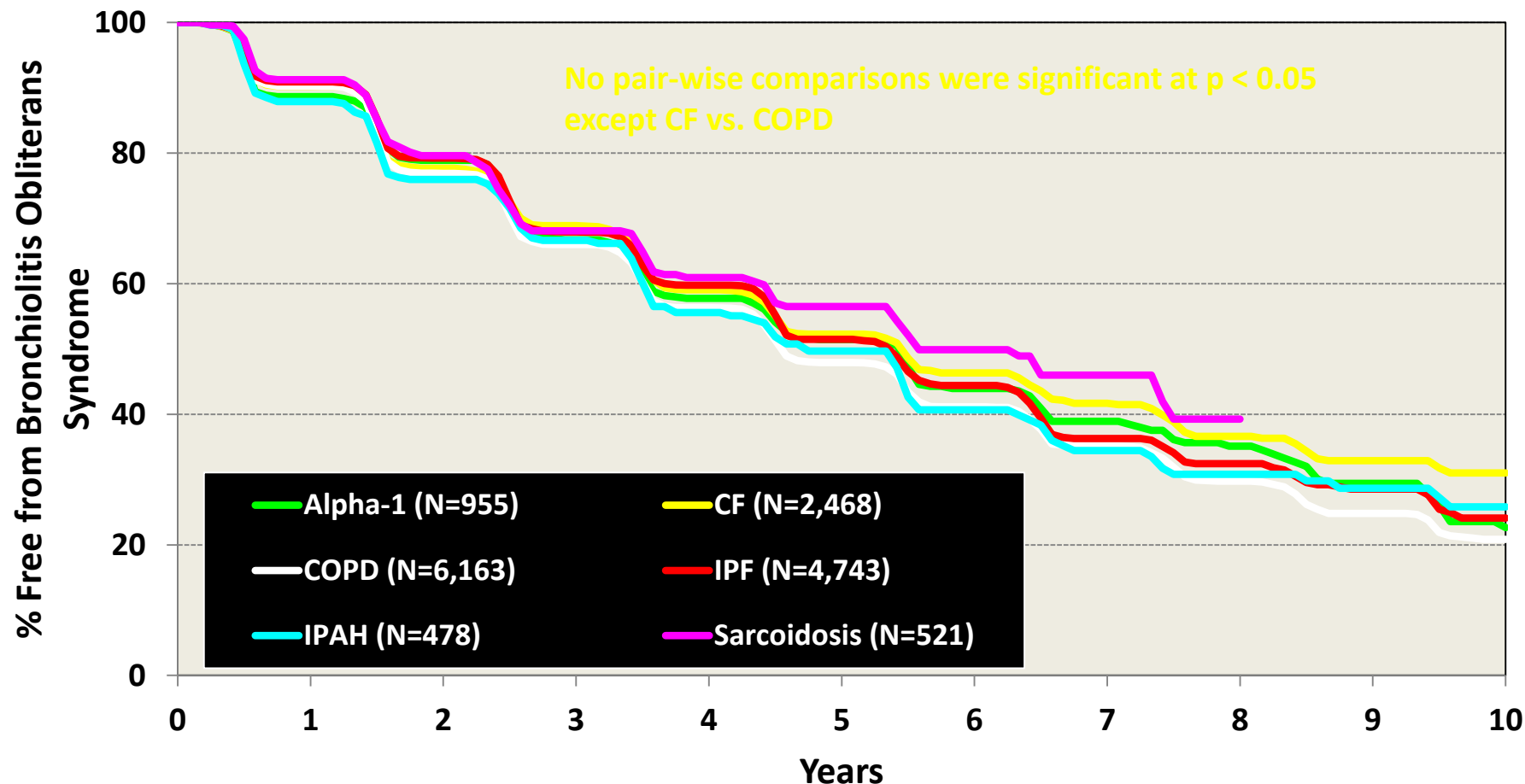
## Freedom from Bronchiolitis Obliterans Syndrome

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



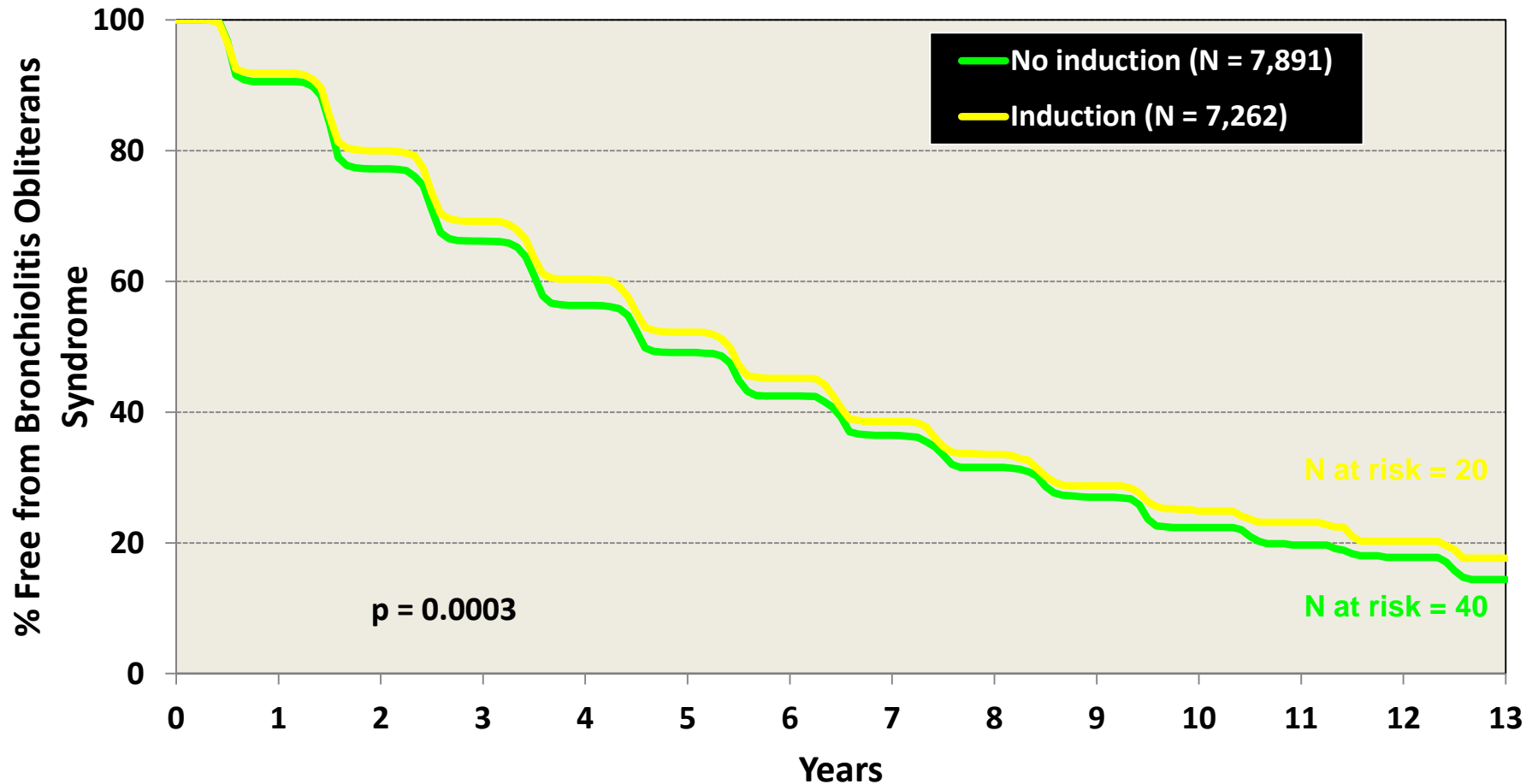
# Adult Lung Transplants

## Freedom from Bronchiolitis Obliterans Syndrome by Diagnosis Conditional on Survival to 14 days (Follow-ups: April 1994 – June 2013)



# Adult Lung Transplants

## Freedom from Bronchiolitis Obliterans Syndrome by Induction Use Conditional on Survival to 1 Year (Follow-ups: April 1994 – June 2013)



# Classical BOS

- BOS may affect **all lung transplant** recipients irrespective of donor and recipient characteristics, type of transplantation, and pretransplant disease.
- BOS may present as an acute illness and imitate a respiratory infection, but in most patients it starts as an **asymptomatic process that produces an insidious decline in lung function**.

- **Auscultation** of the lungs is often **normal**, but squeaks and coarse crackles may be heard.
- High-resolution CT may reveal **air trapping** and **bronchiectasis**, without significant parenchymal infiltrate.
- As the disease progresses, permanent airway **colonization** with pathogens, such as *Pseudomonas aeruginosa* and *Aspergillus fumigatus*, frequently develops.

# Types of CAD (other than BOS)

- (1) a reversible phenotype characterized by airway neutrophilia and functional improvement with azithromycin
- (2) a phenotype characterized by a restrictive ventilatory impairment associated with upper lobe fibrosis or persistent parenchymal or pleural abnormalities,
- (3) exudative or follicular bronchiolitis, and
- (4) large airway stenosis/malacia..

# Pathogenesis and Risk factors

- BO represent a final common pathway lesion secondary to **multiple, repetitive insults to the airway epithelium**
- **Alloimmune Risk Factors:** high number of HLA mismatches have an unfavorable impact on survival.
- Other risk factors:
  - direct injury to airways: gastric aspiration and/or
  - augment the alloimmune response via activation of the innate immune system, as is the case for respiratory bacterial and viral infections.



# Diagnosis

- Lung functions: spirometry
- Exhaled biomarkers: distribution of ventilation
- eNO and eCO

# Treatment

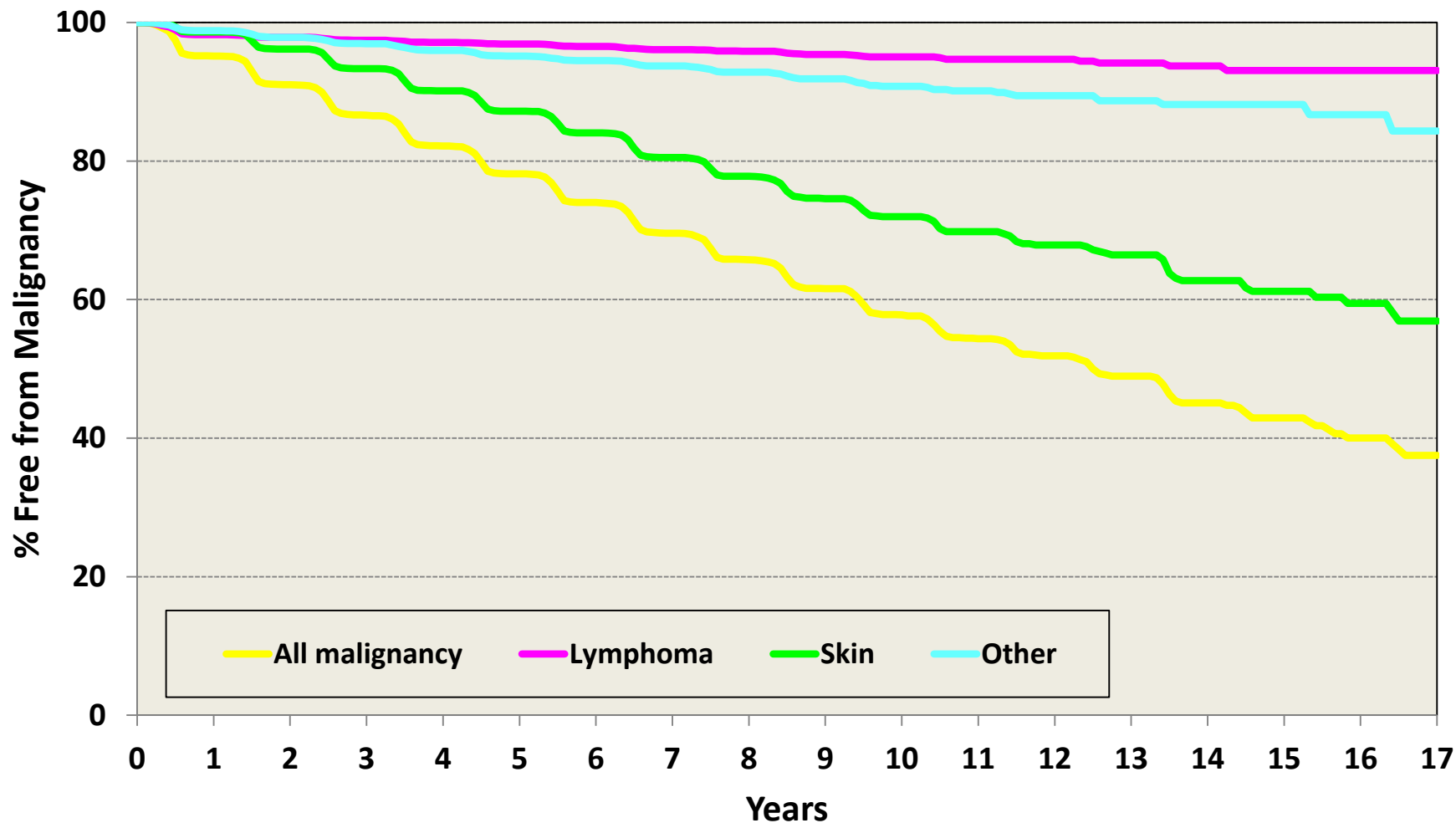
- Optimization and/or Change in Immunosuppressive Regimen: no evidence
- Macrolides: may be used, for ppx also\*
- Statins
- Retransplantation

# Malignancies following lung transplantation

- SOT recipients have **three- to four-fold** increased risk of developing cancer
- malignancy accounts for 13% of deaths between 5 and 10 years after lung transplantation
- Decrease in T cell mediated immune surveillance

# Adult Lung Transplants

Freedom from Malignancy (Follow-ups: April 1994 – June 2013)



# 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

# Extrapolated from Renal transplant...

- Epidemiology differs according to region

Region	Malignancy	Reference
Europe	Skin	Am J Transplant. 2004;4(6):905–13
America	Skin	Pathol Oncol Res. 2007;13(1):63–9
Canada	Lymphoma	Am J Transplant. 2007;7(4):941–8.
Australia	Lip	JAMA. 2006;296(23):2823–31
Japan	Renal CC	Int J Cancer. 1997;71(4):517–20
Korea	GI Cancers	Transplant Proc. 2013;45(8):3019–23
China	Urothelial	<a href="#">Med Oncol.</a> 2014 Jul;31(7):32

- Patients should receive education on avoidance of sun exposure particularly between 11 AM and 3 PM, the use of protective clothing and sunscreen, performing self-examination, and obtaining dermatologic screening at least yearly

# Airway complications

- complication rates :10% to 15%
- with a related rate of mortality of 2% to 3%



AC can be grouped

- **anatomically** (anastomotic or distal to the anastomosis),
- **descriptively** (stricture, granulation tissue, infection, necrosis, dehiscence, and fistula formation),
- **temporally** (early or late), or
- by **cause** (ischemic, infectious, iatrogenic, or idiopathic)

# Description of MDS standardized grading

## *M (macroscopic aspect)*

M0: scar tissue

M1: protruding cartilage

M2: inflammation/granulomas

M3: ischemia/necrosis

- Extent of abnormalities in regard to the anastomosis
  - a. Abnormalities localized to the anastomosis
  - b. Abnormalities extending from the anastomosis to the bronchus intermedius or to the extremity of the left main bronchus, without lobar involvement
  - c. Abnormalities extending from the anastomosis to lobar or segmental bronchi
  - d. Abnormalities affecting the lobar and/or segmental bronchi, without anastomotic involvement

## *D (diameter)*

D0: normal to a fixed reduction less than 33%

D1: expiratory reduction (malacia) greater than 50%

D2: fixed reduction from 33% to 66%

D3: fixed reduction greater than 66%

- Extent of abnormalities in regard to the anastomosis
  - a. Abnormalities localized to the anastomosis
  - b. Abnormalities extending from the anastomosis to the truncus intermedius or to the extremity of the left main bronchus, without lobar involvement
  - c. Abnormalities extending from the anastomosis to lobar or segmental bronchi
  - d. Abnormalities affecting the lobar and/or segmental bronchi, without anastomotic involvement

## *S (sutures)*

S0: absence of dehiscence

S1: limited dehiscence (<25% of circumference)

S2: extensive dehiscence (from 25% to 50%)

S3: very extensive dehiscence (>50%)

- Localization: e: anteriorly; f: other localizations

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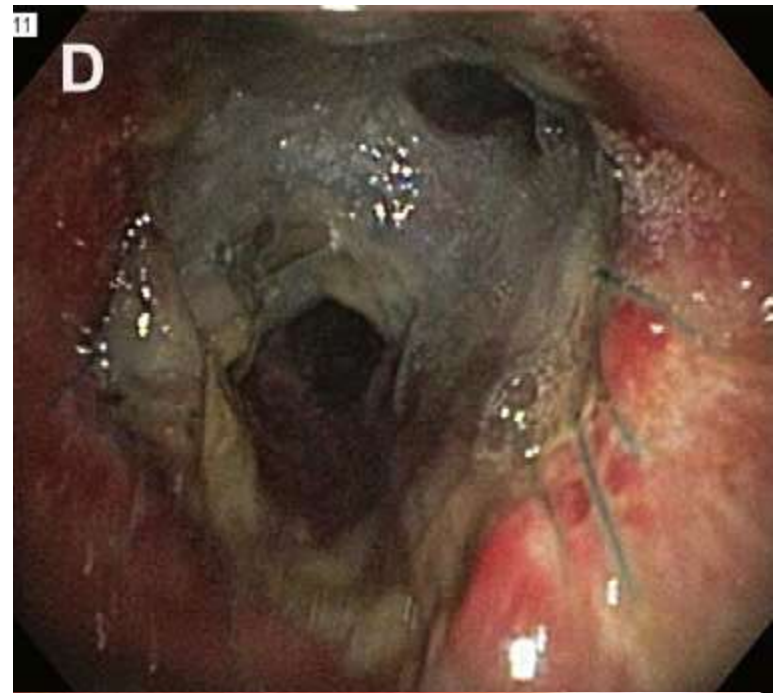
Stenosis/  
stricture

Anastomotic bronchial stenosis

- Stenosis <50% of bronchial diameter
- Stenosis >50% of bronchial diameter

Nonanastomotic bronchial stenosis

- Stenosis <50% of bronchial diameter
  - Stenosis >50% of bronchial diameter
- 



Necrosis and  
dehiscence

Grade I

- No slough or necrosis
- Well-healed anastomosis

Grade II

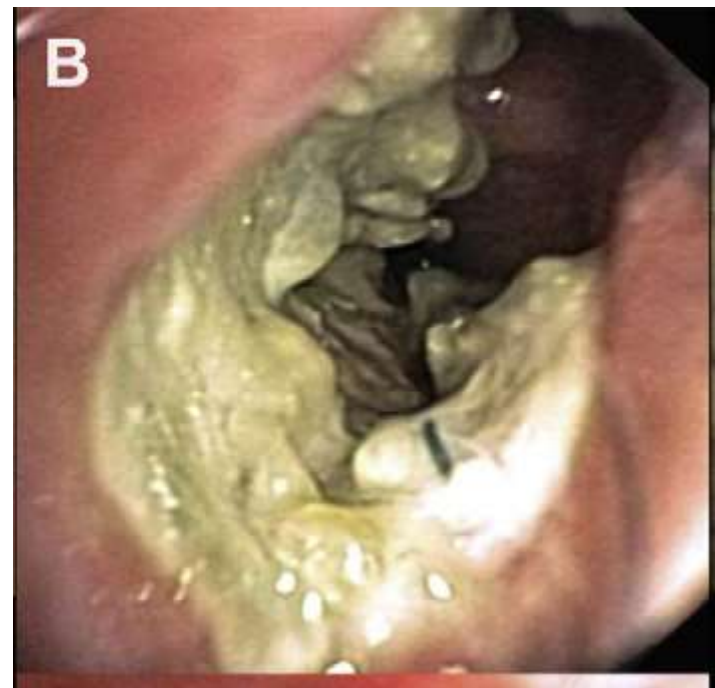
- Any necrotic mucosal slough observed but no bronchial wall necrosis

Grade III

- Bronchial wall necrosis within 2 cm of anastomosis

Grade IV

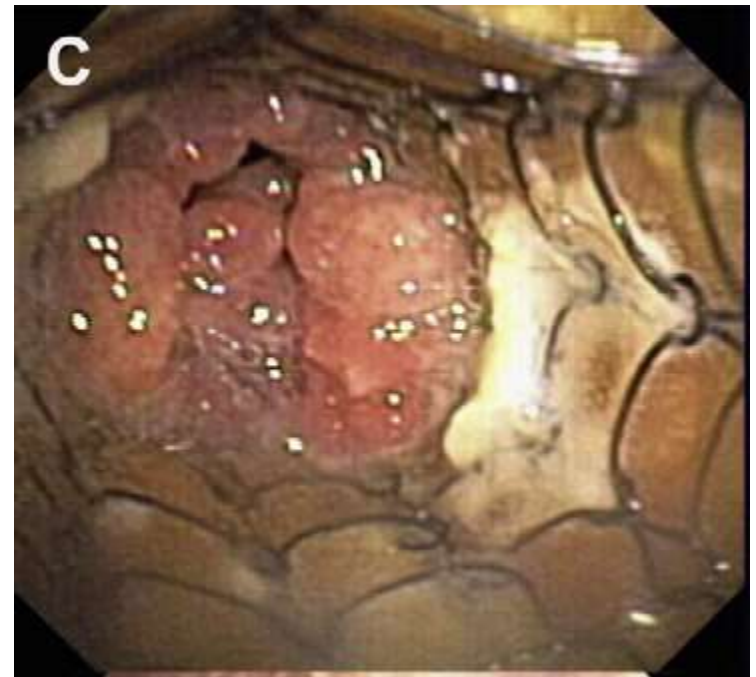
- Extensive bronchial wall necrosis extending >2 cm from anastomosis



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Exophytic  
granulation  
tissue

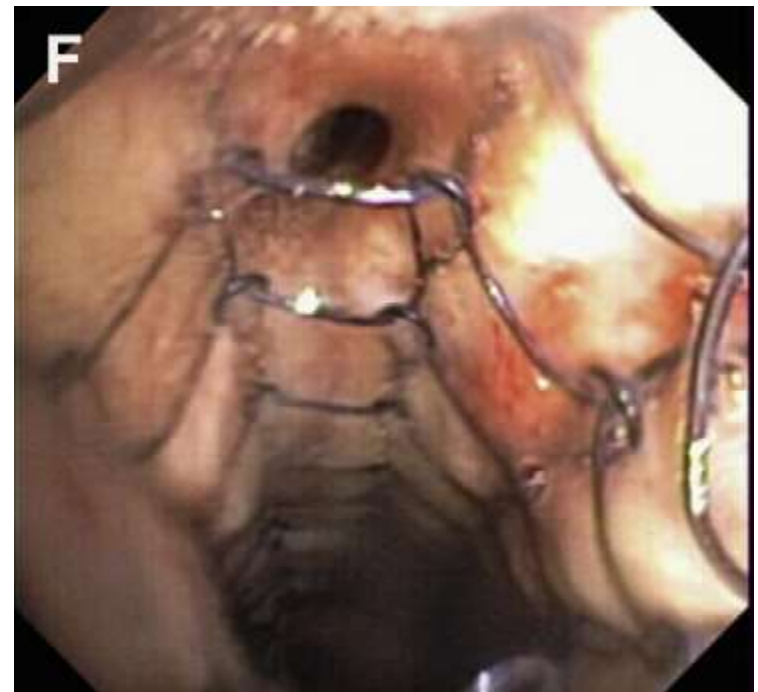
- Obstructing <50% of the bronchial lumen
  - Obstructing >50% of the bronchial lumen
- 



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## Fistula

- Bronchomediastinal fistula
- Bronchopleural fistula
- Bronchovascular fistula





## Infectious

### Anastomotic infections

- Bacterial
- Fungal

### Nonanastomotic infections

- Bacterial
- Fungal
- Viral



# BRONCHIAL ARTERY REVASCULARIZATION

- routine lung transplantation does not restore the bronchial artery supply
- Allowing the anastomosis of bronchial arteries and preservation of blood flow to the airways shows early promising results



# Long term, non pulmonary, non infectious, medical complications

- Renal Failure

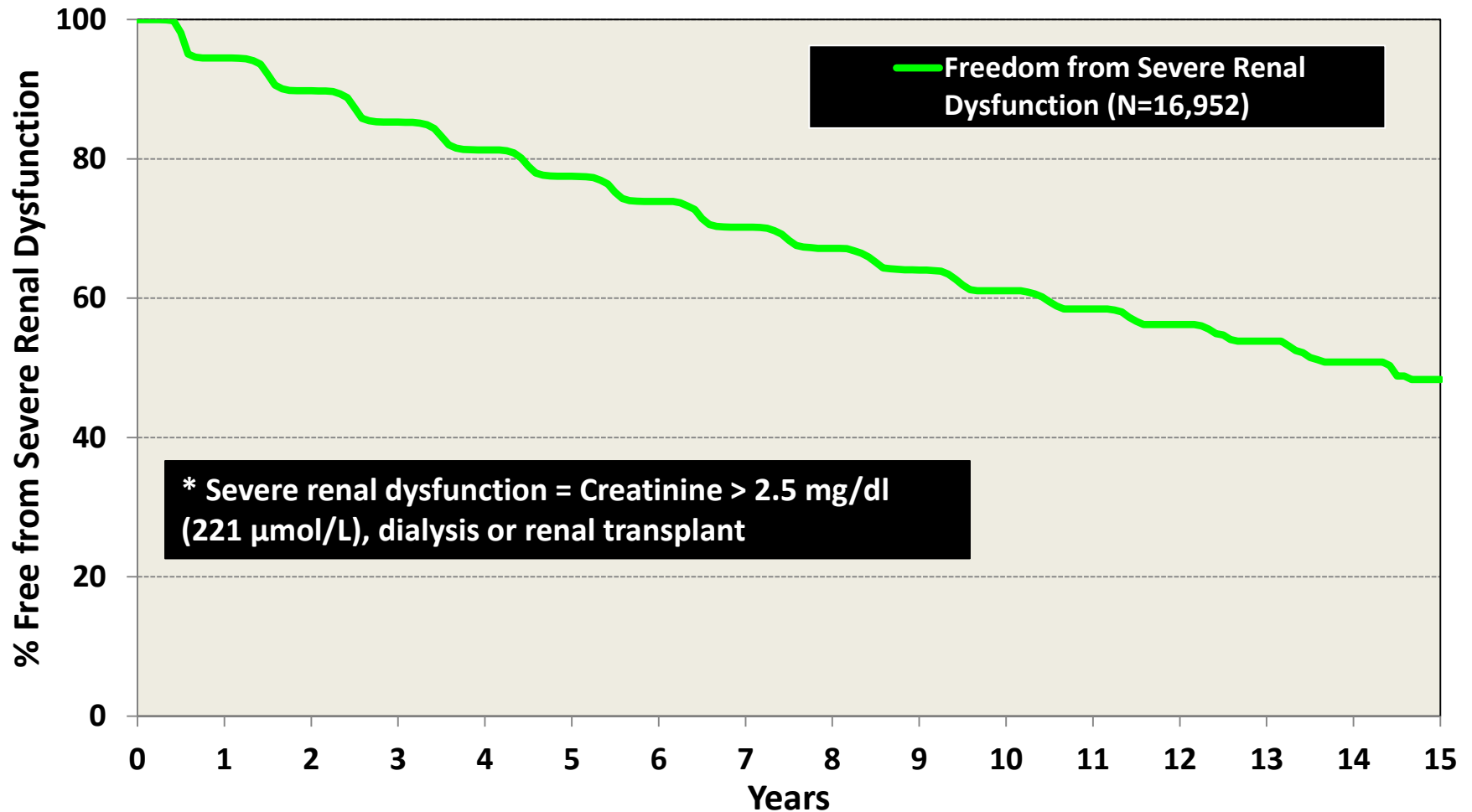
25 % at 1 year, 37 % at 5 years

Calcineurin inhibitor nephrotoxicity  
(tacrolimus < cyclosporine)

ACE inhibitors prevents

# Adult Lung Transplants

Freedom from Severe Renal Dysfunction\* Conditional on Survival to 1 Year  
(Follow-ups: April 1994 – June 2013)



# DIABETES MELLITUS

- 24.3% at 1 year after transplant \*
- 33.5% at 5 years after transplant\*
- glucocorticoid use and calcineurin inhibitor use
- Guidelines for treatment of diabetes for solid organ transplants recommend intervention when patients have fasting glucose levels greater 126 mg/dl and hemoglobin A1C levels greater than 6.5%^.

# CARDIOVASCULAR COMPLICATIONS

	@1 year	@ 5 year
Hypertension	51.9 %	85.6%
Hyperlipidemia	20.5%	52.2%

- Statins
- Follow general population guidelines

# OSTEOPOROSIS

- use of corticosteroids and other immunosuppressive medication
- minimum of 1,000 mg/day of calcium and 800 IU/day of vitamin D
- The greatest effect of bisphosphonates in reducing bone loss occurred when medication was started before transplantation when patients were on the waiting list.<sup>^</sup>

# OSTEOPOROSIS

- evaluate all pre-transplant candidates for osteoporosis by DEXA scan, and begin bisphosphonate therapy on anyone with defined osteopenia or osteoporosis and to continue treatment for at least 6 to 12 months after transplantation

# AVASCULAR NECROSIS:

- 3 to 22%
- Hip pain: MRI

# HEMATOLOGIC COMPLICATIONS

- Cytopenia: immunosuppression medication and prophylactic antiinfectious medication
- Anemia: renal failure, iron deficiency
- Infections such as parvovirus B19, CMV, EBV
- CCI: HUS/TTP



# THROMBOEMBOLIC DISEASE

- Incidence of 8.6 to 29%
- high risk for pulmonary infarction, given the dual blood supply from the bronchial artery is absent or poorly developed

# GASTROINTESTINAL COMPLICATIONS

- over 60% of patients who have undergone lung transplant have at least one gastrointestinal complaint
- Nausea, GERD

# NEUROLOGIC COMPLICATIONS

- 26% of patients having a neurologic complication in the form of severe headaches, seizures, strokes, and confusion
- calcineurin inhibitor toxicity or infections

# 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%)

# THANK YOU