POST OPERATIVE MANAGEMENT AND IMMUNOSUPPRESSION IN LUNG TRANSPLANT

DM SEMINAR

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POST OPERAGTIVE MANAGEMENT

- VENTILATORY SUPPORT
- FLUID AND HAEMODYNAMIC Mx
- IMMUNOSUPPRESSION
- DETECTION OF EARLY REJECTION
- PREVENTION OF INFECTION

Ventilatory Support

- Limited evidence – extrapolation from other diseases(ARDS)

- No prospective randomized studies

Murine model

- de Perrot and colleagues utilized a rat model of LTx to demonstrate
- Protective ventilatory strategy minimized pulmonary mechanical stress by low VT was associated with improved lung function after LTx
- VILI contributes significantly to PGD after LTx transplantation

De Perrot et al, J Thorac Cardiovasc Surg 2002;124:1137–1144

Program	Initial mode	Vt(ml/kg)	Initial PEEP	Initial FiO2	SpO2 goal	pH goal	PIP goal	Plateau limit
Alfred hospital	SIMV	6-8(recipient)	5-10	-	-	-	-	
Cedars Sinai	VAC	6 (recipient)	5	50	>92	>7.35	<35	<30
Cleveland clinic	PAC	6-8(donor)	10	30	>90	>7.25	<35	<30
Uni of Colorado	PRVC	6-8(recipient)	5	100	>94	7.32-7.4	<35	
Uni of Iowa	PRVC	6(donor)	5	100	>94	>7.25	<35	<30

Mode of Ventilation

- In a survey by Beer et al(149 individuals/18 countries)
- Protocols for MV(36 %)
- Mode used :PAC: 37% ; VAC :35%

Beer A et al, Ann Am Thorac Soc. 2014; 11:546–553

Mode of ventilation

VAC

- consistent tidal volumes
- but require attention to peak and plateau airway pressures

PAC

- avoid high peak
- *but not transpulmonary pressures*
- May provide larger Vt

PREFER: VAC/PRVC > PAC

Lindsey Barnes et al, Curr Pulmonol Rep. 2015 June ; 4(2): 88–96
Beer A et al, Ann Am Thorac Soc. 2014; 11:546–553

Vt – Donor lung

- In a multicenter RCT comparing a low Vt Vs standard donor ventilation strategy, a significantly higher proportion of donor lungs could be utilized from the low Vt group (54% Vs 27%)

- If a lower tidal volumes approach is protective before transplantation, the same may be true after transplantation

Mascia Let al. JAMA 2010;304:2620–2627

Tidal volume

- In a retrospective study comparing mismatch lung transplant: undersized Vs oversized

- Undersized allografts received relatively higher Vt
  - PGD grade 3 → 20% Vs 0
  - Tracheostomy → 40 % Vs 10 %

Rebecca Debuze et al, Interactive CardioVascular and Thoracic Surgery 16 (2013) 275–281

PEEP

- Extrapolation from ARDS
- PEEP is limited by increased risk of air leaks

  (expert opinion;no RCT)

- After SLT for COPD or emphysema, PEEP is not used or kept to 5 cm of H2O → to avoid overinflation of native lung

PEEP & airway pressures

	Mean (cm of H2O)	Median (cm of H2O)	IQR (cm of H2O)
PEEP max	11.3	11	10-12.5
PEEP min	4.9	5	5-5
PIP limit	32.6	30	30-35
PIP limit – VAC	36.4	35	35-40
PIP limit – PAC	30.8	30	29-33.5
PIP limit (other)	31	30	20-35
Pplat limit	29.1	30	30-30
Pplat –VAC	29.2	30	30-30
Pplat- PAC	29	30	28-30
Pplat (others)	29.5	30	30-30

Beer et al, Ann Am Thorac Soc. 2014; 11:546–553

Airway pressures and complications

- Higher PEEP hypothesized to cause bronchial wall and anastomotic stress
- Higher pressures and prolonged MV had higher incidence of airway complications(1)
- Dog model of LTx increasing the PEEP from 5 to 10 cm H2O was associated with ***increased*** bronchial mucosal blood flow to the bronchial anastomoses(2)

1-Date et al, J Thorac Cardiovasc Surg. 1995; 110:1424–1432
2-Yokomise et al, . J Thorac Cardiovasc Surg. 1991; 101:201–208

PEEP

- Maximum PEEP limit was 11.3 and minimum 4.9 cm of H2O
- Little evidence guiding optimal setting of PEEP and PIP
- PEEP and airway complications
  - Conflicting data
- How much pressure is too much for the anastomoses?

1-Beer et al, Ann Am Thorac Soc. 2014; 11:546–553

Proposed Ventilator Settings

- ***Mode of ventilation*** :
  - Vary between centers
  - VAC/PRVC > PAC
- ***Tidal volume*** :
  - should be based on **donor** predicted body weight (6 ml/kg)
- ***Airway pressures*** :
  - PEEP – 5 cm of H2O
  - PEEP > 12.5 cm of H2O avoided
  - P peak < 35 cm of H2O
- ***FiO2*** : Post Op PO2 → 60 – 80 mm of Hg

FLUID MANAGEMENT

- Adequate filling pressures
- Cardiac output

Vs

- Minimize pulm edema

[INDIVIDUALIZED]

Fluid Management

- Pulm edema of newly transplanted lung is universal
  - Vascular permeability is increased
  - Lymphatic drainage is severed

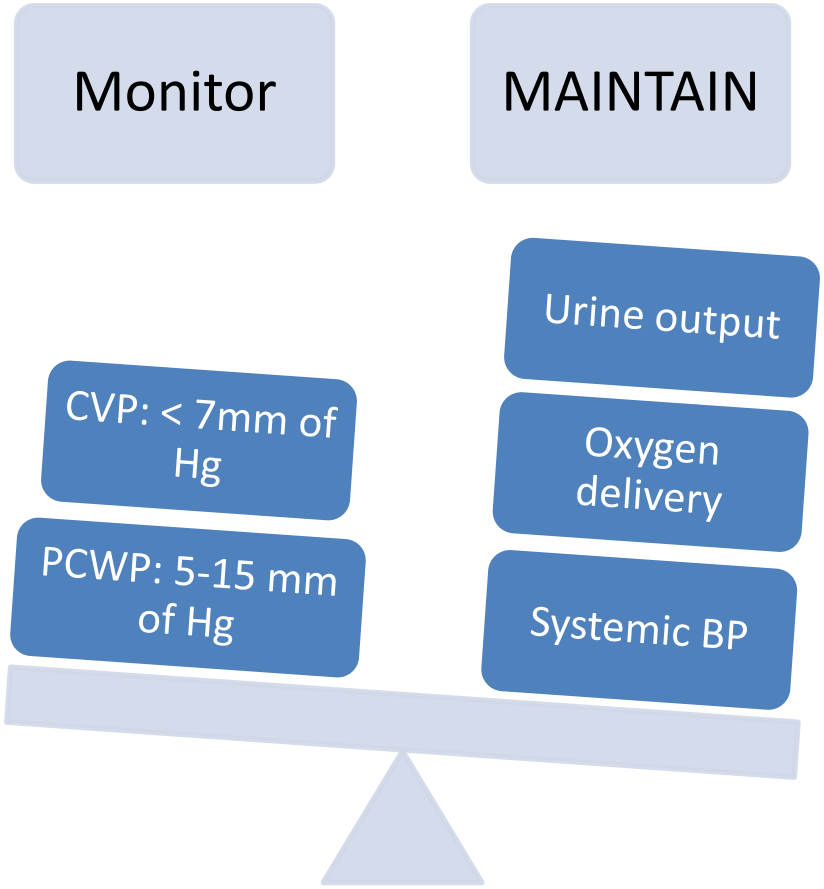
Kaplan JD et al, Am Rev Respir Dis. 1992;145:954
KunduS et al, Radiology. 1998;206(1):75

Fluid management

- To guide fluid therapy
  - Fluid balance (input/output; monitoring weight)
  - Central venous catheterization
  - Swan – Ganz catheter
  - Echocardiography

Kotsimbos T etal, Eur Respir Rev 2012; 21: 126, 271–305

FLUID MANAGEMENT



VASOPRESSORS
INOTROPES
DIURETICS

Fluid management

Fluid balance (1)	Negative fluid balance, with cautious use of diuretics (not surpassing a weight reduction of >1 kg/day)
Central venous catheterization (2)	< 7 mm of Hg
Cardiac index(2)	2.2 – 2.5 l/min/sq m
PAWP(1)	5-15 mm of Hg
ECHO	To evaluate for hypotension

1- Schuurmans MM et al; Swiss Med Wkly. 2013;143:w13773
2-Currey J et al,J Thorac Cardiovasc Surg;2010:139,154-161

FLUID MANAGEMENT

- CVP guided
  - CVP > 7 mm of Hg(9.5 cm of H2O) was associated with higher ICU and hospital mortality
  - In a retrospective study involving 118 lung Tx patients by Pilcher DV
    - High CVP was associated with prolonged MV (OR: 1.57)

	CVP ≤7 mm Hg (n = 56)	CVP >7 mm Hg (n = 62)	*P* value
Prolonged mechanical ventilation	4% (n = 2)	40% (n = 25)	<.001
Duration of ICU stay (d)	3 (2-3)	5 (3-7)	<.001
Duration of hospital stay: survivors (d)	19 (16-25)	27 (16-46)	.02
ICU mortality	0% (n = 0)	8% (n = 5)	.02
Hospital mortality	4% (n = 2)	13% (n = 8)	.09

Fluid management

- In analysis of 109 patients, managed as per guidelines for haemodynamic statusin a single center

- Cardiovascular management was aimed at maintaining adequate
  - cardiac index
  - Blood pressure
  - CVP 7 mm Hg or lower if possible

Currey J et al,J Thorac Cardiovasc Surg;2010:139,154-161

Fluid management

- Lower postoperative fluid balances and vasopressor doses were seen, with no associated renal dysfunction

- There were no differences in duration of mechanical ventilation or mortality

Lung Transplant Guideline

Hemodynamic Management in first 72 hours

Check target MAP (usually 65 - 75 mmHg)
Check target cardiac index (usually 2.2 – 2.5 l/min/m^2)
Repeat "BASIC CHECKS" and check ventilator settings

RE- ASSESS AT LEAST EVERY HOUR

IF TARGETS NOT ACHIEVED SEEK SENIOR HELP

CVP ≤ 7 mmHg

MAP ≥ Target

If cardiac index > Target
- Wean adrenaline / noradrenaline
- (If PaO_2/FiO_2<200 and pulse<100 consider Frusemide 20mg)

If cardiac index < Target
- Start Nitroprusside 10µ/min
- Consider fluid challenge with 4% NSA (or blood if required)
- Rewarm patient if temp < 36° C

MAP < Target

If cardiac index > Target
- Start Noradrenaline 2µ/min & titrate to target MAP
- Consider fluid challenge if CVP ≤ 4 with 4% NSA (or blood if required)

If cardiac index < Target
- Rewarm patient if temp < 36° C
- Check drainage in ICC's
- Fluid challenge with 4% NSA (or blood if required)

CVP > 7 mmHg

MAP ≥ Target

If cardiac index > Target
- Wean adrenaline / noradrenaline
- Consider reduction of iv fluid rate
- (If PaO_2/FiO_2<300 & pulse<100) consider Frusemide 20mg)

If cardiac index < Target
- Consider Inodilator or Nitroprusside
- Rewarm patient if temp < 36° C

MAP < Target

If cardiac index > Target
- Start Noradrenaline 2µ/min & titrate to target MAP

If cardiac index < Target
CONTACT SENIOR HELP
- Start Adrenaline 5µ/min & increase by 2µ/min until target MAP
- Consider fluid challenge
- Assess dynamic hyperinflation & consider ↓RR, Vt, Inspiratory time
  Repeat CXR and consider TOE

FLUID MANAGEMENT

- Optimal fluid for volume replacement- ??? (local policy – crystalloid Vs colloid)
  - No RCT in lung tx
  - In extrapolation from ARDS, colloids improves oxygenation transiently but no difference in mortality or duration of MV(1)
  - No evidence to support albumin as resuscitation fluid(2)

- Target Hb – maintain at 10 mg/dl (expert opinion)[3]

1-Roch et al,. *Annals of Intensive Care*. 2011;1:16
2-Lira A, *Annals of Intensive Care*. 2014;4:38.
3-Sharqall Y et al, J Heart Lung Transplant.2005 Oct;24(10):1489-500

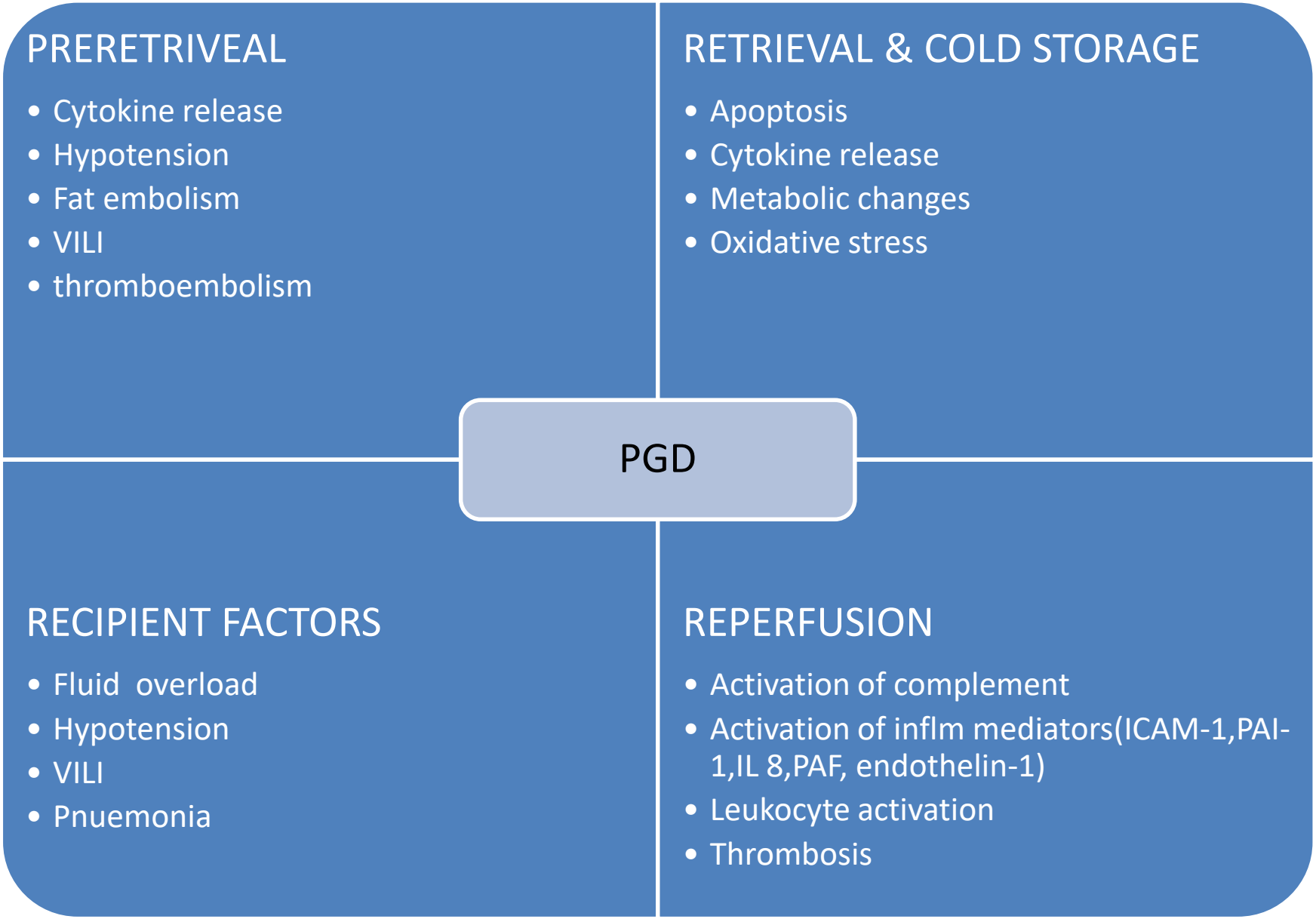
Primary graft dysfunction

- Represents multifactorial injury to transplanted lungs that develops in first 72 hrs

- Clinically: Hypoxemia & pulm edema
- Radiographically: diffuse pulm opacities
- Pathologically: diffuse alveolar damage

- Inicdence : 10 – 25 %

Christie JD et al, Chest 2003;124(4):1232–41
Turlock EP et al,J Heart And Lung Transplant.2005;24(8):956


PRERETRIVEAL
• Cytokine release
• Hypotension
• Fat embolism
• VILI
• thromboembolism
RETRIEVAL & COLD STORAGE
• Apoptosis
• Cytokine release
• Metabolic changes
• Oxidative stress
PGD
RECIPIENT FACTORS
• Fluid overload
• Hypotension
• VILI
• Pnuemonia
REPERFUSION
• Activation of complement
• Activation of inflm mediators(ICAM-1,PAI-1,IL 8,PAF, endothelin-1)
• Leukocyte activation
• Thrombosis

PGD-RISK FACTORS

- DONOR
  - Donor age(> 45 and < 21)
  - Smoking history
  - Fat embolism/ Thromboembolism
  - Sarcoidosis
  - Elevated PAP
- RECIPIENT
  - PAH
  - Preformed antibodies to intracellular antigens(tubulin and collagen V)

PGD - Grading

Grade	p/f ratio	Radiographic infiltrates consistent with pulm edema
0	> 300	Absent
1	> 300	Present
2	200 - 300	Present
3	< 200	Present

Consensus statement of ISHLT, Journal of Heart Lung Transplant 2005,

PGD – when to suspect

- In first 72 hrs
- Declining oxygenation
- Diffuse opacities on radiology
- Decreasing pulmonary compliance
- Increased pulm vascular resistance

PGD – differntials

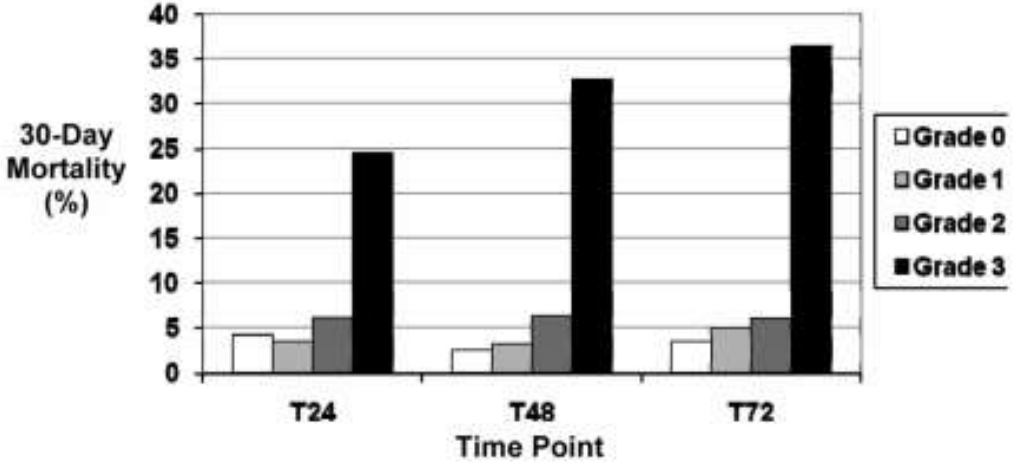
Pulmonary edema	Assess volume status CVP < 7 mm Hg; PCWP <10 mm Hg In severe cases of PGD; PCWP > CVP
Pnuemonia	Clinical + lab All cases of suspected PGD should undergo FOB
Antibody mediated rejection (hyperacute and acute AMR)	Pretransplant PRA to be reviewed Risk is more with increasing PRA levels(>10%) Perform a direct cross match between donor and recipient

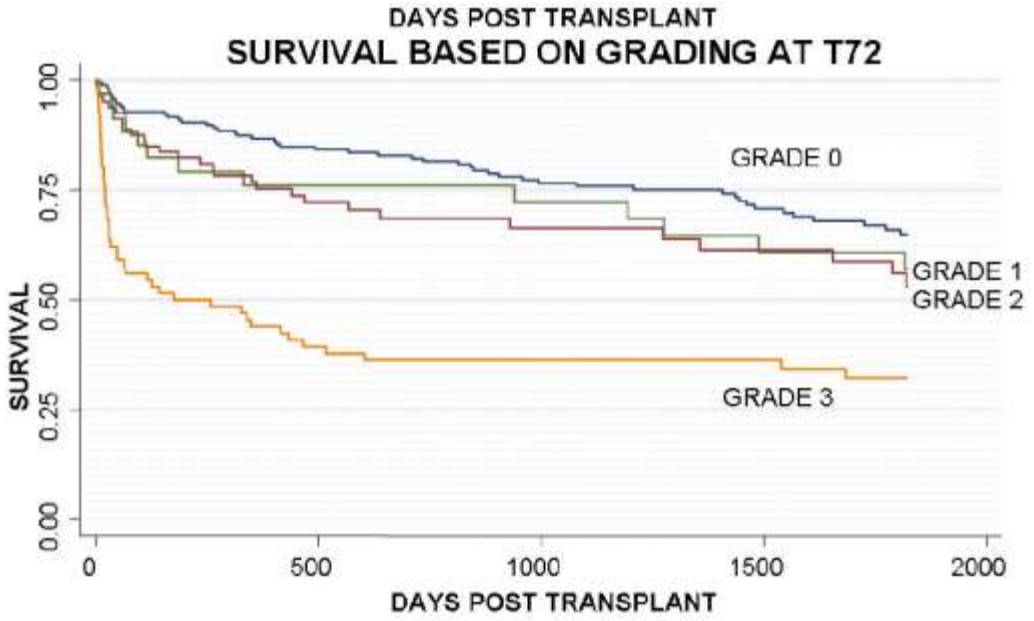
PGD

- Severe PGD :
  - 30 day mortality : 63% Vs 9 %
  - Duration of MV : 15 days Vs 1 day

  [Christie JD et al, clinical risk factors for primary graft failure following lung Tx, Chest 2003]

- Scores to be calculated at
  - Arrival to ICU
  - 24 hrs
  - 48 hrs
  - 72 hrs





Construct Validity of the Definition of Primary Graft Dysfunction, J Heart Lung Transplant. 2010 November

PGD - TREATMENT

- Ventilate as ARDS
- Inhaled NO
- ECMO
- Retransplantation

- EXPERIMENTAL
  - Prostaglandin E1 & I2
  - Surfactant therapy
  - Complement inhibition

PGD -iNO

- Not effective as preventive therapy
- No difference in incidence of PGD/duration of stay/mortality
- 3 RCT's

	No of pts	Intervention	iNO(PPM)
Meade et al	84	10 min after reperfusion	20
Perrin et al	30	At reperfusion for 12 hrs	20
Both et al	20	30 min at reperfusion	20

Meade et al, *Am J Respir. Crit Care Med*. 2003; 167: 1483–1489
Perrin et al,*Chest* 2006;129:1024-30
Botha et al, *J Heart Lung Transplant*. 2007; 26: 1199–1205

PGD - iNO

- No prospective randomized clinical studies
- Case series have suggested that administration of NO is associated with improved clinical outcome(1)
- Can be used in treatment of severe PGD(2)
  - reduce PAP without affecting systemic pressures
  - combined with improvement in ventilation perfusion matching

1-Macdonald et al, J Thorac Cardiovasc Surg 1995;110:861-3
2-Shargall Y et al, J Heart Lung Transplant.2005 Oct;24(10):1489-500

iNO –Extrapolation from ARDS

- In cases of severe ARDS
  - Improved oxygenation transiently upto 72 hrs
  - But no difference in mortality and time of assisted ventilation

Taylor RW et al, *JAMA*. 2004; 291: 1603–1609
Sokol J et al, *Cochrane Database Syst Rev*. 2003

PGD - iNO

- Use for severe PGD
  - grade 3 PGD with refractory hypoxemia and elevated pulmonary artery pressures
- Dose
  - 10-40 PPM
  - Used upto 110 PPM(1)
- Duration : till clinical response(15-217hrs)[2]
- Monitor MetHb levels : 2-6 hrly(2)

1-1-Macdonald et al, J Thorac Cardiovasc Surg 1995;110:861-3
2- Date te al; , J Thorac Cardiovasc Surg 1996:5, 913-919

PGD- ECMO

- Life saving measure for severe PGD and not responding to trial of iNO

- ECMO is the only way to provide the patient with adequate oxygenation and gas exchange ***while awaiting lung function recovery***

PGD-ECMO

- 151 lung transplant recipients treated with ECMO 42 % survived hospital stay as per ELSO registry(1)
- In 28 patients managed with ECMO, survivals at 30 days, 1 year, and 5 years were 82, 64, and 49% respectively(2)
  - Survival improved
  - Maximal achieved lung function was significantly inferior compared with non ECMO recipients(58% vs 83%)

1-Fischer S et al, J Heart Lung Transplant. 2007;26(5):472
2-Hartwig MG et al, Ann Thorac Surg. 2012 Feb;93(2):366-71

PGD - ECMO

- **Initiate early**
  - Early Vs Late (7 days post transplant)
  - Early group had 10 patients and 7 long term survivors
  - Late group had 6 patients and no long term survivors

    Glassman LR et al, J Thorac Cardiovasc Surg. 1995 Sep;110(3):723-6

  - In 14 patients who recieved ECMO, post lung Tx, 9 had early graft failure(<24 hrs) and 7 were successfully weaned.
  - 5 patients had late graft failure and had 100% mortality

    Nguyen et al, J Heart Lung Transplant. 2000 Mar;19(3):313-6

PGD - ECMO

- ECMO **should not be initiated later than 7 days** post transplant,unless considered as bridge for retransplant

- May have a prophylactic role in lung transplant recipients having pulmonary hypertension

Shargall Y et al, J Heart Lung Transplant.2005 Oct;24(10):1489-500

PGD - Treatment

- Goal is **to support** the patient while the injured lung recovers

- To **avoid adding further injury** to the already injured lung

IMMUNOSUPPRESSION

- Aim : to strike a balance between rejection/immunosuppression and infections

- First successful lung transplantation in 1963 was due to prevention of allograft rejection by using
  - Azathioprine
  - Prednisone
  - Cobalt-60

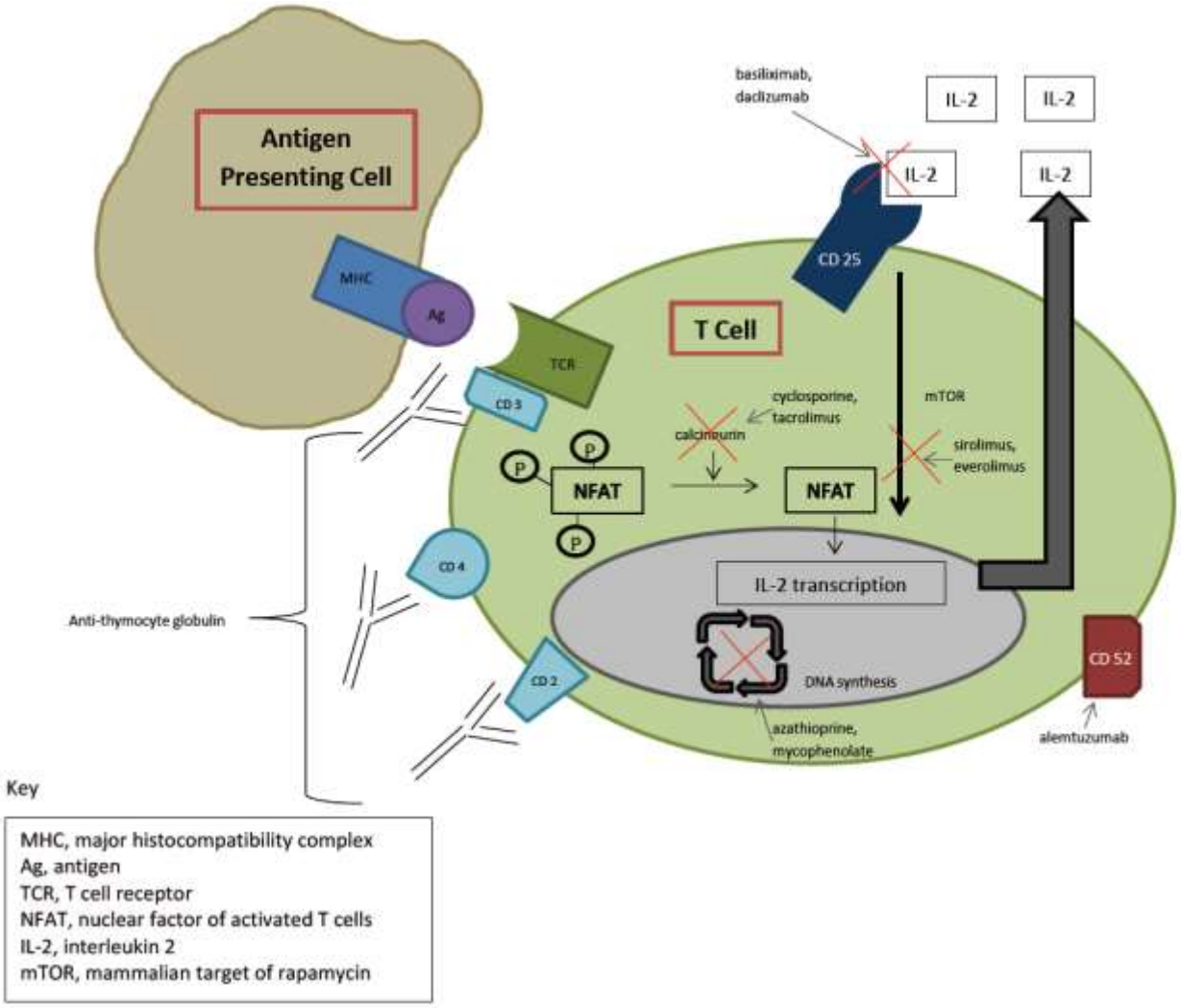
PRINCIPLES OF IMMUNOSUPPRESSION

- Immune reactivity and tendency for graft rejection are highest initially & decrease with time
- Low doses of several drugs with non overlapping toxicities
- Avoid over immunosuppression (infection/malignancy)

PRINCIPLES OF IMMUNOSUPPRESSION

- Based on other solid organ transplantation
- None are US FDA approved in lung transplant
- No consensus for optimal regimen

INDUCTION


Antigen Presenting Cell
MHC
Ag
TCR
CD 3
CD 4
CD 2
Anti-thymocyte globulin
T Cell
basiliximab, daclizumab
IL-2
IL-2
IL-2
IL-2
CD 25
cyclosporine, tacrolimus
calcineurin
mTOR
sirolimus, everolimus
P
P
P
NFAT
NFAT
IL-2 transcription
DNA synthesis
azathioprine, mycophenolate
CD 52
alemtuzumab
Key
MHC, major histocompatibility complex
Ag, antigen
TCR, T cell receptor
NFAT, nuclear factor of activated T cells
IL-2, interleukin 2
mTOR, mammalian target of rapamycin

Induction

- Aim: To reduce the initial robust immune response of T cells to the transplanted organ
- Induction agents cause depletion of T cells and/or interruption of T cell activation and proliferation
- MOA: T cell recognition of antigens on the transplanted lung initiates calcineurin mediated stimulation of the transcription, translation, and secretion of interleukin-2 (IL-2)

INDUCTION

- Controversial
- 41% in 2001 to 56 % in 2013(32 annual report ISHLT)

- Tailored to individual patient
  - Withheld: elderly (>55 yrs); high risk of infection
  - Used : PRA to donor MHC antigens

INDUCTION

- In a meta analysis of 6 RCTs (total of 278 adult lung transplant recipients) that assessed the use of T-cell antibody induction

- Polyclonal or monoclonal T-cell antibody induction Vs no induction (3 studies, 140 participants)
- Polyclonal T-cell antibody Vs no induction (3 studies, 125 participants)
- IL-2RA Vs no induction (1 study, 25 participants)
- Polyclonal T-cell antibody Vs muromonab-CD3 (1 study, 64 participants)
- Polyclonal T cell antibody Vs IL-2RA (3 studies, 100 participants).

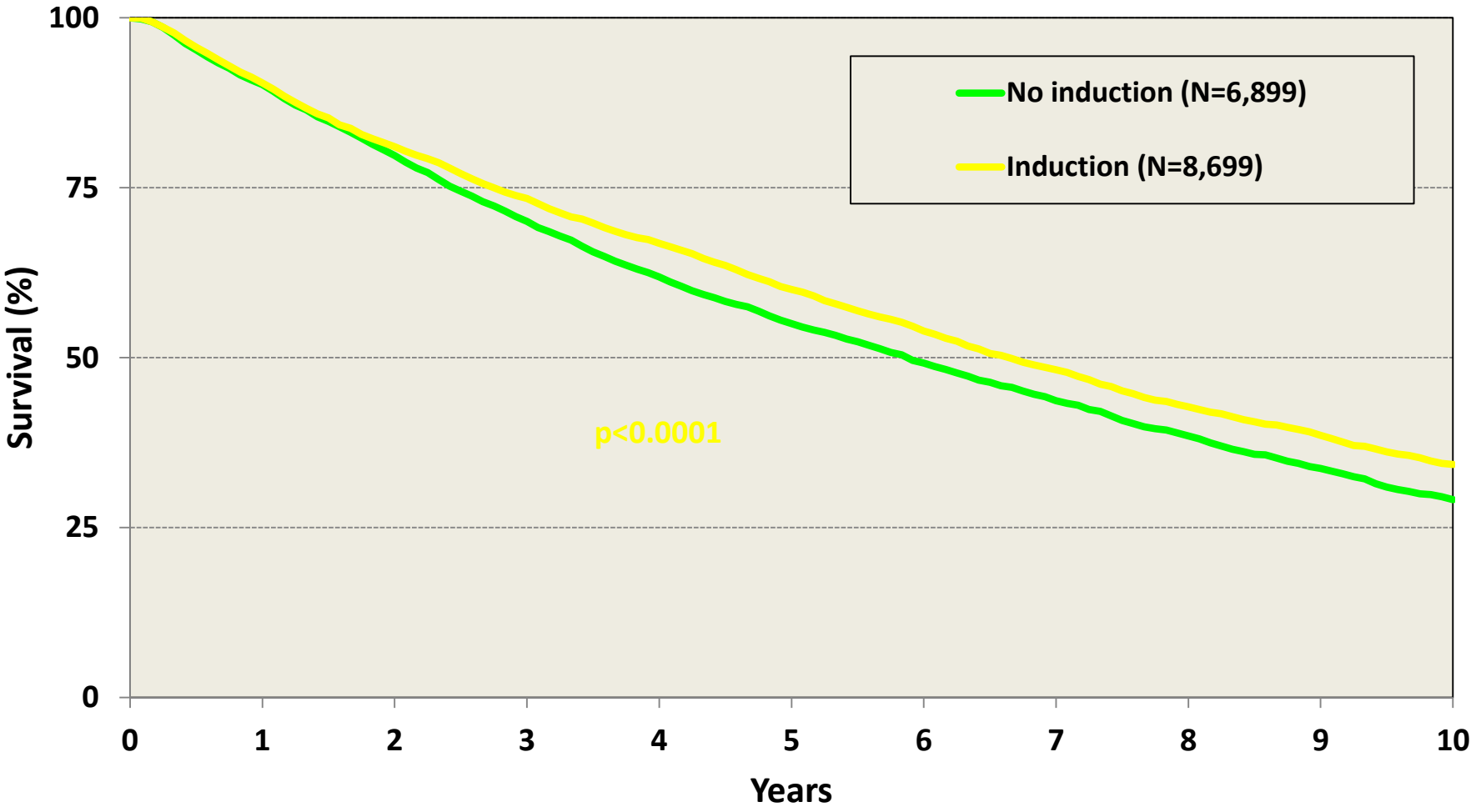
- Overall no significant differences in terms of mortality, acute rejection, adverse effects, infection, pneumonia, CMV infection, BOS, PTLD, or cancer

Penninga L et al, Antibody induction therapy for lung transplant recipients; Cochrane Database Syst Rev. 2013

INDUCTION – EFFECT ON SURVIVAL

- According to ISHLT registry **use of any induction therapy** compared with no induction therapy is associated with **a slight but statistically significant improvement** in survival contingent upon survival to 14 days post transplantation

- Difference between the groups is not apparent until at least a year following transplant


100
75
50
25
0
Survival (%)
0
1
2
3
4
5
6
7
8
9
10
Years
No induction (N=6,899)
Induction (N=8,699)
p<0.0001

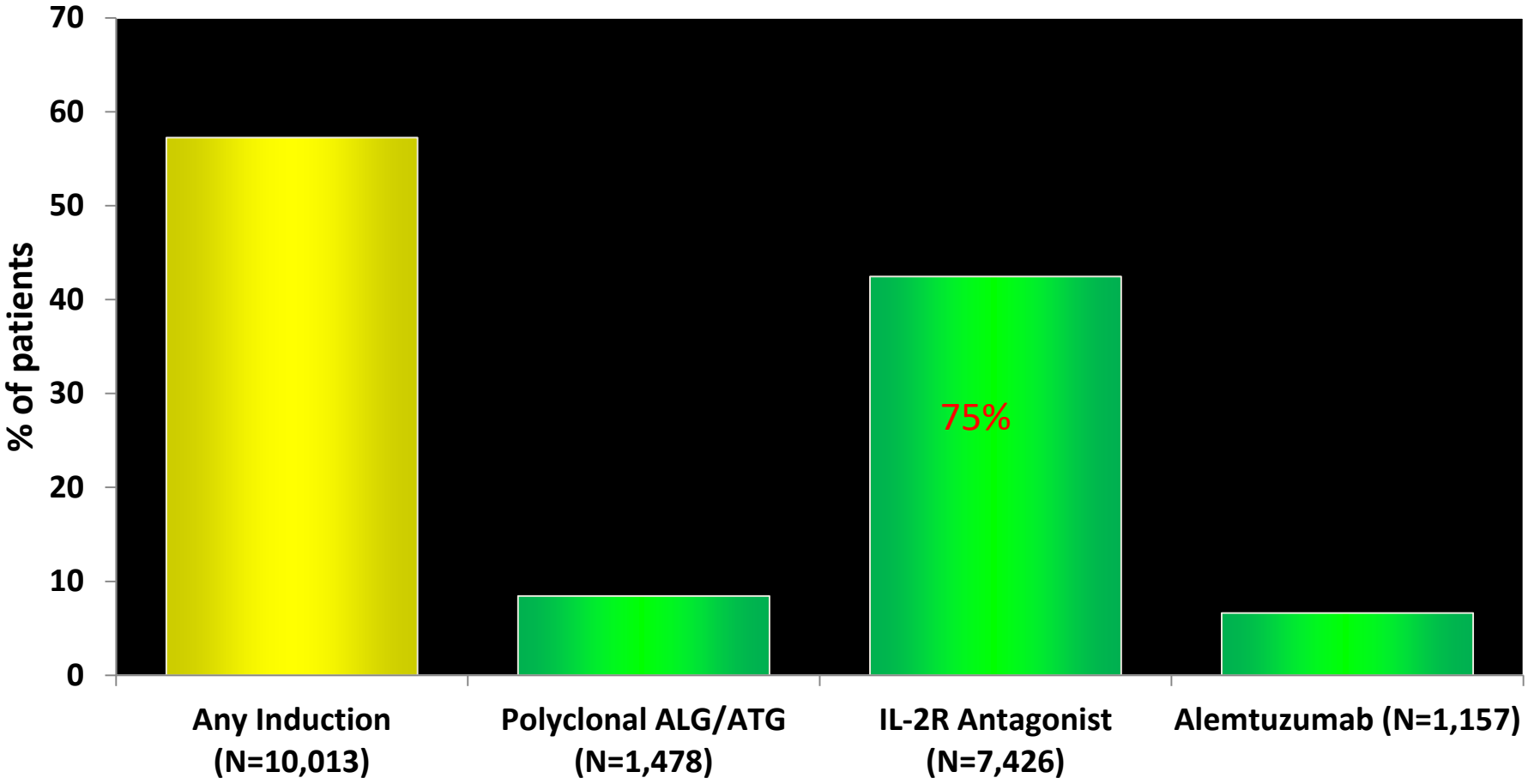
INDUCTION

- 60 % received any induction therapy

- IL2 antagonist proportion has increased over time(>80%).... i.e 38% of all lung transplants

[ISHLT Registry2016]

Analysis limited to patients receiving prednisone



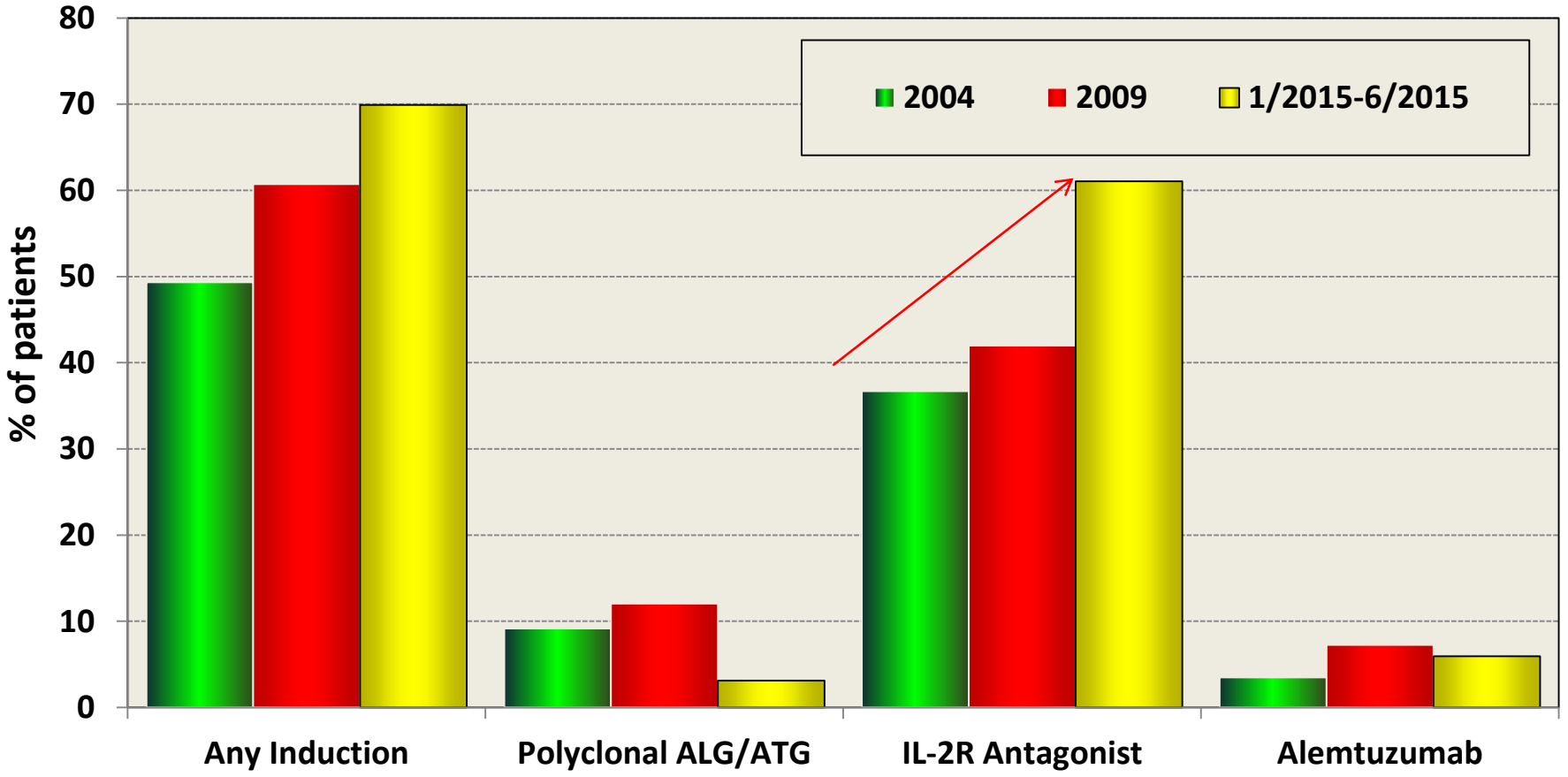
Analysis is limited to patients who were alive at the time of the discharge.

Adult Lung Transplants

Induction Immunosuppression

Analysis limited to patients receiving prednisone

(Transplants: 2004, 2009 and January 2015 – June 2015)



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

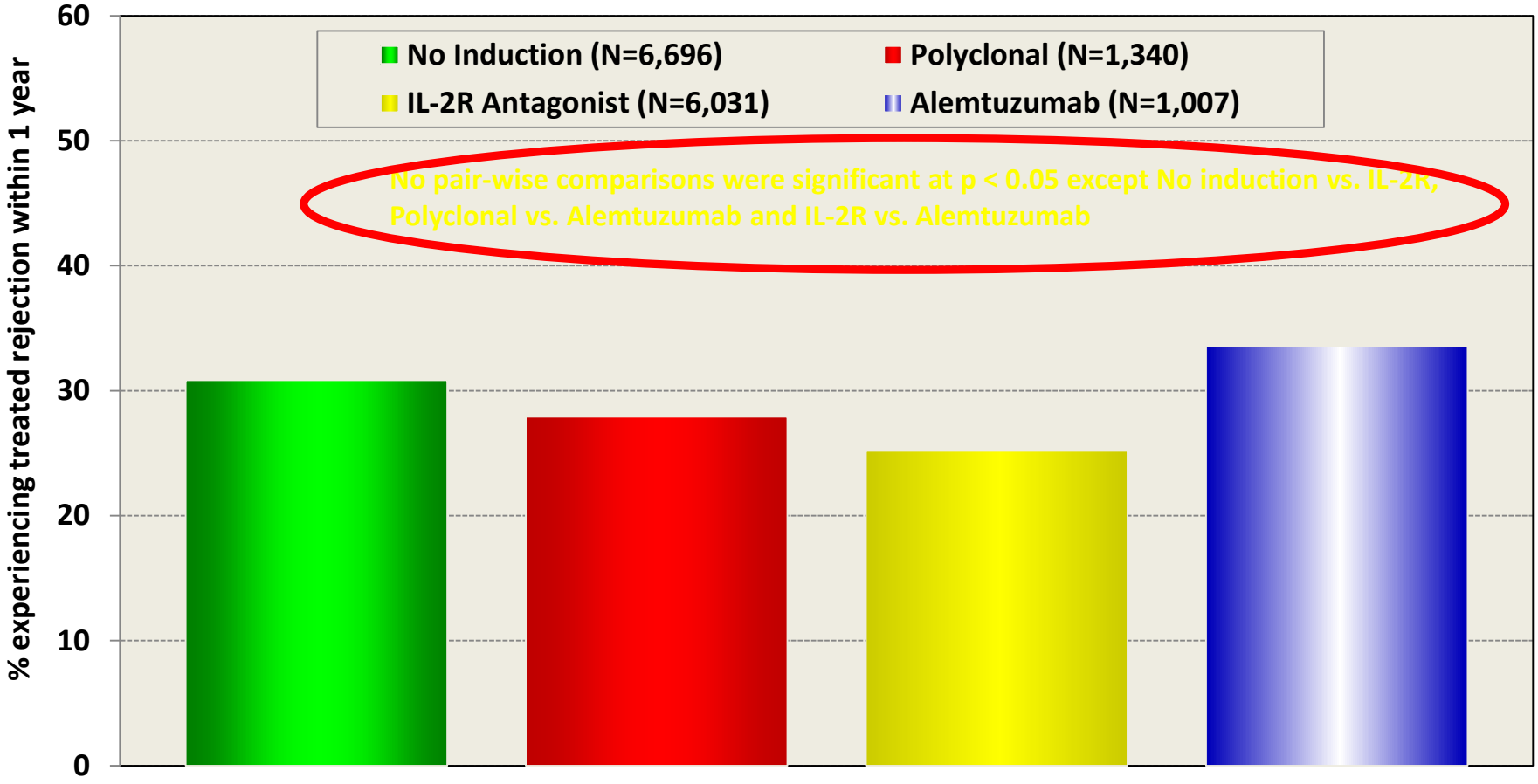
INDUCTION : AGENT

- In a retrospective, analysis of the ISHLT data on 3970 adult lung recipients, graft survival at four years
  - IL-2 receptor antagonist (64 %)
  - ATG (60 %)
  - No induction (57 %)

Hachem RR et al, clinical transplant 2008 Sep-Oct;22(5):603-8

Induction – effect on rejection

- Strongest data in favor of the IL-2 antagonists comes from the ISHLT registry



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

Treated rejection = Recipient was reported to (1) have at least one acute rejection episode that was treated with an anti-rejection agent; or (2) have been hospitalized for rejection.

INDUCTION

- IL- 2 receptor antagonist may be preferred
- BASILIXIMAB
- Dosing: 20 mg iv over 20 min on D1 and D4
- Timing: prior to implantation
  - Had lower cumulative acute rejection score over 1 year
  - But no significant difference in freedom from BOS or survival

Swarup et al, J Heart Lung Transplant. 2011;30(11):1228

INDUCTION – other agents

- Daclizumab : 1mg/kg every 2 wks for 5 doses
- ATG: 3–6 mg/kg, begun slowly with rate escalation every 30 minutes
- Alemtuzumab: 30 mg infused over 2 hours

MAINTENANCE

- Glucocorticoids:
  - inhibit both humoral and cell-mediated immunity
  - turns off gene transcription of multiple inflammatory genes

  - results is a decrease in the inflammatory response through reduced production of cytokines (IL1,IL2,IL6,IFN gamma,TNF alpha)

GLUCOCORTICOIDS

- At time of transplant: 500 to 1000 mg methylprednisolone iv
- Maintenance oral prednisone dose: 0.5 to 1 mg/kg/day initially after transplant and taper to a goal of 5 to 10 mg/day over several months to one year
- Diabetes, hypertension, weight gain, osteoporosis , increased incidence of infections are the common side effects
- Episodes of acute rejection are treated with high dose parenteral glucocorticoids

CALCINEURIN INHIBITORS

- CYCLOSPORIN A(CSA)
  - Trough levels 250-350 ng/ml 1st year then 200-300 ng/ml
  - Levels are measured 2 hours after intake
- TACROLIMUS
  - More potent than CSA
  - Trough levels 10-12 ng/ml 1st year then 6-8 ng/ml

- Side effect profile: HUS, HTN, hyperlipidemia, hyperkalemia, hypomagnesemia,renal insufficiency

Cyclosporine Vs Tacrolimus

- In RCT by Keenan RJ et al in 133 lung transplant recipients

- BOS in Tac Vs Cyc was 21.7% Vs 38%(p=0.025)
- 1 year and 2 year survival were similar

Keenan et al,Ann Thorac Surg. 1995,60(3):580–4 Clinical trial of tacrolimus versus cyclosporine in lung transplantation.

Cyclosporine Vs Tacrolimus

- In RCT of 90 lung transplant
  - Acute rejection developed in Tac & Cyc were 41 and 63 % (p=0.036)
  - No significant difference in graft survival,20 Vs 25%(p=0.7)
  - No difference HTN,CKD or cancer between the 2 groups

Hacheem RR et al, A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation, J Heart Lung Transplant. 2007

Cyclosporine Vs Tacrolimus

- In a multicenter RCT comparing TAC to CsA when combined with MMF and prednisone in 149 lung transplant recipients
  - BOS at 3 years :12% in Tac Vs 21% in with CsA (p=0.037)
  - 3 year cumulative incidence of acute rejection was 67.4% (tacrolimus) vs 74.9% (cyclosporine) (p 0.118)

Hendrik Treede et al, Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: Results of a prospective, randomized international trial in lung transplantation, J Heart Lung Transplant. 2012

Cyclosporine Vs Tacrolimus

- In RCT of 2 center study of 74 lung transplant recipients who received induction therapy with ATG and randomized to CsA/MMF/steroids was compared with Tac/MMF/steroids
  - Acute rejection at 6 and 12 months was comparable between groups (46% vs 51% and 35% vs 46%, respectively; P =.774 at 12 months)
  - No significant difference was noted in the incidence of acute rejection or survival

Zuckermann et al , Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial, J Thorac Cardiovasc Surg. 2003

Anti proliferative agents

- Nucleotide blocking agents:

  mycophenolate (1000-1500 mg bid)

  azathioprine (2 mg/kg/day)

- Approximately 80% in the United States are receiving MMF as a core constituent of their maintenance immunosuppression

MMF Vs AZA

- Data from other solid organ transplant support MMF over AZA

- 2 RCTs comparing MMF to AZA in lung transplantation did not show a clear superiority of MMF

Palmer SM,et al,Transplantation. 2001, Results of a randomized, prospective, multicenter trial of mycophenolate mofetil versus azathioprine in the prevention of acute lung allograft rejection

McNeil K etal, Transplantation. 2006, Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients

mTOR inhibitors

- Who do not tolerate
  - nucleotide blocking agents or have
  - allograft rejection that is refractory to nucleotide blocking agents
  - progressive renal insufficiency to permit reduction in CNI dosing or as part of a CNI-free regimen

mTOR

- Due to synergistic effects, the dose of concomitant CNI should be decreased by 2/3 after starting sirolimus or everolimus

- Initiation of sirolimus or everolimus should be delayed until after *the bronchial anastomosis is completely healed*

- Sirolimus → VTE/interstitial pnuemonitis

Aza Vs mTORs

- In an RCT of 213 patients,
  - Everolimus resulted in fewer episodes of acute rejection (8 Vs 32 %) and less deterioration (9 Vs 20 %) in FEV_1, a marker for chronic rejection
  - But resulted in **more adverse effects** including serious bacterial and fungal infections, pneumonia, hyperlipidemia, anemia, and thrombocytopenia($p<0.05$)

Snell et al, Everolimus Versus Azathioprine in Maintenance Lung Transplant Recipients: An International, Randomized,Double-Blind Clinical Trial ; Am J Transplant. 2006

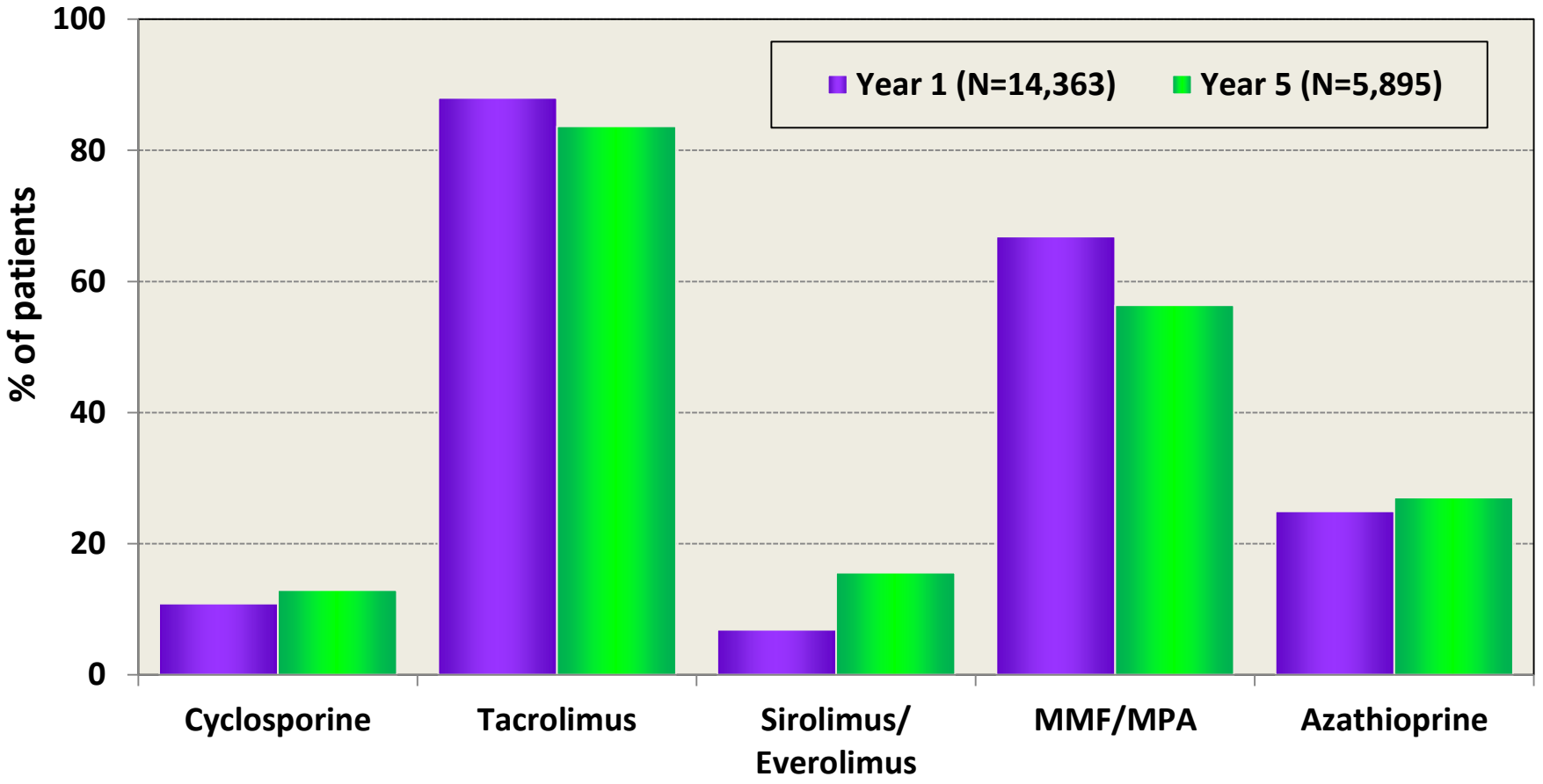
Aza Vs mTORs

- In a multicenter trial, 181 lung transplant recipients
  - At 1 year after transplantation, there was no significant difference in the incidence of acute rejection or graft survival between the two study groups
  - There was a higher rate of adverse events leading to early discontinuation of sirolimus (64 %) compared with azathioprine (49 %) during the course of this study

Bhorde et al, Comparison of sirolimus with azathioprine in a tacrolimus-based immunosuppressive regimen in lung transplantation, Am J Respir Crit Care Med

- ISHLT Registry

Analysis limited to patients receiving prednisone



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

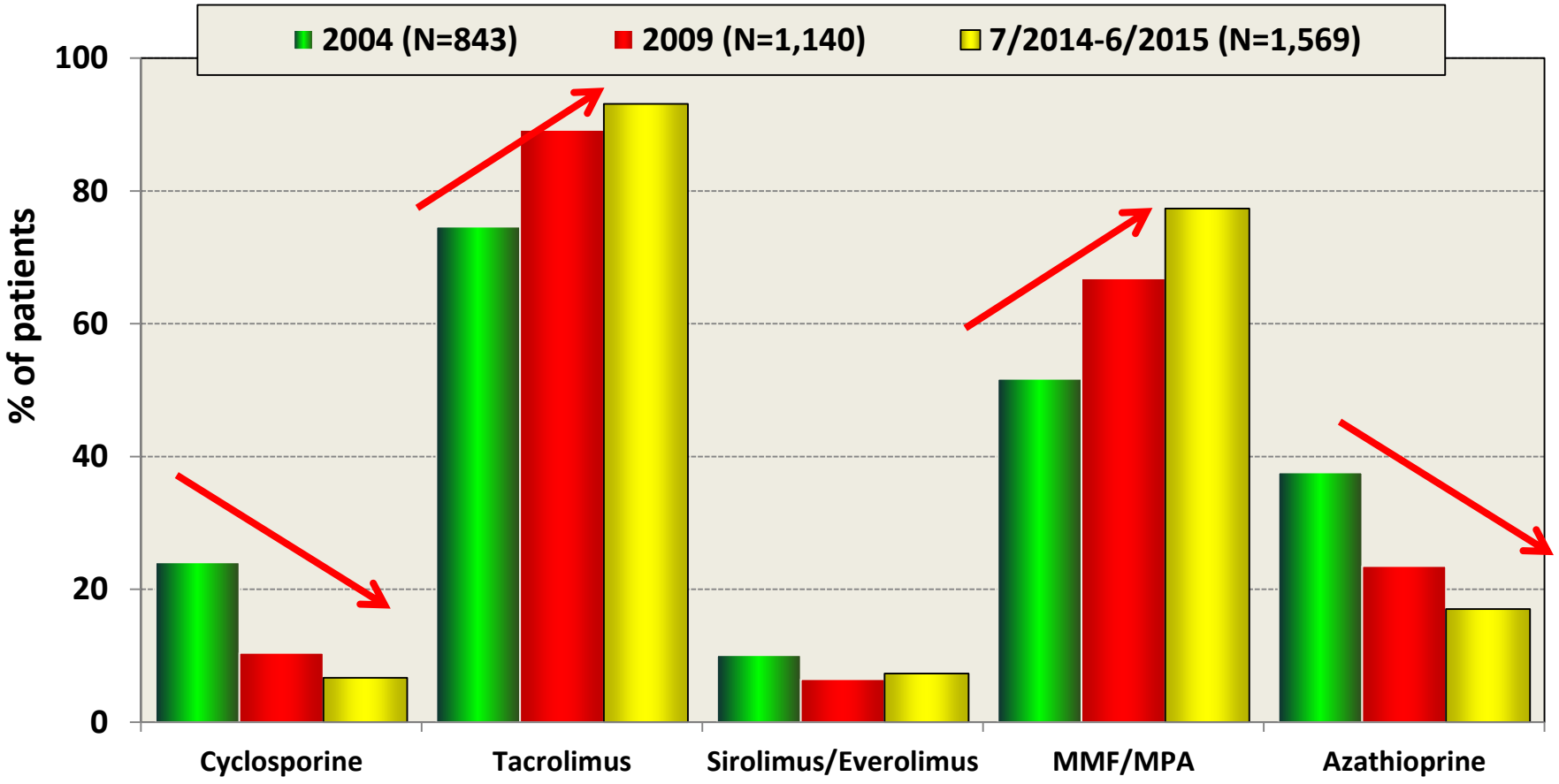
Analysis is limited to patients who were alive at the time of the follow-up.

Adult Lung Transplants

Maintenance Immunosuppression at Time of 1 Year Follow-up

Analysis limited to patients receiving prednisone

(Follow-ups: 2004, 2009 and July 2014 – June 2015)



NOTE: Different patients are analyzed in each time frame

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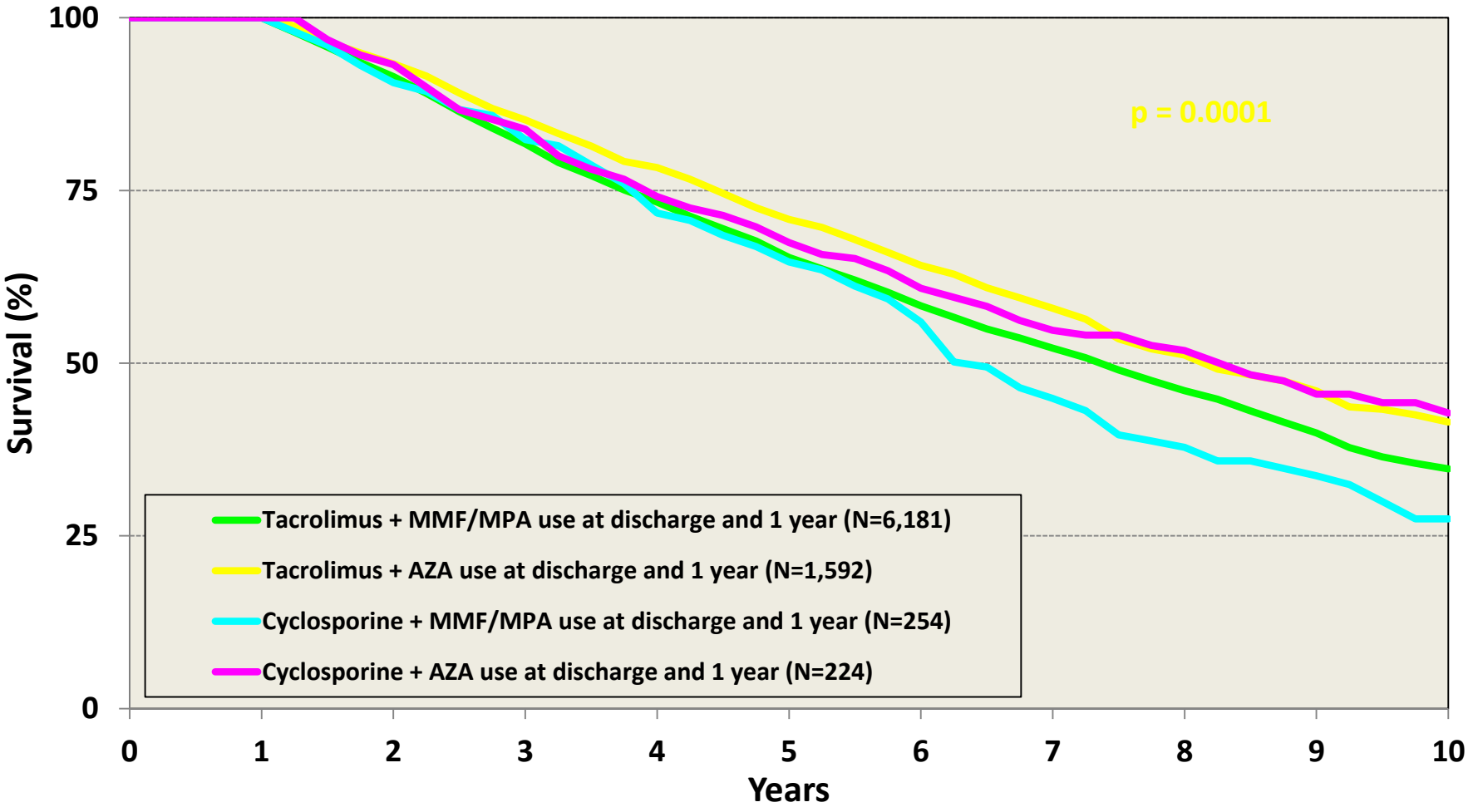
Analysis is limited to patients who were alive at the time of the follow-up.

Adult Lung Transplants

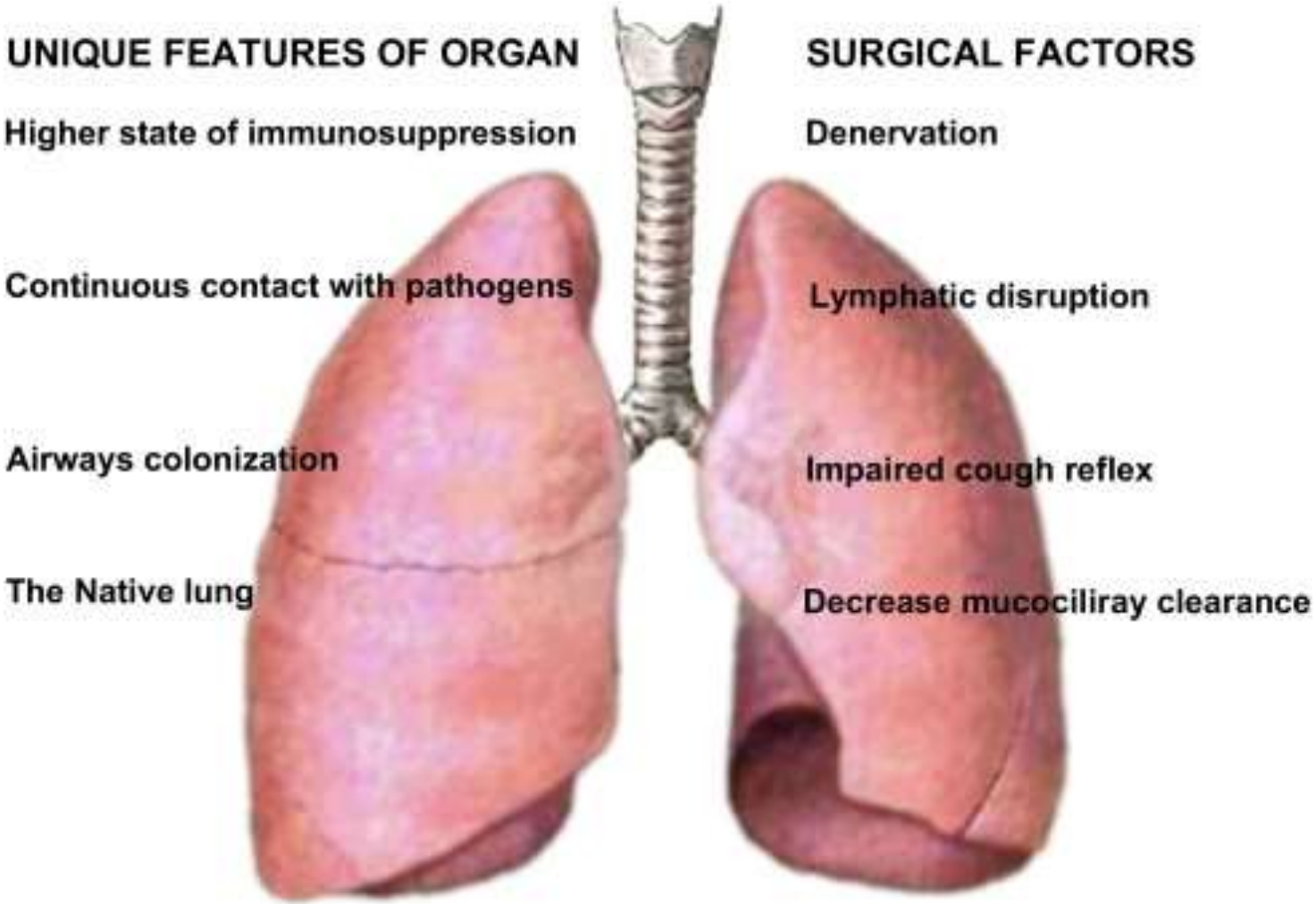
Kaplan-Meier Survival by Maintenance Immunosuppression Combinations

Conditional on Survival to 1 Year (Transplants: January 2004 – June 2014)

Analysis limited to patients receiving prednisone



Infection Prophylaxis



Infection prophylaxis

Transplant Period	Time	Infection
Early	One to six months after	Donor derived: Donor-derived bacteria (MRSA, VRE, tuberculosis), fungi (Candida), and parasite (toxoplasmosis, Chagas disease) Nosocomial/Surgery-related: Aspiration pneumonia, surgical site infection, urinary tract infection, superinfection of graft tissue, vascular access infection, C. difficile colitis
Intermediate	One to six months after	Most at risk for opportunistic infection: Pneumocystis jirovecii, Histoplasma, Coccidioides, Cryptococcus, Hepatitis B or C, BK polyomavirus, Kaposi's sarcoma, Cytomegalovirus (CMV), Tuberculosis, Epstein-Barr virus (EBV) Surgical site infections are common Reactivation of dormant host infection: CMV, HZV, HSV, EBV
Late	Greater than 6 months after	Community-acquired infection: Respiratory viruses, Pneumococcus, Legionella, Listeria, Influenza, EBV

Anti microbial therapy

- Bacterial prophylaxis
- HSV propylaxis → Acyclovir
- CMV → Ganciclovir
- PCP → Cotrimoxazole
- Fungal → Amphotericin,Voriconazole

Antibacterial prophylaxis

Institution	Antibiotics	Duration	CF
Toronto General Hospital	Cefuroxime	48 hrs	Based on colonizing organisms Inhaled tobramycin
Henry Ford Hospital	Cetazidime & Vancomycin	7 days	Perioperative cultures
Duke university	Cetazidime & Vancomycin	7 days	Perioperative cultures Inhaled colistin & tobramycinfor 3 months
University of Pittsburgh	Ceftazolin & Aztreonam	48 hrs	Perioperative cultures

Antibacterial Prophylaxis

- Initiated before “time of incision“
- Optimal duration: uncertain (atleast 48 to 72 hours; allow time to determine whether donor cultures are positive)
- In septic lung disease (cystic fibrosis /bronchiectasis) & complicating factors such as a chest that remains open → longer duration

Antifungal prophylaxis

- Candidemia : first month following transplantation
- Aspergillosis:
  - median 3.2 months
  - 72% in first 6 months
- High risk factors for invasive aspergillosis
  - Airway colonization (Aspergillus cultured from airway specimens in absence of invasive aspergillosis or tracheobronchitis)
  - Airway ischemia
  - Bronchiolitis obliterans

Singh N et al, J Heart Lung Transplant. 2003;22(3):258

Anti fungal prophylaxis

- Neb ABLC → 50 - 100 mg/day. Regimen should continue for 4days following transplantation, then weekly while hospitalized
  - Conventional ampho B 20 mg BD
- Nystatin suspension 100,000 U/mL; 5 mL swish & swallow 4 times/day x 6 months post-transplant
- Voriconazole 400 mg/day X 4 months post-transplant (in high risk individuals)

PJP Prophylaxis

- 5-15 % develop PCP pnuemonia
- PCP was highest among lung transplant recipients compared with other organ recipients (22 Vs 4.8 cases/1000 person-transplant years)
- 10 (36%) of 28 PCP cases occurred >or = 1 yr after transplantation
- No patient developed PCP while receiving prophylaxis for PCP

Gordon et al, Should prophylaxis for Pneumocystis carinii pneumonia in solid organ transplant recipients ever be discontinued? Clin Infect Dis. 1999;28(2):240

PJP Prophylaxis

- Trimethoprim-sulfamethoxazole
- Starting within one week postoperatively & continuing indefinitely
  - 1 DS tablet orally daily
  - 1 DS tab 3 times per week
  - 1SS tablet orally daily
- If sulfonamide hypersensitivity
  - Atovaquone 1500 mg OD
  - Dapsone 50 mg OD
  - Pentamidine 4 mg/kg IV monthly or 300 mg aerosolized monthly

CMV prophylaxis

- 2nd most common infection following bacterial pnuemonia

- Incidence of CMV infection and disease following lung transplantation in the post ganciclovir era ranges from 30 to 86% with an associated mortality rate of 2–12%

Martin R. Zamora, American Journal of Transplantation 2004; 4: 1219–1226 , Cytomegalovirus and Lung Transplantation

CMV prophylaxis

- **Universal prophylaxis** of recipients at high risk for infection (all but CMV donor-negative, recipient-negative [CMV D-/R-] recipients)

- **Preemptive treatment** of recipients with infection and demonstrable viral replication

- Universal prophylaxis is preferred

  (2013 American Society of Transplantation (AST) guidelines & 2013 Transplantation Society International CMV Consensus Group guidelines)

CMV

- Uncertainity in duration of prophylaxis
  - 12 months following transplantation in lung transplant recipients who are CMV D+/R-
  - 6 to 12 months in CMV D+/R+ and D-/R+ patients

- CMV seronegative (CMV D-/R-) lung transplant recipients should receive only CMV negative or leuko reduced blood products to decrease the risk of transfusion related CMV transmission

CMV

- CMV prophylaxis should be **reinitiated** during the treatment of *acute rejection if antilymphocyte antibody* therapy or high-dose steroids are used

  – continued for 1-3 months after the anti-rejection therapy has been completed

Kotton CN et al, Transplantation. 2013;96(4):333

Indian Scenario –TB in Tx

- 5-15 % in India in renal transplant recipients(1)
- Most common is reactivation of TB(1)

- Pretransplant screening for LTBI
- Preventive chemotherapy/chemoprophylaxis

- Different regimens: INH/ RIF+PZD/ INH+RIF
- MC used is INH for 9-12 months

1-M. tuberculosis Infection in Transplant Recipients, CID 1998;27

? Anti TB prophylaxis

- Anti TB prophylaxis : not suggested
  - Prophylactic administration of INH reduced the risk of developing TB post transplant
  - Bu there was **no significant effect** on all cause mortality

The Cochrane Library 2014, Issue 3

VACCINATION

Vaccine	Pretransplant		Starting 2 to 6 months posttransplant	
	Recommendation	Strength, evidence quality	Recommendation	Strength, evidence quality
Haemophilus influenzae b conjugate	U	Strong, moderate	U	Strong, moderate
Hepatitis A	U: age 12 to 23 months R: age ≥2 years	Strong, moderate Strong, moderate	R, if not completed pretransplant	Strong, moderate
Hepatitis B	U: age 1 to 18 years R: age ≥18 years	Strong, moderate Strong, moderate	R, if not completed pretransplant*	Strong, moderate
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, moderate	U, if not completed pretransplant	Strong, moderate
Human papillomavirus	U: females 11 to 26 years U: males 11 to 26 years	Strong, moderate Strong, low	U: females 11 to 26 years U: males 11 to 26 years	Strong, moderate Strong, low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, moderate	U¶	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, low	X	Weak, low
Measles, mumps, and rubella-live	R‡: age 6 to 11 months U*: age ≥12 months	Weak, very low Strong, moderate	X	Strong, low
Measles, mumps, and rubella-varicella-live	U*	Strong, moderate	X	Strong, low
Meningococcal conjugate	U	Strong, moderate	U	Strong, moderate
Pneumococcal conjugate (PCV13)	U: age ≤5 years R: age ≥6 years§	Strong, moderate Strong, very low	U: age 2 to 5 years R: age ≥6 years if not administered pretransplant§	Strong, moderate Strong, very low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 years	Strong, moderate	R: age ≥2 years, if not administered pretransplant	Strong, moderate
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate
Rotavirus-live	U‡	Strong, moderate	X	Strong, low
Varicella-live	R‡: age 6 to 11 months U*	Weak, very low Strong, low	X*	Strong, low
Zoster-live	R*: age 50 to 59 years U**: age ≥60 years	Weak, low Strong, moderate	X	Strong, low

U:ususal
R:recomended
X:contraindicated

Rubin LG et al, 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2013; 58:e44

Vaccination

- Preferably vaccination should be completed in pretransplant period
- Live vaccines are contraindicated: post transplant
- Influenza(inactivated),pnuemococcol , HBV, HAV vaccination should be recommended

Acute Graft Rejection

- 1/3 of lung transplant recipients are treated for acute rejection in 1 year after transplant
- It is responsible for approximately 4 % of deaths in the first 30 days following transplantation
- Is a major risk factor for bronchiolitis obliterans syndrome (BOS)

Yusen RD et al,ISHLT, J Heart Lung Transplant. 2015;34(10):1264

Acute Graft Rejection

- Constitutes
  - acute cellular perivascular (A-grade) rejection
  - acute cellular airway/ lymphocytic bronchiolitis (B-grade) rejection

- Also includes acute humoral rejection (anti HLA antibody)

Clin Chest Med 32 (2011) 295–310

A: Acute rejection*: characterized by perivascular and interstitial mononuclear cell infiltrates
Grade 0: none
Grade 1: minimal
Grade 2: mild
Grade 3: moderate
Grade 4: severe
B: Airway inflammation (lymphocytic bronchiolitis)*: characterized by mononuclear cell infiltrates in the submucosa of bronchioles
Grade 0: none
Grade 1R¶: low grade
Grade 2R¶: high grade
Grade X: ungradeable
C: Chronic airway rejection (obliterative bronchiolitis): manifest by fibrous scarring that is often dense and eosinophilic
0: absent
1: present
D: Chronic vascular rejection - accelerated graft vascular sclerosis: characterized by fibrointimal thickening of the pulmonary arteries and veins. These lesions are not seen on TBB as they affect larger blood vessels than those accessed with TBB.

Stewart S et al, J Heart Lung Transplant 2007; 26:1229

Acute Allograft Rejection

- Patients are asymptomatic, and the diagnosis is made from surveillance transbronchial biopsies
- Clinically
  - Fever
  - SOB
  - Nonproductive cough
  - Leukocytosis

-Crackles

-Decline in oximetry with exercise

-Decline in spirometry (>10%)

Acute Cellular Rejection-TBLB

- 6 to 10 biopsies in order to achieve 5 "adequate" or "good" specimens, defined as samples with at least 5 alveoli
- Sensitivity : 61 to 94 %
- Specificity > 90 %

Trulock EP et al, Chest. 1992;102(4):1049
Faro A et al, Pediatr Transplant. 2004;8(4):322

Acute rejection

- A1 may increase risk of severe A2 or BOS(1)
- Grade B lymphocytic bronchiolitis is a risk factor BOS related deaths(2)

- Grade A2 & higher should be treated
- Grade A1 & lymphocytic bronchiolitis may be treated

1-Transplantation 2005;80(10):1406–13.
2-J Heart Lung Transplant 2005;24(2): 152–5

Acute rejection - treatment

- Pulse steroid (iv methylprednisolone 15mg/kg X 3 days)
- Symptomatic improvement usually occurs over 24 to 48
- In symptomatic acute rejection, 55% responded to glucocorticoid pulse(1)

Fuehner et al, Respir Med. 2009 Aug;103(8):1114-21

Persistent/Refractory Rejection

- 2 nd pulse steroid for 3 days
- Shift to cyclosporine based regimen
- Add mTOR inhibitor
- Suspect humoral rejection

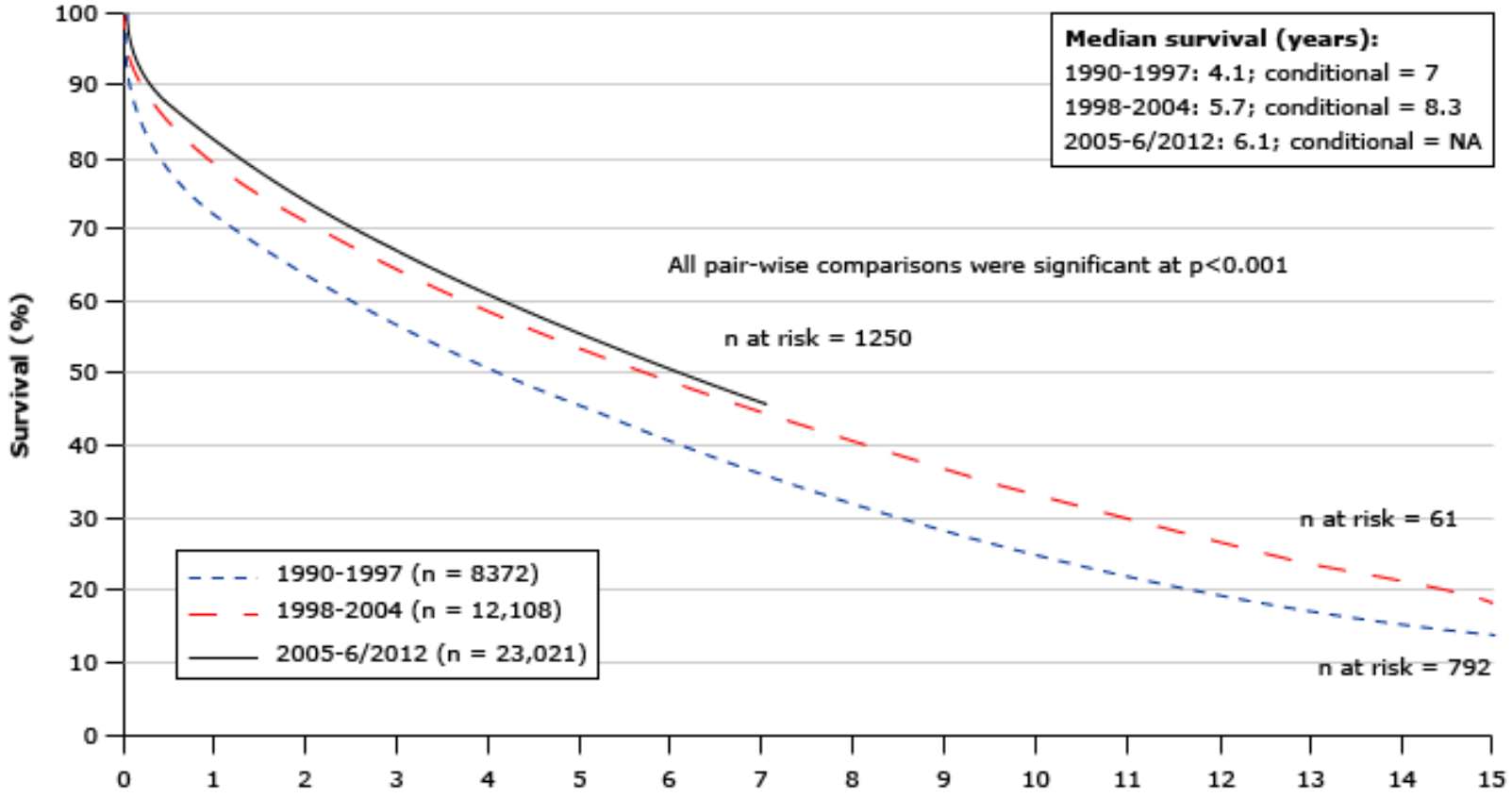
- Aersolized cyclosporine
- ATG
- Extracorporeal photopheresis

Humoral rejection

- IVIG is to be used
- Rituximab may also be used along withIVIG
- Plasmapheresis for severe cases

Chronic Rejection

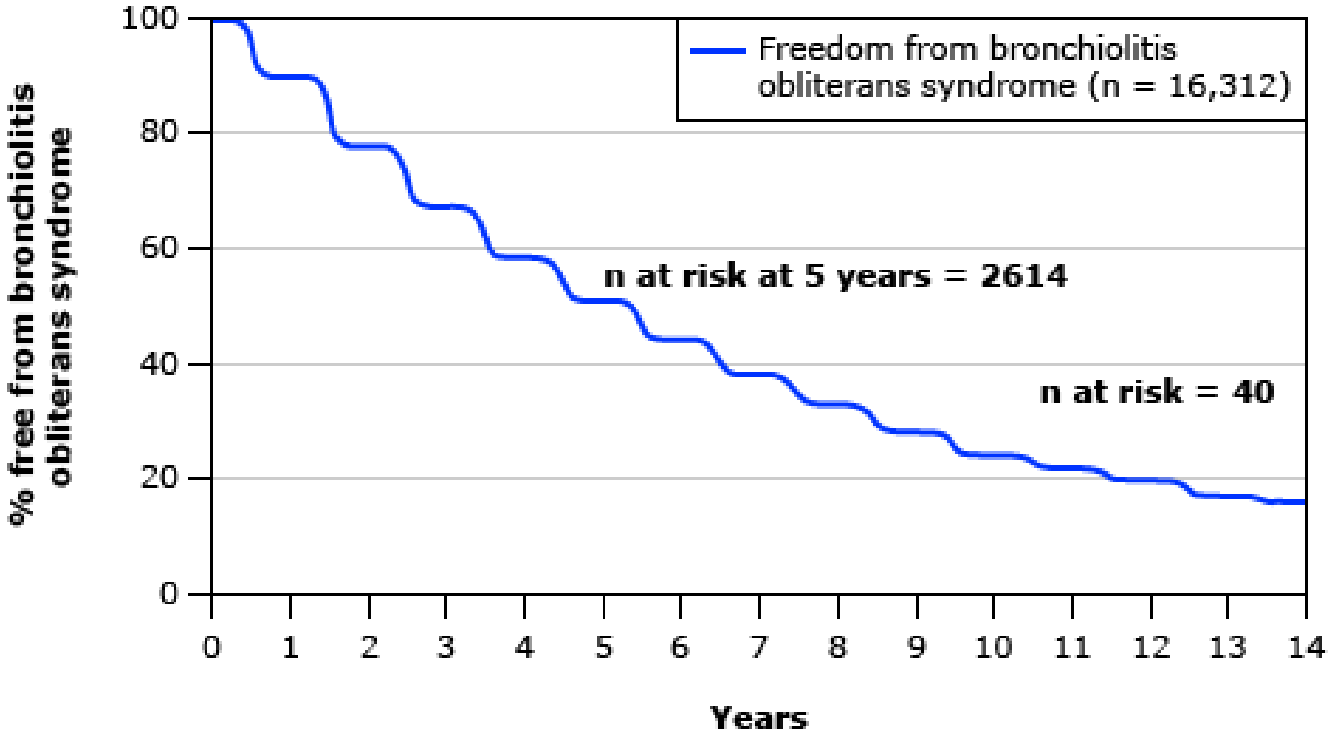
- Major source of morbidity and mortality following lung transplantation
- Significant improvement in the early (up to one year) survival of transplant recipients over the past two decades
- But the rate of decline in survival after the first year is unchanged



Yusen RD et al,31st ISHLT report 2014, J Heart Lung Transplant 2014; 33:1009

Outcome	Within 1 Year	Total number with known response	Within 5 Years	Total number with known response
Hypertension	51.7%	(N = 18,463)	80.3%	(N = 6,207)
Renal Dysfunction	22.5%	(N = 21,536)	53.6%	(N = 8,317)
Abnormal Creatinine ≤ 2.5 mg/dl	*15.4%*		*34.9%*	
Creatinine > 2.5 mg/dl	*5.1%*		*14.5%*	
Chronic Dialysis	*1.8%*		*3.3%*	
Renal Transplant	*0.1%*		*0.8%*	
Hyperlipidemia	26.7%	(N = 19,136)	58.2%	(N = 6,638)
Diabetes	22.3%	(N = 22,053)	37.4%	(N = 8,844)
Bronchiolitis Obliterans Syndrome	9.2%	(N = 20,747)	41.5%	(N = 7,581)

Chronic Rejection



BO or BOS : 48 % of by 5 years

76 % by ten years

Yusen RD et al, J Heart Lung Transplant 2013; 32:965

Cause of Death	0-30 Days (N=3,424)	31 Days - 1 Year (N=6,029)	>1 Year - 3 Years (N=5,746)	>3 Years - 5 Years (N=3,353)	>5 Years - 10 Years (N=4,135)	>10 Years (N=1,551)
OB/BOS	10 (0.3%)	277 (4.6%)	1,503 (26.2%)	992 (29.6%)	1,024 (24.8%)	333 (21.5%)
Acute Rejection	113 (3.3%)	110 (1.8%)	91 (1.6%)	21 (0.6%)	20 (0.5%)	3 (0.2%)
Lymphoma	1 (0.0%)	130 (2.2%)	101 (1.8%)	51 (1.5%)	72 (1.7%)	47 (3.0%)
Malignancy, Non-Lymphoma	5 (0.1%)	182 (3.0%)	480 (8.4%)	397 (11.8%)	600 (14.5%)	212 (13.7%)
CMV	3 (0.1%)	124 (2.1%)	51 (0.9%)	9 (0.3%)	5 (0.1%)	1 (0.1%)
Infection, Non-CMV	655 (19.1%)	2,120 (35.2%)	1,201 (20.9%)	608 (18.1%)	739 (17.9%)	256 (16.5%)
Graft Failure	838 (24.5%)	974 (16.2%)	1,067 (18.6%)	585 (17.4%)	666 (16.1%)	241 (15.5%)
Cardiovascular	397 (11.6%)	321 (5.3%)	251 (4.4%)	164 (4.9%)	236 (5.7%)	111 (7.2%)
Technical	390 (11.4%)	212 (3.5%)	53 (0.9%)	16 (0.5%)	29 (0.7%)	10 (0.6%)
Multiple Organ Failure	420 (12.3%)	722 (12.0%)	296 (5.2%)	137 (4.1%)	199 (4.8%)	87 (5.6%)
Other	592 (17.3%)	857 (14.2%)	652 (11.3%)	373 (11.1%)	545 (13.2%)	250 (16.1%)

Percentages represent % of deaths in the respective time period.

Risk factors for BOS

Probable

- Acute rejection
- Lymphocytic bronchitis/bronchiolitis
- CMV pneumonitis
- Medication noncompliance
- Primary graft dysfunction

Potential

- CMV infection (without pneumonitis)
- Organizing pneumonia
- Recurrent infection other than CMV
- Older donor age
- Prolonged allograft ischemia
- Gastroesophageal reflux with aspiration
- HLA-mismatching
- Underlying cause of lung disease

Estenne M et al, J Heart Lung Transplant 2002; 21:297

BO Vs BOS

- ISHLT makes a distinction between histologically proven BO and suspected BO, which is called bronchiolitis obliterans syndrome (BOS)

- BOS: graft deterioration secondary to progressive airways disease for which there is no other cause

BOS classification

	1993 Classification	2002 Classification	
	FEV_1 80% or more of baseline	FEV_1 >90% of baseline *and* FEF_{25-75} >75% of baseline	BOS 0
		FEV_1 81% to 90% of baseline *and/or* FEF_{25-75} = or <75% of baseline	BOS 0-p
BOS 1	FEV_1 66% to 80% of baseline	FEV_1 66% to 80% of baseline	BOS 1
BOS 2	FEV_1 51% to 65% of baseline	FEV_1 51% to 65% of baseline	BOS 2
BOS 3	FEV_1 50% or less of baseline	FEV_1 50% or less of baseline	BOS 3

Estenne M et al, J Heart Lung Transplant 2002; 21:297

BOS classification

- Prerequisites to be classified are

I. Functional loss ≥ 3 wks

II. Decrease in both FEV1 and FEV1/VC

III. Exclusion of confounding conditions

(infection/acute rejection/anastomotic complications/disease recurrence)

Other types of chronic rejection

- A phenotype characterized by a **restrictive** ventilatory impairment associated with upper lobe fibrosis
- A reversible phenotype characterized by **airway neutrophilia** and functional improvement with azithromycin
- Exudative or follicular bronchiolitis
- Large airway stenosis/malacia

Estenne M et al, J Heart Lung Transplant 2002; 21:297

Treatment- BOS

First line	Second line	Refractory BOS
Azithromycin	Substitution of sirolimus for azathioprine	Photopheresis
Substitution of tacrolimus for cyclosporine	Everolimus	Total lymphoid irradiation
Substitution of MMF for azathioprine	Montelukast	Plasmapheresis ATG Retransplantation

	Hyperacute	Acute	Chronic	PGD
Timing	First 24 hrs	Mostly 1 st six months	> 1 year	In first 72 hs
Mechanism	Humoral Preformed HLA Ab	Cellula /Humoral CD8 T cells against MHC	Cellula and humoral CD4 T cells respond to recipient APC	Reactive oxygen radicles
Symptoms	Rapidly worsening SOB,hypoxia	SOB,Cough,fever,reduction in spirometry	Progressive SOB, Reduction in spirometry(FEV1 &FEV 25-75)	Pulm edema
Radiology	B/L opacities Pl effusion	CXR: perihilar opacities/pl effusion HRCT: GGO/Septal thickening	CXR:mild decrease in peripheral vascularity CT: bronchiectasis Patchy areas of air trapping	Non specific Airspace consolidation Interstitial opacities in perihilar or basal regions
Diagnosis	Review PRA	TBLB	TBLB	Timing FOB

Other Perioperative Complications

- Hemorrahge
- Anastomotic stenosis
- Pleural effusion/empyema
- Pericardial effusion/tamponade
- Acute renal failure
- Phrenic nerve injury
- Systemic embolism

SURVIVAL AFTER LUNG TRANSPLANTATION

- Median survival is 5.7 years as per 2014 ISHLT registry

- Upto 1 year following tx → Non CMV infections and graft failure (45-50% of mortality)

- > 1 year → OB/BOS is the major cause of mortality(> 20%)

Adult Lung Transplants

Cause of Death (Deaths: January 1990 – June 2015)

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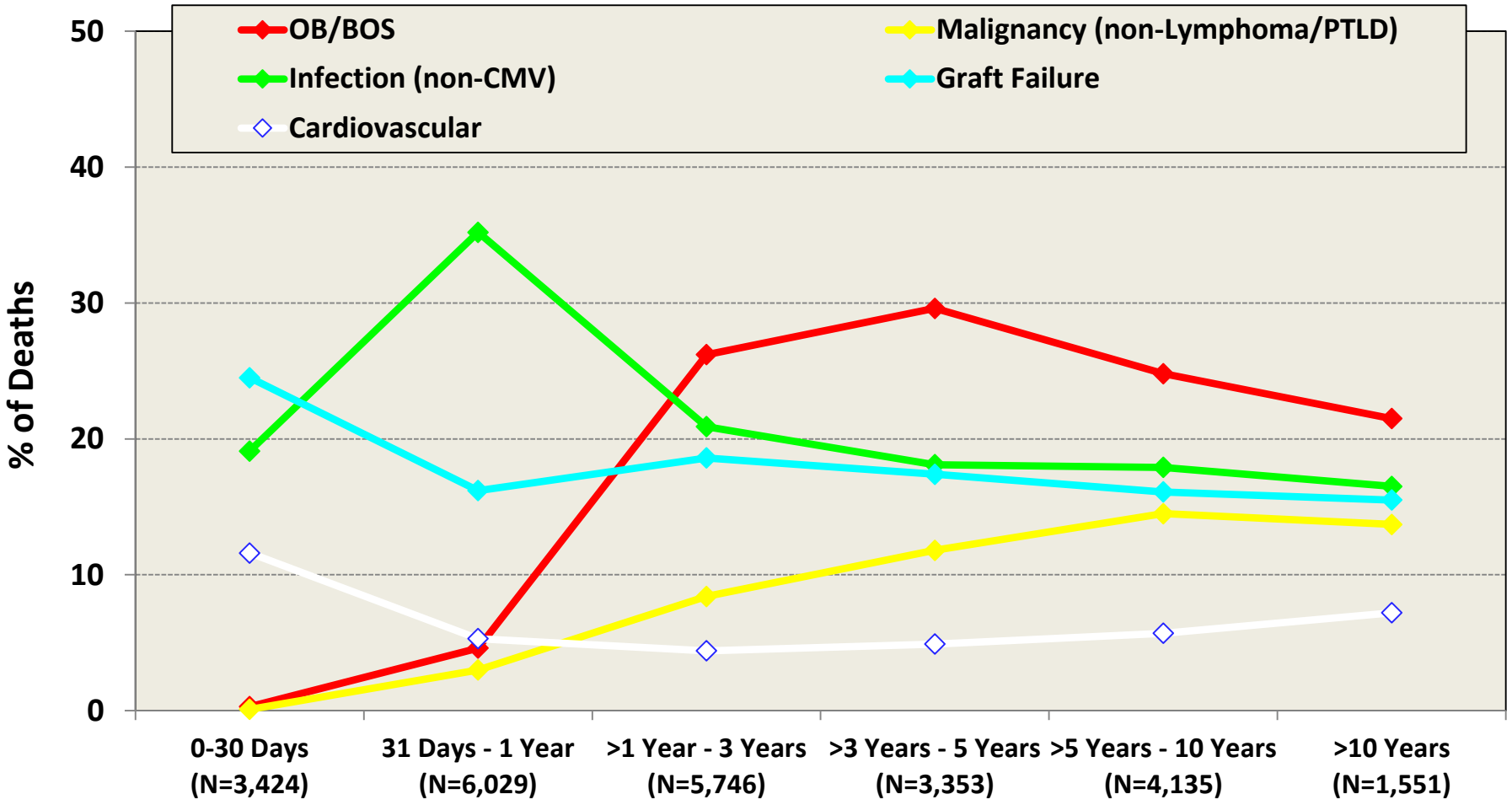
Percentages represent % of deaths in the respective time period.

Adult Lung Transplants

Relative Incidence of Leading Causes of Death

(Deaths: January 1990 – June 2015)



Take Home Message

- Much of the evidence is extrapolated
- Identify early graft failure
- Protocolized management is the need of the hour
  - Ventilation strategy
  - Fluid management
  - Immunosuppression
  - Prophylaxis
  - Follow up