Management of Post-Transplant Complications for Non-Transplant Centers

APACVS Annual Meeting

Miami, FL

April 7, 2018

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Speaker Disclosures:

- None to disclose
- The speaker will only discuss adult implications
- The speaker will not speak to off label use of medications

Why This Presentation

- Goal of thoracic transplant is that the patient can return home…. LIVE AT HOME
- Most patients do not come from implanting center area
- Thoracic transplant patients are surviving longer due to improved medications
- The ability to take care of the patient in their community is key to quality of life for most patients
- Co-management of patients is possible to achieve that goal!

Why This Presentation

- This presentation starts about 1 year after transplant
  - Most patients are on a routine biopsy or follow-up schedule
  - Difficult management of immunosuppression related to rejection and ability to wean as quickly as possible to decrease future complications
  - Greatest number of life-threatening complications occur in 1st year

Epidemiology of the Post-Thoracic Transplant Patient

- Highest risk for infection: 1st year
- Highest risk for renal failure: 1st year
- Highest risk for diabetes: 1st year

- Although risk is highest in 1st year, the risks continue to be a lifelong issue

Epidemiology of the Post-Thoracic Transplant Patient

ISHLT 2016 DATA REVIEW

Epidemiology

Adult Heart Transplants

Cumulative Morbidity Rates in Survivors within 1, 5 and 10 Years Post Transplant (Transplants: January 1994 – June 2015)

Outcome	Within 1 Year	Total N with known response	Within 5 Years	Total N with known response	Within 10 Years	Total N with known response
Renal Dysfunction	25.7%	(N=34,983)	51.1%	(N=19,655)	68.4%	(N=8,261)
Abnormal Creatinine ≤ 2.5 mg/dl	*17.2%*		*32.7%*		*39.2%*	
Creatinine > 2.5 mg/dl	*6.3%*		*13.8%*		*18.7%*	
Chronic Dialysis	*1.9%*		*3.2%*		*6.7%*	
Renal Transplant	*0.4%*		*1.4%*		*3.8%*	
Diabetes*	22.2%	(N=37,659)	35.5%	(N=21,429)	-	
Cardiac Allograft	7.8%	(N=34,438)	29.3%	(N=16,016)	47.4%	(N=5,468)

* Data are not available 10 years post-transplant.

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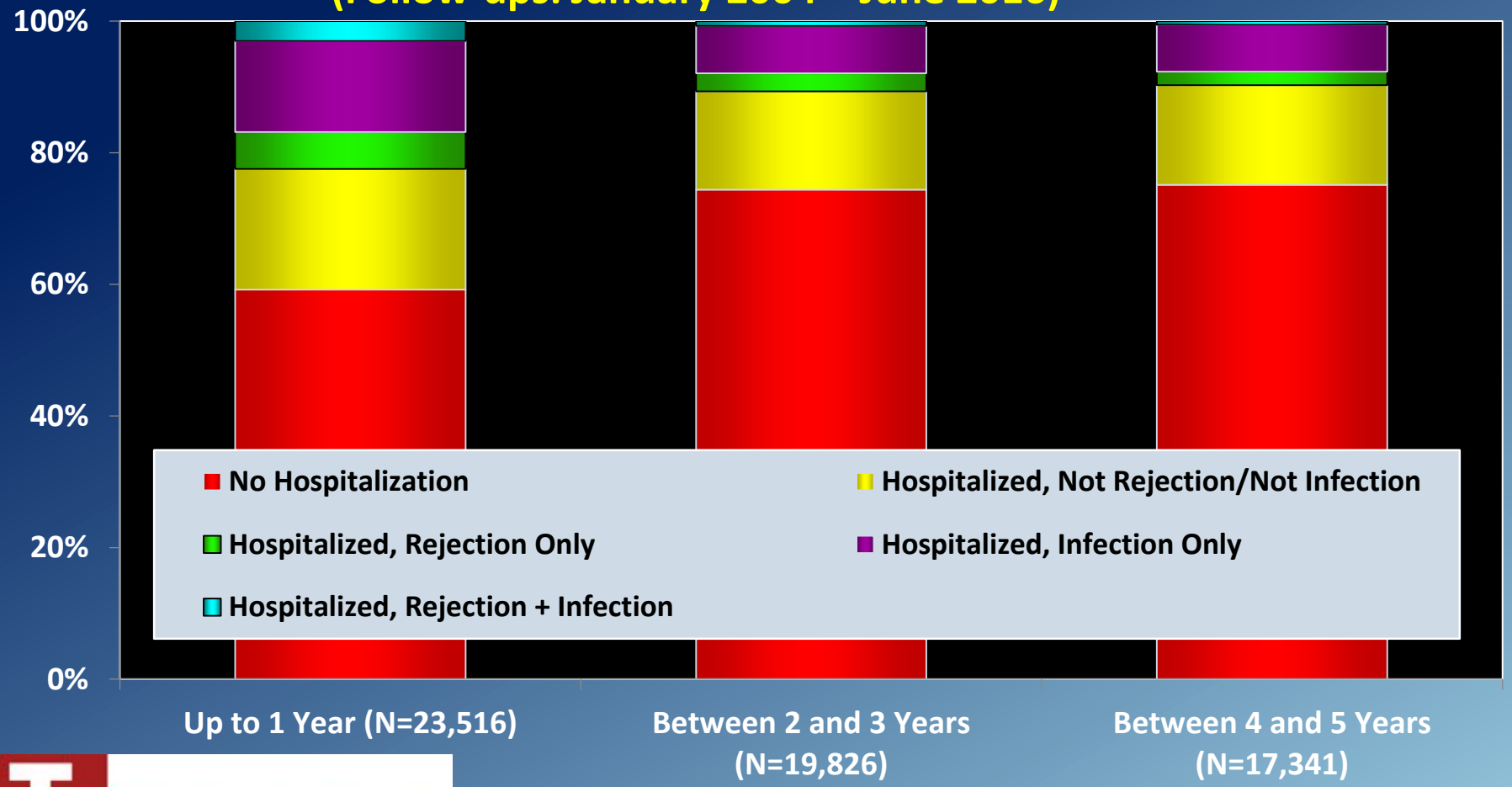
Epidemiology

Adult Heart Transplants

Rehospitalization Post Transplant of Surviving Recipients

(Follow-ups: January 2004 – June 2016)



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Epidemiology

Adult Heart Transplants

Cumulative Morbidity Rates in Survivors

Post Transplant Malignancy (Transplants: January 1994 – June 2015)

Malignancy/Type		1-Year Survivors	5-Year Survivors	10-Year Survivors
No Malignancy		35,644 (94.8%)	19,728 (84.1%)	7,834 (72.3%)
Malignancy (all types combined)		1,945 (5.2%)	3,736 (15.9%)	3,001 (27.7%)
*Malignancy Type**	*Skin*	*639 (1.7%)*	*2,228 (9.5%)*	*1,999 (18.4%)*
	Lymphoma	*198 (0.5%)*	*260 (1.1%)*	*196 (1.8%)*
	Other	*1,067 (2.8%)*	*1,458 (6.2%)*	*1,095 (10.1%)*
	Type Not Reported	*41 (0.1%)*	*37 (0.2%)*	*17 (0.2%)*

"Other" includes: prostate (11, 31, 19), adenocarcinoma (7, 2, 1), lung (6, 5, 1), bladder (2, 3, 0), Kaposi's sarcoma (0, 2, 0), breast (1, 4, 2), cervical (2, 3, 2), colon (2, 4, 3), and renal (2, 6, 1). Numbers in parentheses are those reported within 1 year, 5 years and 10 years, respectively.

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

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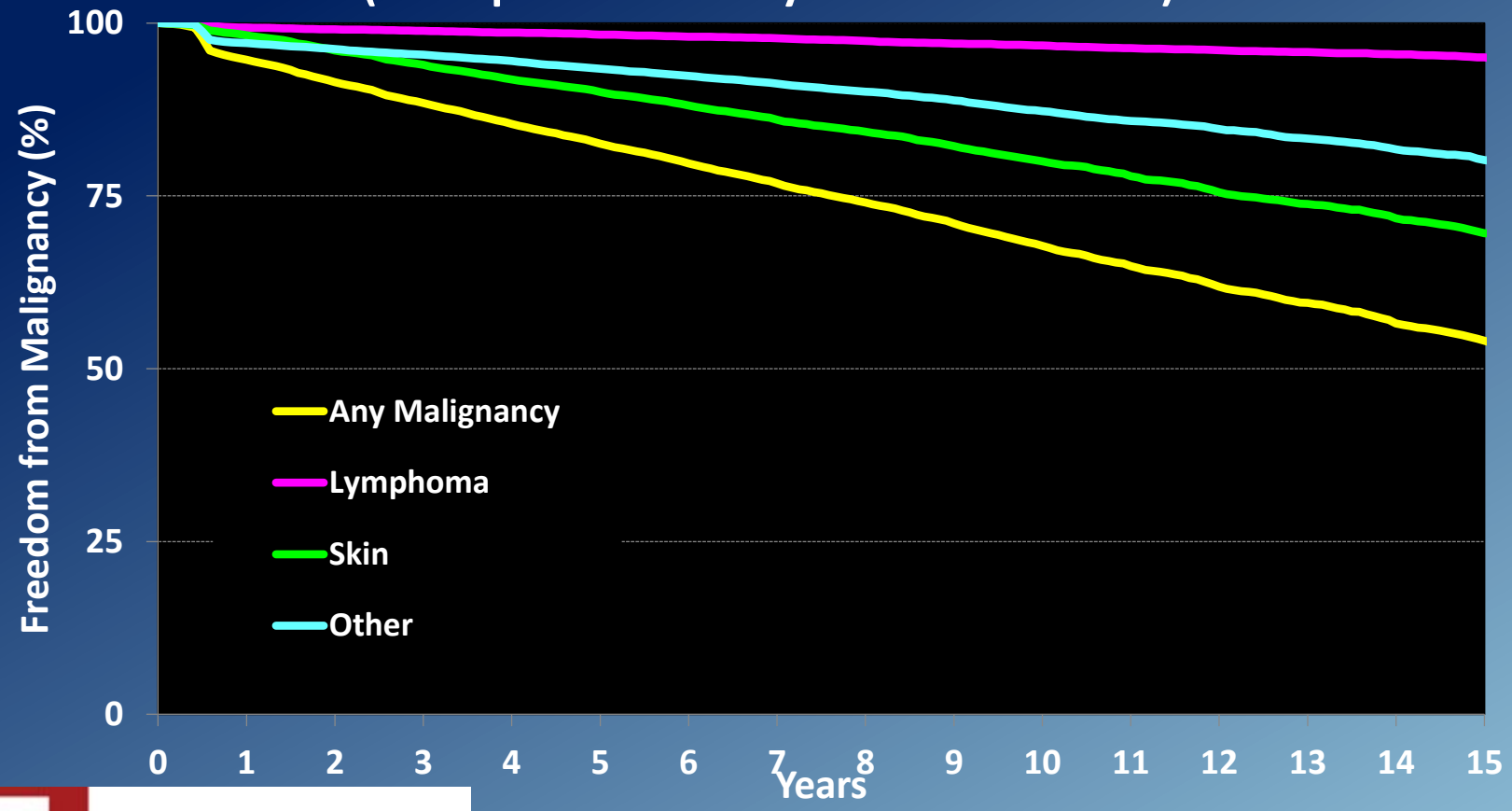
Epidemiology

Adult Heart Transplants
Freedom from Malignancy by Type

(Transplants: January 1994 - June 2015)



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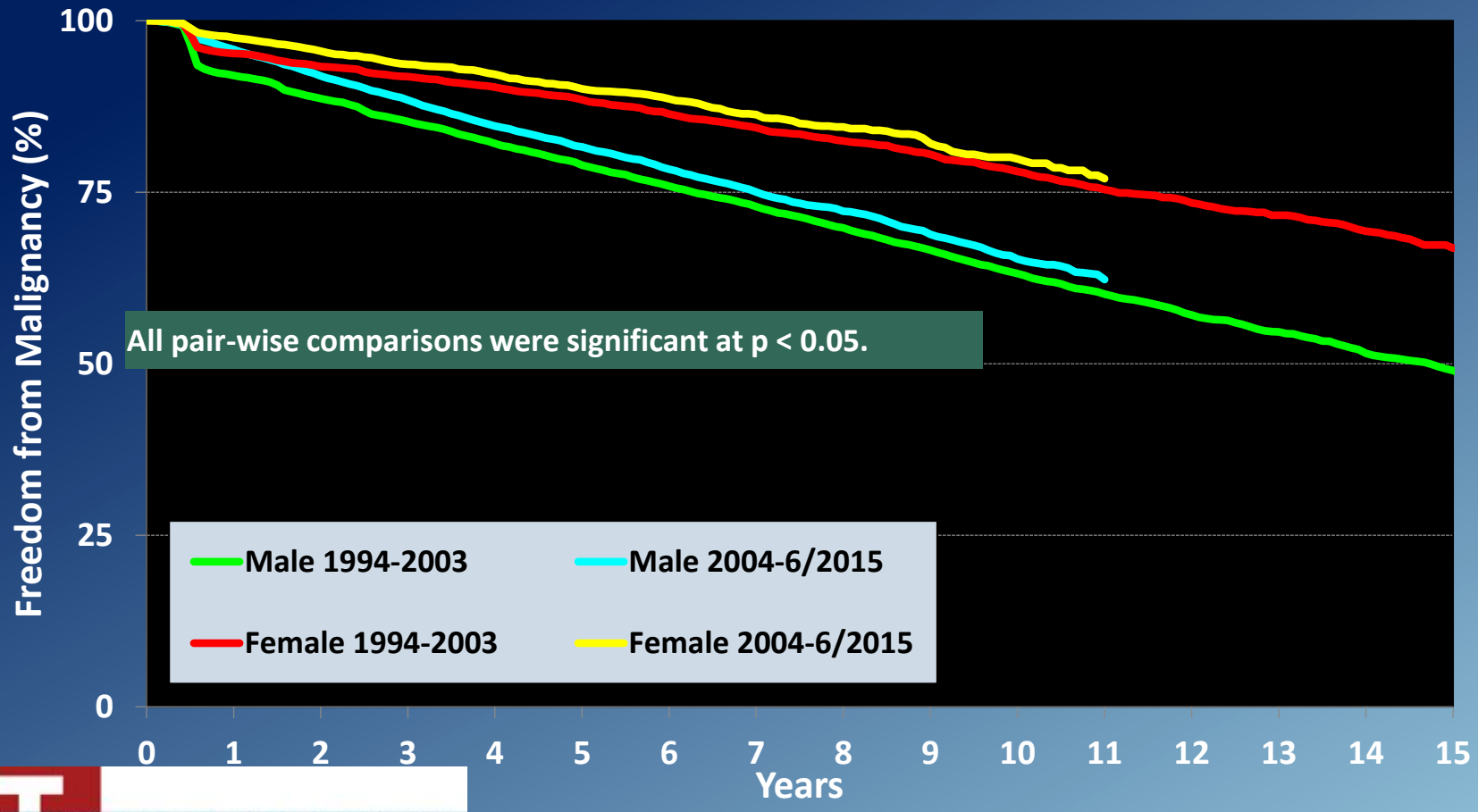
Epidemiology

Adult Heart Transplants

Freedom from Malignancy by Era and Gender

(Transplants: January 1994 – June 2015)



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Epidemiology

Adult Lung Transplants

Cumulative Morbidity Rates in Survivors within 1 Year Post Transplant

(Transplants: January 1994 – June 2015)

Outcome	Transplants: January 1994 – December 2003		Transplants: January 2004 – June 2015	
	Within 1 Year	Total number with known response	Within 1 Year	Total number with known response
Renal Dysfunction	26.2%	(N = 7,108)	21.3%	(N = 14,580)
Abnormal Creatinine ≤ 2.5 mg/dl	*16.8%*		*14.7%*	
Creatinine > 2.5 mg/dl	*7.6%*		*4.3%*	
Chronic Dialysis	*1.9%*		*2.1%*	
Renal Transplant	*0.0%*		*0.1%*	
Diabetes	22.5%	(N = 7,060)	20.4%	(N = 16,843)
Bronchiolitis Obliterans Syndrome	8.7%	(N = 6,602)	9.2%	(N = 15,837)

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Epidemiology

Adult Lung Transplants

Cumulative Post Transplant Malignancy Rates in Survivors

(Transplants: January 1994 – June 2015)

Malignancy/Type		1-Year Survivors	5-Year Survivors	10-Year Survivors
No Malignancy		21,701 (94.8%)	8,073 (80.9%)	2,087 (69.4%)
Malignancy (all types combined)		1,187 (5.2%)	1,905 (19.1%)	921 (30.6%)
*Malignancy Type**	*Skin*	403	1347	692
	Lymphoma	239	146	71
	Other	515	518	245
	Type Not Reported	30	12	1

Other malignancies reported include: adenocarcinoma (2; 2; 1), bladder (2; 2; 1), lung (2; 2; 0), breast (1; 7; 3); prostate (0; 5; 2), cervical (1; 1; 0); and colon (0; 1; 0). Numbers in parentheses represent the number of reported cases within each time period.

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

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Epidemiology

Adult Lung Transplants

Cause of Death

(Deaths: January 1990 – June 2016)

Cause of Death	0-30 Days (N=3,574)	31 Days - 1 Year (N=6,367)	>1 Year - 3 Years (N=6,194)	>3 Years - 5 Years (N=3,656)	>5 Years - 10 Years (N=4,578)	>10 Years (N=1,837)
OB/BOS	10 (0.3%)	292 (4.6%)	1,633 (26.4%)	1,095 (30.0%)	1,146 (25.0%)	407 (22.2%)
Acute Rejection	115 (3.2%)	114 (1.8%)	92 (1.5%)	20 (0.5%)	21 (0.5%)	4 (0.2%)
Lymphoma	1 (0.0%)	137 (2.2%)	107 (1.7%)	54 (1.5%)	83 (1.8%)	56 (3.0%)
Malignancy, Non-Lymphoma	5 (0.1%)	193 (3.0%)	514 (8.3%)	430 (11.8%)	676 (14.8%)	258 (14.0%)
CMV	3 (0.1%)	129 (2.0%)	55 (0.9%)	9 (0.2%)	6 (0.1%)	1 (0.1%)
Infection, Non-CMV	682 (19.1%)	2,213 (34.8%)	1,290 (20.8%)	655 (17.9%)	785 (17.1%)	303 (16.5%)
Graft Failure	870 (24.3%)	1,039 (16.3%)	1,162 (18.8%)	651 (17.8%)	737 (16.1%)	277 (15.1%)
Cardiovascular	429 (12.0%)	345 (5.4%)	275 (4.4%)	173 (4.7%)	267 (5.8%)	120 (6.5%)
Technical	414 (11.6%)	226 (3.5%)	55 (0.9%)	17 (0.5%)	33 (0.7%)	13 (0.7%)
Multiple Organ Failure	440 (12.3%)	766 (12.0%)	319 (5.2%)	151 (4.1%)	213 (4.7%)	98 (5.3%)
Other	605 (16.9%)	913 (14.3%)	692 (11.2%)	401 (11.0%)	611 (13.3%)	300 (16.3%)

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Percentages represent % of deaths in the respective time period.

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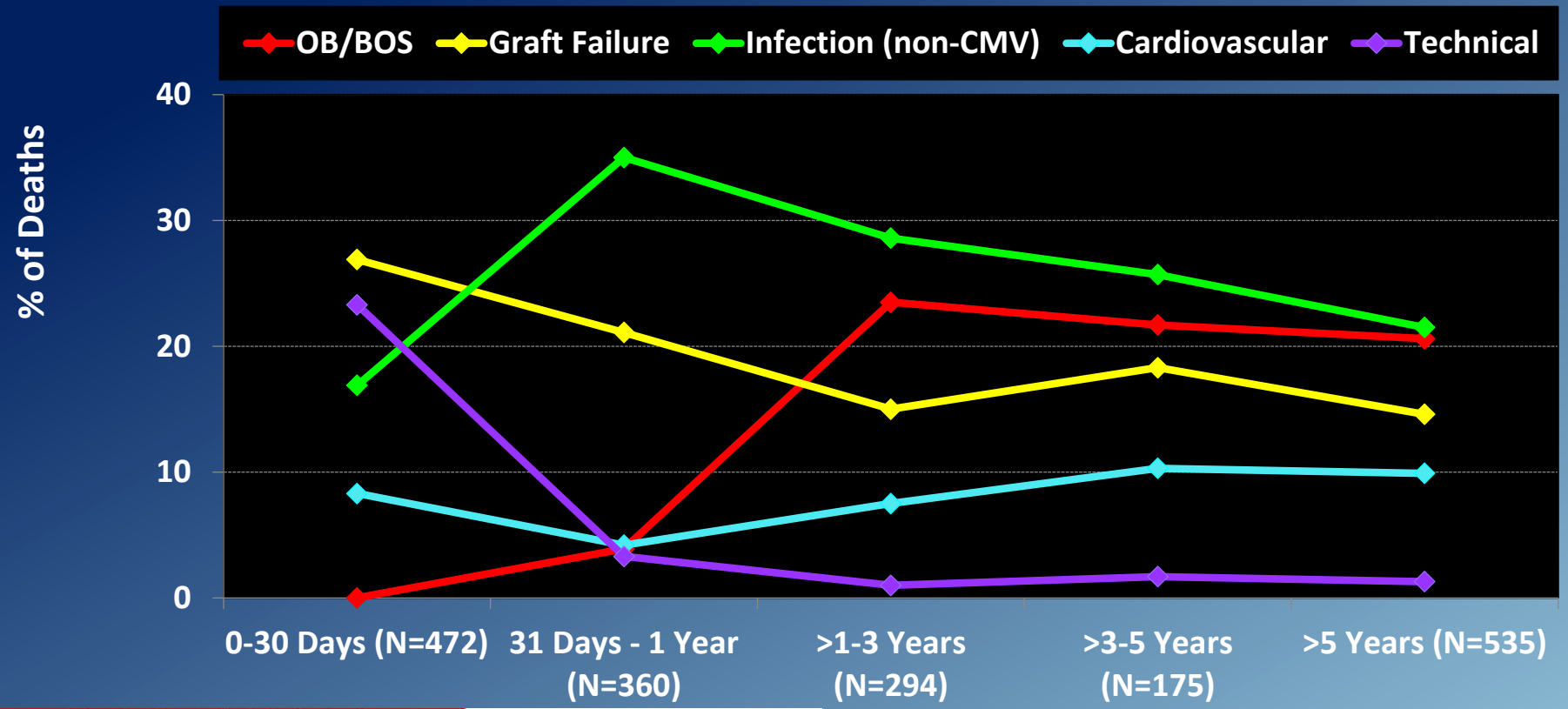
Epidemiology

Adult Heart-Lung Transplants
Relative Incidence of Leading Causes of Death
(Deaths: January 1992 – June 2014)



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Common Issues

Common Issues

- Infection
- Renal failure
- Diabetes
- Vaccination schedules

Common Issues

INFECTION

Common Issues: Infection

- Pneumonia continues to be the biggest issue for thoracic transplant patients
- Bacteremia is also a frequent problem
  - Lower respiratory
  - Urine
  - Intravascular catheters
- Viral infections
  - Herpes
  - CMV
- Fungal infections are always a concern
  - *Aspergillus*
  - *Histoplasmosis, Blastomycosis*
  - *Candida*

Common Issues: Bacterial Infection

- Extremely high risk depending upon if induction therapy use
    - Polyclonal antibody (ATG, RATG, NRATS)
    - Interlukin-2 (IL-2) receptor blockers (basiliximab [Simulect], daclizumab [Zinbryta])
    - Monoclonal Antibody (anti CD52 -alemtuzumab [Campath], anti-CD3-OKT3 [Muromonmab])
- If other than high dose corticosteroid induction used, patient at higher risk for infection for lifetime
- Rejection episodes requiring rescue with medications other than pulse steroids places patient at higher risk for lifetime

Common Issues: Bacterial Infection

- Only macrolide that can be used, and sparingly, is azithromycin
- Increasing trimethoprim-sulfamethoxazole SS or DS (Bactrim) for UTI not recommended as patient is on prophylactic TMP/SMX for toxoplasmosis, *P. jiroveci* (pneumocystis pneumonia), *Listeria monocytogenes*, and nocardia
  - If patient is sulfa allergic, s/he will be maintained on low dose diaminodiphenylsulfone (Dapsone), not recommended to increase for acute infection
- Renal function/creatinine clearance extremely important in deciding what antibiotic to give a patient
- **Drug interaction review prior to prescribing given number of medications**

Common Issues: Viral Infection

- Higher risk if:
  - CMV mismatch
  - EBV mismatch
  - Induction therapy used
  - High dose steroids maintained, or 3-4 drug therapy used for rejection prevention

Common Issues: Viral Infection

- CMV/EBV Mismatch
  - Usually managed at implanting center immediately post-operative for several weeks to months after transplant
  - If does not seroconvert, at risk at any time
  - Routine monitoring for conversion performed at implanting center
- Herpes Simplex/Varicella Zoster
  - Very painful
  - Can reactivate at any time
  - Can reactivate multiple times
  - Acyclovir for Herpes Simplex
  - Valaciclovir for Herpes Zoster

Common Issues: Viral Infection

- Disseminated VZ needs to be hospitalized, and most likely will need to be at implanting center
  - Oral, esophageal
  - Cross mid-line
- Shingles on the head/face that have a blister on the tip of the nose should be immediately referred to an ophthalmologist as eye will be affected, potential for blindness very real!

Common Issues

RENAL

Common Issues: Renal

- Pre-heart transplant, kidneys are usually in a chronically hypoperfused state
- CPB during thoracic organ transplant surgery
- Post-thoracic organ transplant, patients maintained on calcineurin inhibitors

Common Issues: Renal

- When ordering new medications, renal adjustments may be necessary
- High risk for gout
  - Increased prednisone not recommended for flares unless severe
    - Higher risk for rejection when weaning
  - Colchicine appropriate but may need to be renal adjusted and can cause hypovolemia
  - Allopurinol may be required for chronic management
    - Renal adjustment necessary with higher degree CKD
    - Must monitor CBC as can cause pancytopenia, anemia, or neutropenia

Common Issues

DIABETES

Common Issues: Diabetes

- Many patients are diabetic, even if not lifelong, after transplant
- May require multidrug therapy, diet counseling
- As steroid doses decrease, insulin requirements may decrease to only oral agents
  - Many patients remain on medication after discontinuing steroids or steroids at basal rate
- Increased risk for infection, renal complications
- Routine diabetic screening necessary (eyes, feet)

Common Issues

VACCINATION SCHEDULE

Common Issues: Vaccination Schedule

- 1st 6 months after transplant most patients are too immunosuppressed to receive any vaccine, including influenza
  - Unable to mount an antibody reaction to the vaccine
- After 6 months, most vaccine schedules are appropriate as long as the patient is **NOT** receiving **live vaccine** (MMR or Varicella)
- Care must be taken when children living in the home or visiting have their vaccines given as many are live vaccines

Common Issues: Vaccination Schedule[2,3,4,5]

VACCINE	RECOMMENDED AFTER TRANSPLANT	COMMENTS
Hepatitis A or B Virus	Depending upon serostatus	Seronegative adults
Tetanus and diphtheria toxoid	Yes	Booster at least once before or after transplant
Influenza	Yes	≥ 6 months after transplant; annually
Pneumococcal Vaccine (polysaccarhide)	Yes	Repeat once 3-5 years after transplant
Rabies	Yes	Only for exposure, otherwise NO
MMR	NO	
Varicella	NO	Can be given before transplant

Management of Thoracic Transplants in Non-Transplant Centers

Questions???

Many Thanks To:

Management of Thoracic Transplants in Non-Transplant Centers: References

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