THE TORONTO
TRANSPLANT ID
PROGRAM *for infection-free transplantation*

FDA - Inhaled Antifungal Virtual Workshop

Antifungal Prophylaxis and Treatment in Solid Organ Transplant:

Potential End Points of Inhaled Antifungal Administration

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25 – September - 2020

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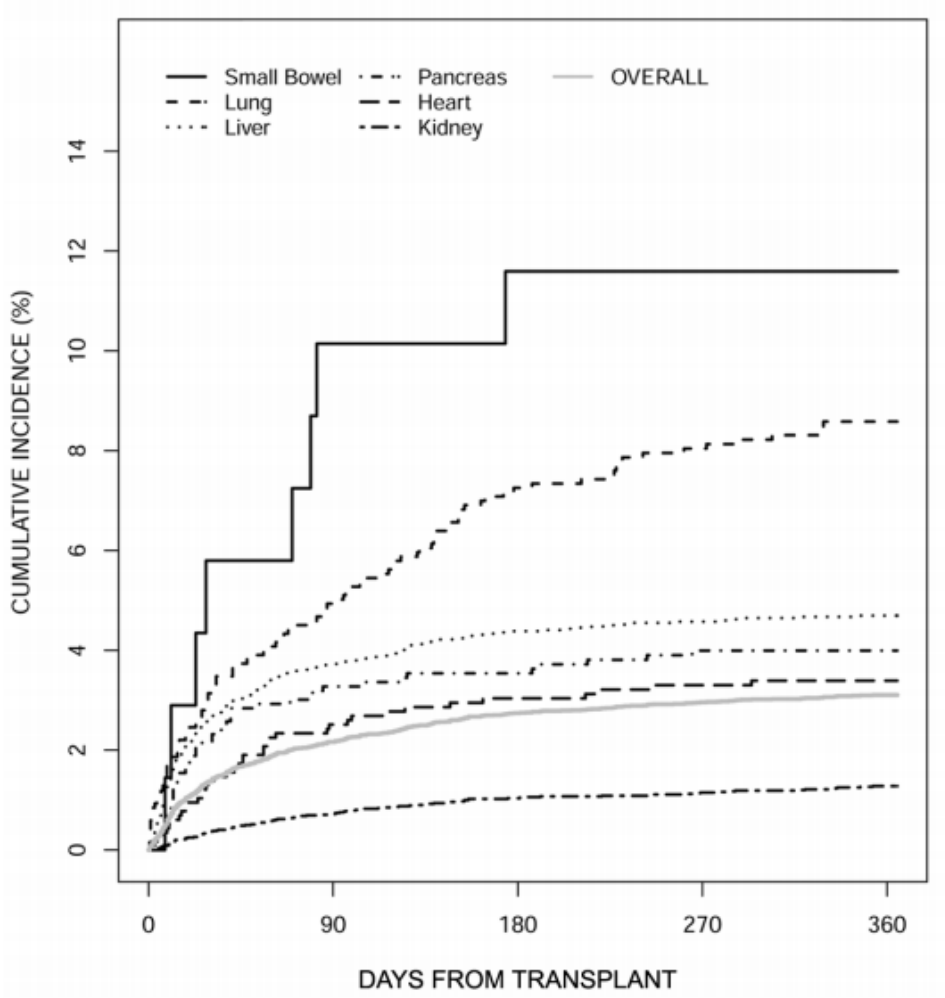
Cumulative Incidence of Invasive Fungal Infection in Solid Organ Transplantation



Pappas P et al. Clin Infect Dis 2010;50(8):1101-11

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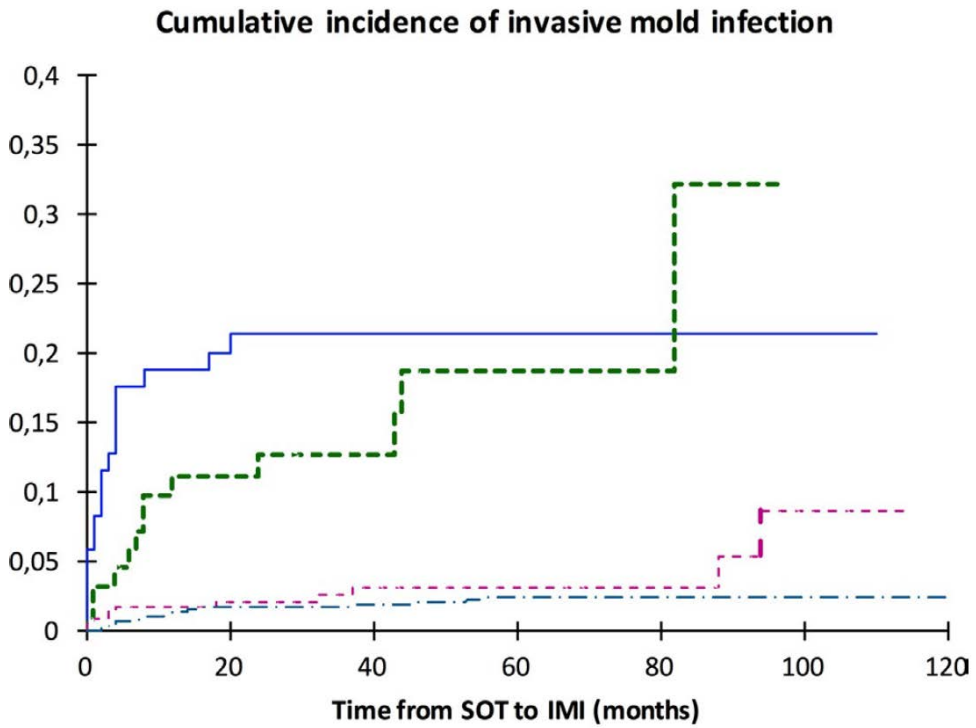
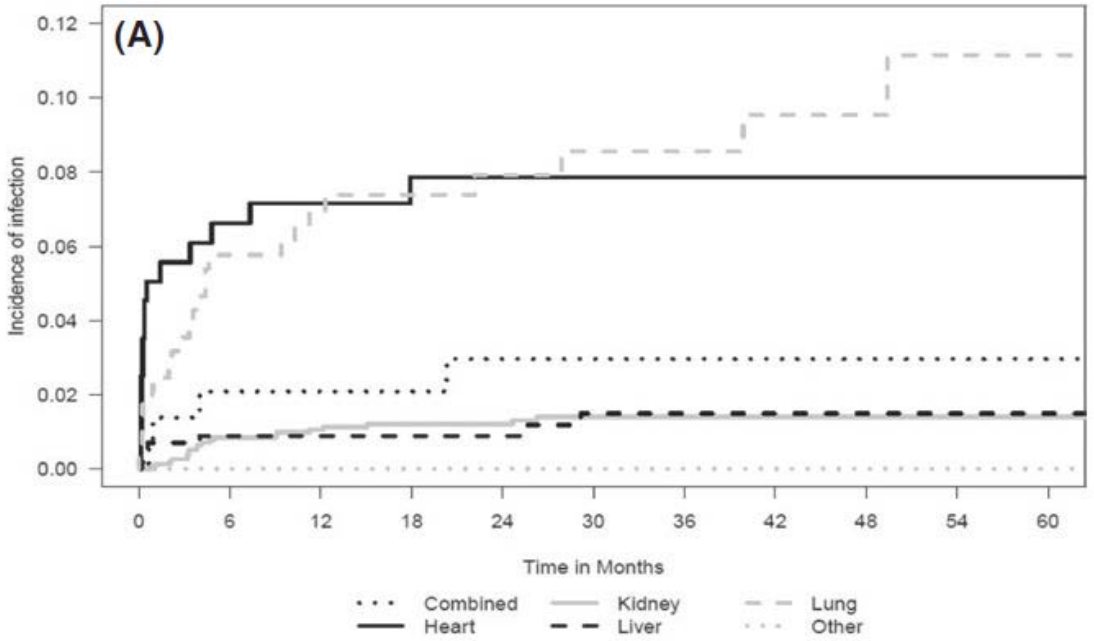
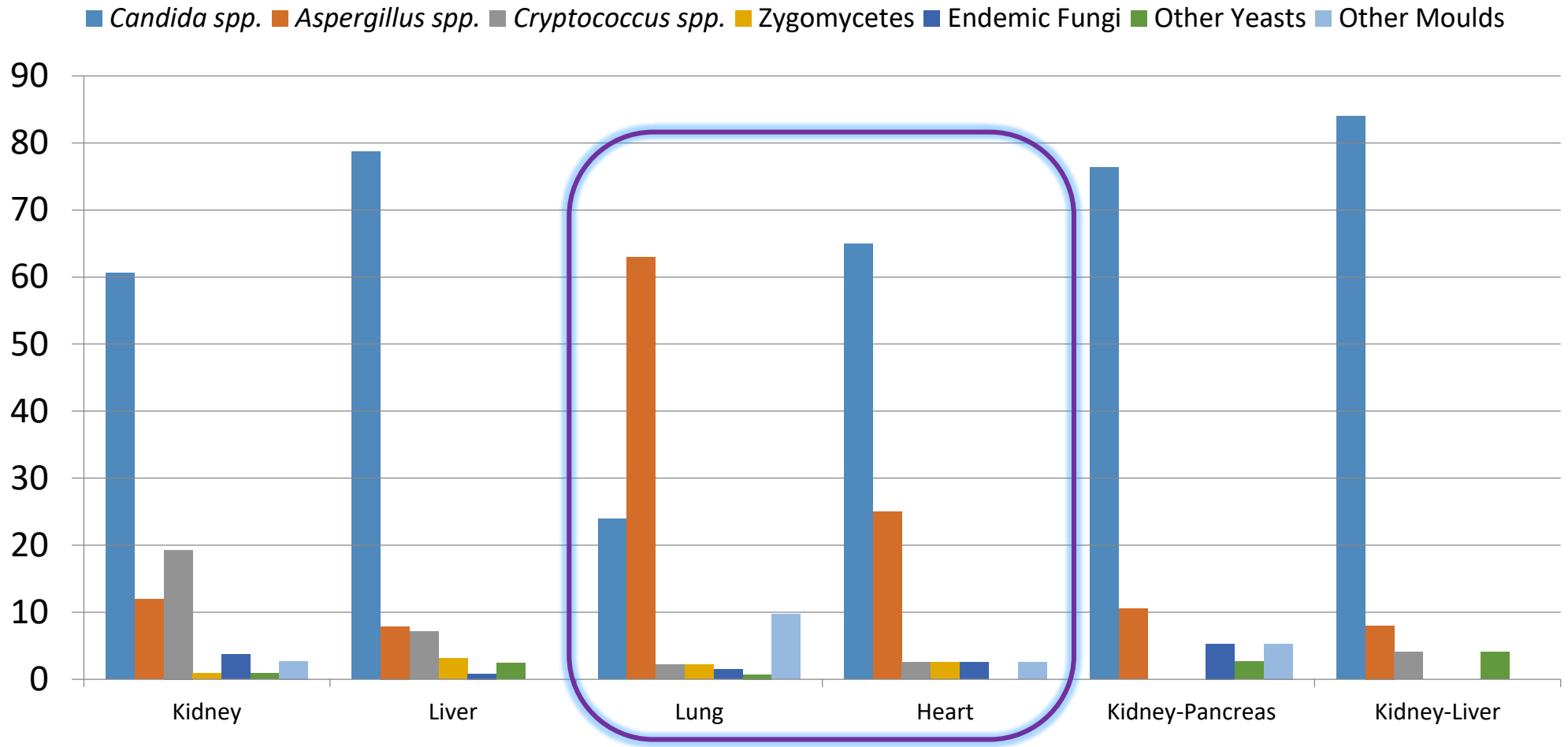
Current Epidemiology





1. Farges C, Cointault O et al, Transpl Infect Dis. 2020;22:e13200.
2. Neofytos D, Chatzis O, et al Transpl Infect Dis. 2018 Aug;20(4):e12898.

Data on Distribution of Invasive Fungal Infection in SOT



IFIs: Invasive Fungal Infections; **SOT:** Solid Organ Transplant

Neofytos D et al. *Transplant Infect* Dis 2010;12(3):220-9.

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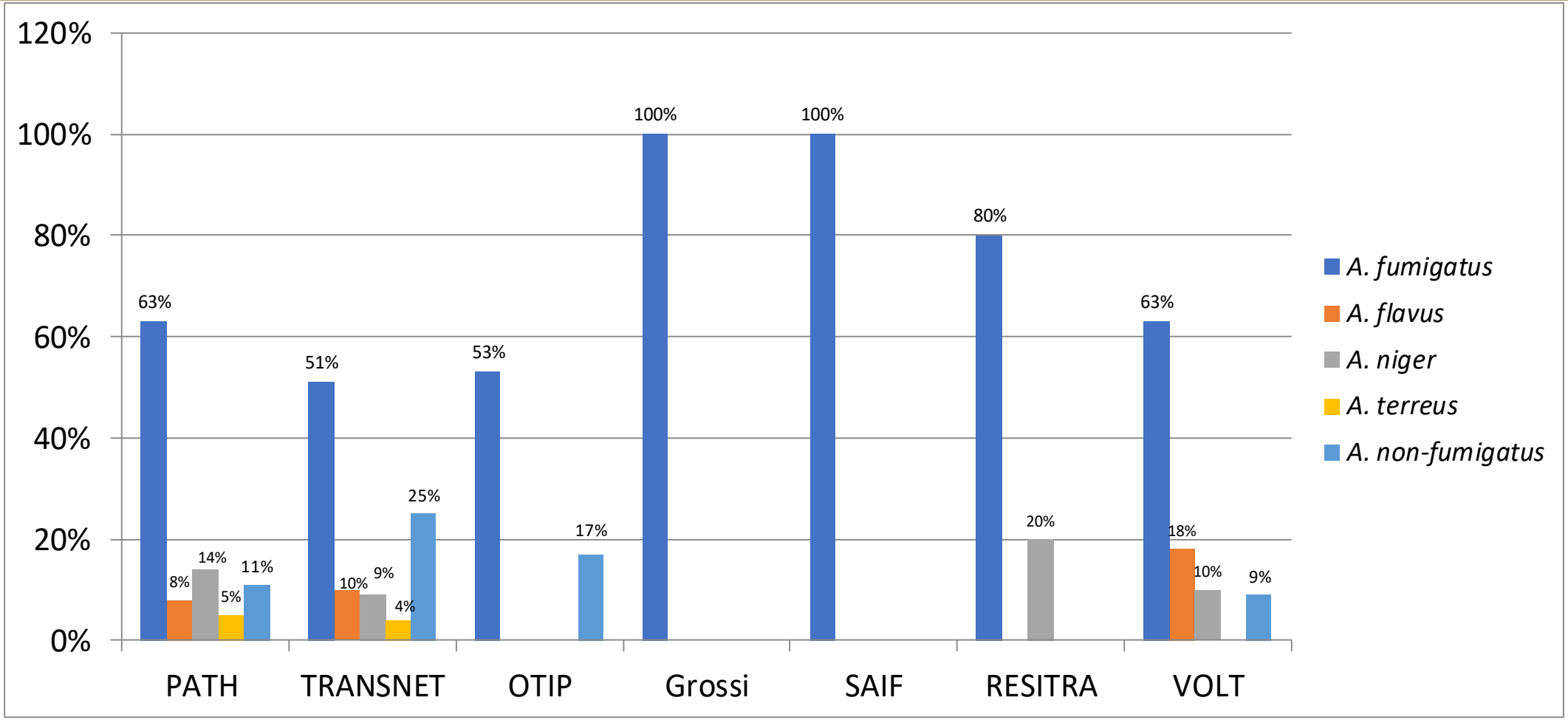
Aspergillus in Lung Transplants



1. Neofytos D. *Transplant Infect Dis* 2010;12:220–9; Pappas PG. *Clin Infect Dis* 2010;50(8):1101-11; Silveira F. Poster #K861 ICAAC 2011; Grossi P.
2. *Transplantation* 2000;70(1):112-6; Lortholary O. *Clin Microbiol Infect* 2011;17(12):1882-9; Aguilar-Guisado M. *Am J Transplant* 2007;7(8):1989-96.
3. C.A. Aguilar, Journal of Heart and Lung Transplantation (2018), doi: 10.1016/j.healun.2018.06.008

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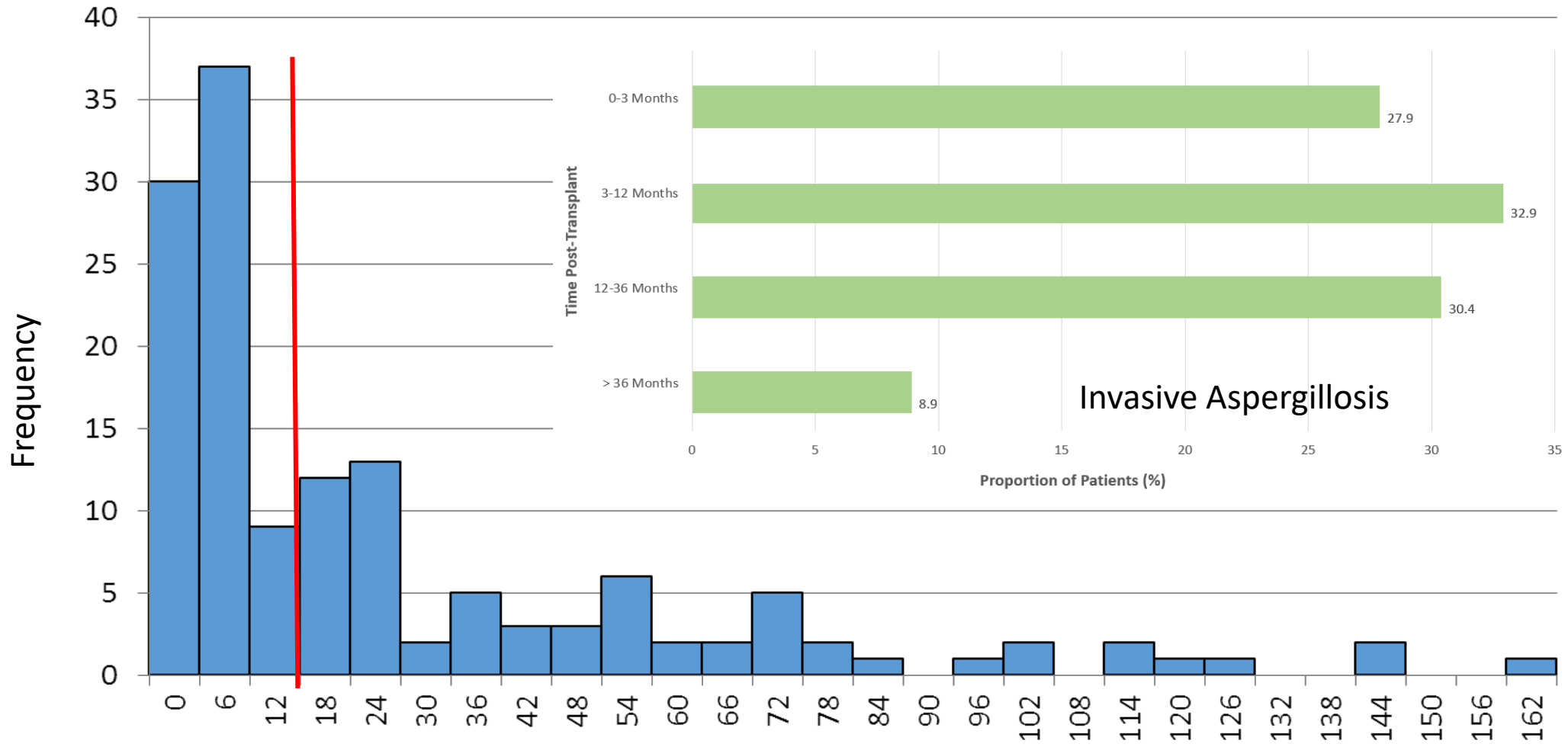
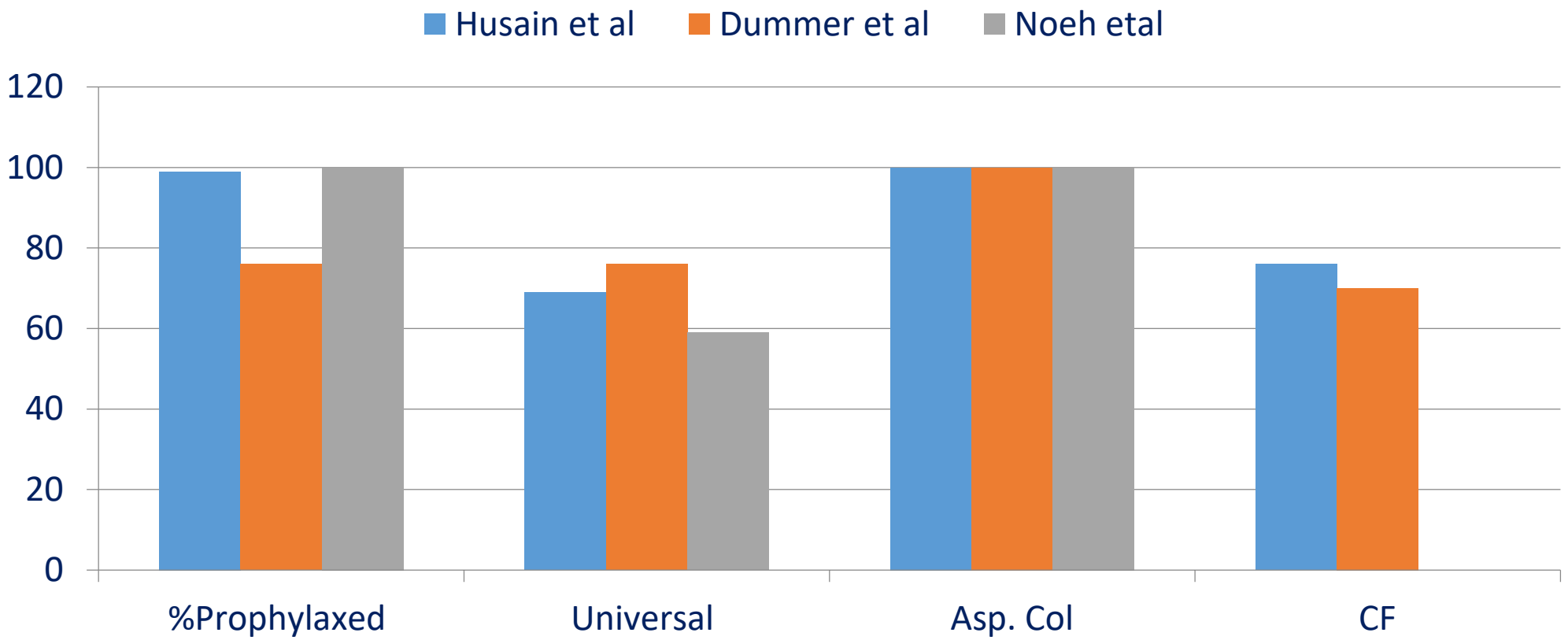
Time to Onset of Mold Infections in Lung Transplant



C.A. Aguilar, Journal of Heart and Lung Transplantation (2018), 37:10: 1226-1234
Doligalski CT et al. *Am J Transplant* 2014;14:1328–33.

Lay of the Land : Antifungal Prophylaxis in Lung Transplant



1. Neoh CF. Am J Transplant. 2011 Feb;11(2):361-6
2. Husain S .Transpl Infect Dis. 2006 Dec;8(4):213-8
3. Dummer JS .J Heart Lung Transplant. 2004 Dec;23(12):1376-81

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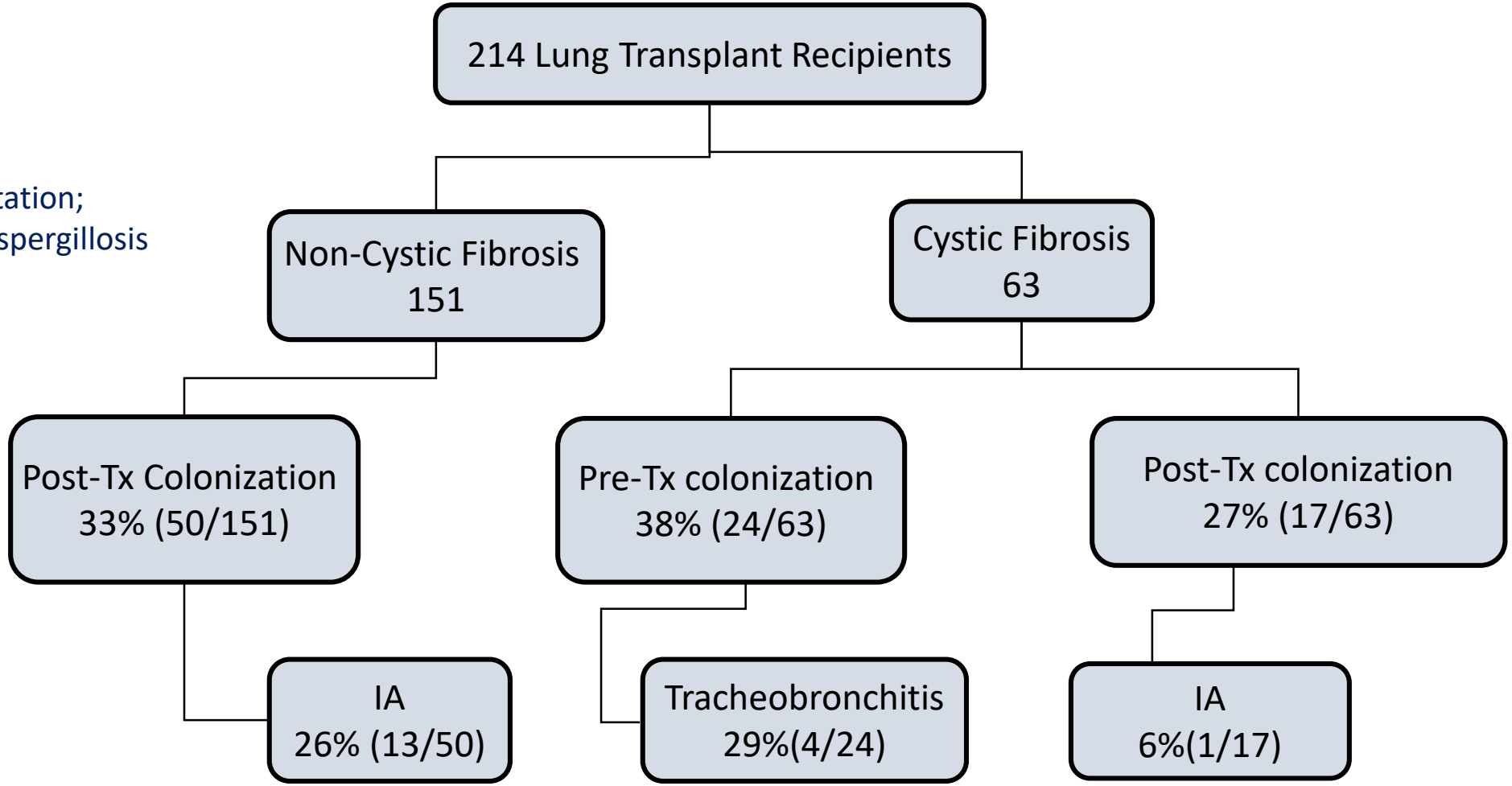
Colonization of *Aspergillus*

Tx: Transplantation;
IA: Invasive Aspergillosis



Helmi M. *Chest* 2003;123:800–8; Nunley. *Chest* 1998;114:1321–9.

Results: Risk Factors in Multivariate Analysis of 855 Lung Transplant Recipients

	HR (95% CI)	P-value
Single Lung Transplant	1.84 (1.09-3.10)	0.022
Acute Rejection, number of episodes		
1 – 2	0.95 (0.57-1.57)	0.83
3 – 4	0.90 (0.42-1.93)	0.792
> 4	1.94 (0.90-4.20)	0.092
CMV Infection	1.65 (0.99-2.76)	0.055
Aspergillus sp. colonization at 1 year	2.11 (1.28-3.49)	0.003
Antifungal Prophylaxis	0.86 (0.54-1.39)	0.544

Cystic Fibrosis was not associated with higher risk of IA

C.A. Aguilar, Journal of Heart and Lung Transplantation (2018), 37:10: 1226-1234

Uni- and Multivariate Models for Associations Between Risk Factors and Development of IA

	Univariate Cox model		Multivariate Cox model	
Risk factor	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Aspergillus culture positive only (yes vs no)	5.22 (2.94 to 9.29)	<0.001	11.46 (5.86 to 22.43)	<0.001
GM positive only (yes vs no)	8.92 (4.16 to 19.12)	<0.001	21.86 (9.32 to 51.27)	<0.001
Underlying disease: cystic fibrosis vs COPD	1.41 (0.56 to 3.55)	0.47	0.93 (0.35 to 2.47)	0.88
Pre-emptive therapy (received vs not received)	1.04 (0.46 to 2.32)	0.93	0.23 (0.09 to 0.58)	0.002
Pre-transplant *Aspergillus* culture positive (yes vs no)	1.95 (0.97 to 3.92)	0.06	2.21 (1.01 to 4.83)	0.05
CMV mismatch (D^+/R^- vs non-D^+/R^-)	1.69 (0.91 to 3.12)	0.10	1.29 (0.68 to 2.46)	0.44
Biopsy-proven rejection (yes vs no)	2.00 (1.04 to 3.83)	0.04	1.80 (0.94 to 3.47)	0.08

Total number of patients = 519; total number of invasive aspergillosis (IA) cases = 47. CI, confidence interval; COPD, chronic obstructive pulmonary disease; D, donor; GM, galactomannan; HR, hazard ratio; IA, invasive aspergillosis; R, recipient.

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Ref. Husain S, The Journal of Heart and Lung Transplantation, Vol 37, No 7, July 2018 | pg. 886-893

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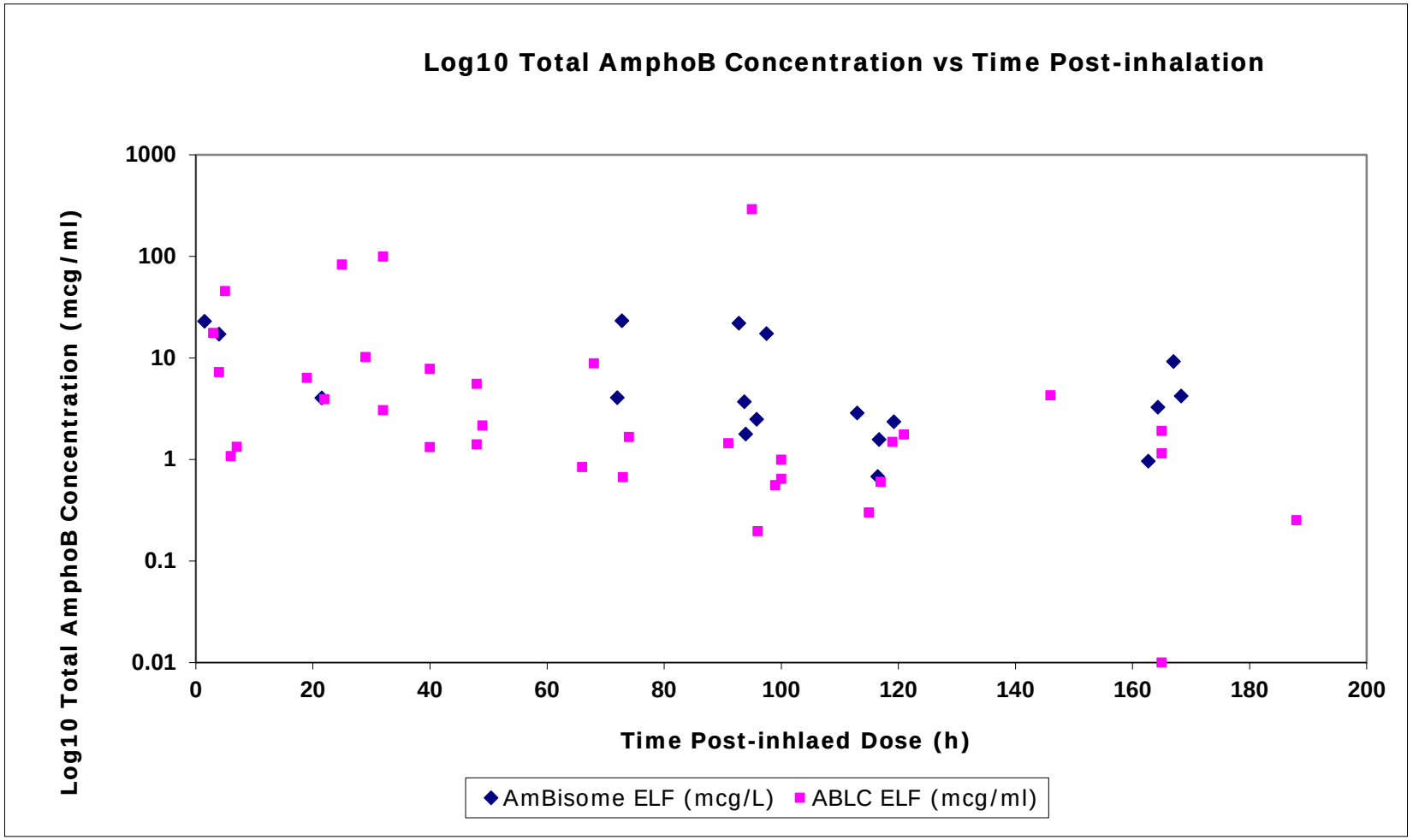
Other Consequences of Colonization

- Pre-BOS colonization with small conidia *Aspergillus* species, but not large, was a risk factor for BOS (p = 0.002, HR 1.44, 95% CI 1.14–1.82)
- Colonization with small conidia species also associated with risk of death (p = 0.03, HR 1.30, 95% CI 1.03–1.64)
- Not associated with CLAD[2]
    - No differentiation between small and large conidia

1. Weigt SS American Journal of Transplantation 2013; 13: 919–927
2. Peghin M Transplant IntlVolume 29, issue 1,January 2016 :51-62

Epithelial Lining Fluid Concentrations of Liposomal and Lipid Complex Amphotericin B



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Capitano B, FOCUS 2007.Poster#82
Husain S, Transplantation 2010 Dec 15;90(11):1215-9

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Reports of Prophylaxis with Inhaled Amphotericin in Lung Transplants

Author	Year	No. of Pts	Type of AMB	Duration	Efficacy
Calvo V	1999	65	AMB d	120 days	100%
Reichenspurner H	1999	127 AMBd 101 placebo	AMB d	During hospital stay	92% 80%
Monforte V	2001	72	AMB d	42 days	75%
Drew RH	2004	49 AMBd 51 ABLC	AMB d ABLC	7 weeks	86% 88%
Peghin M	2016	412	Liposomal AMB	Life long	94.7%
Baker AW * +/- Systemic antifungals	2020	815	ABLC	During Hospital stay	80.9% 11.4% candida

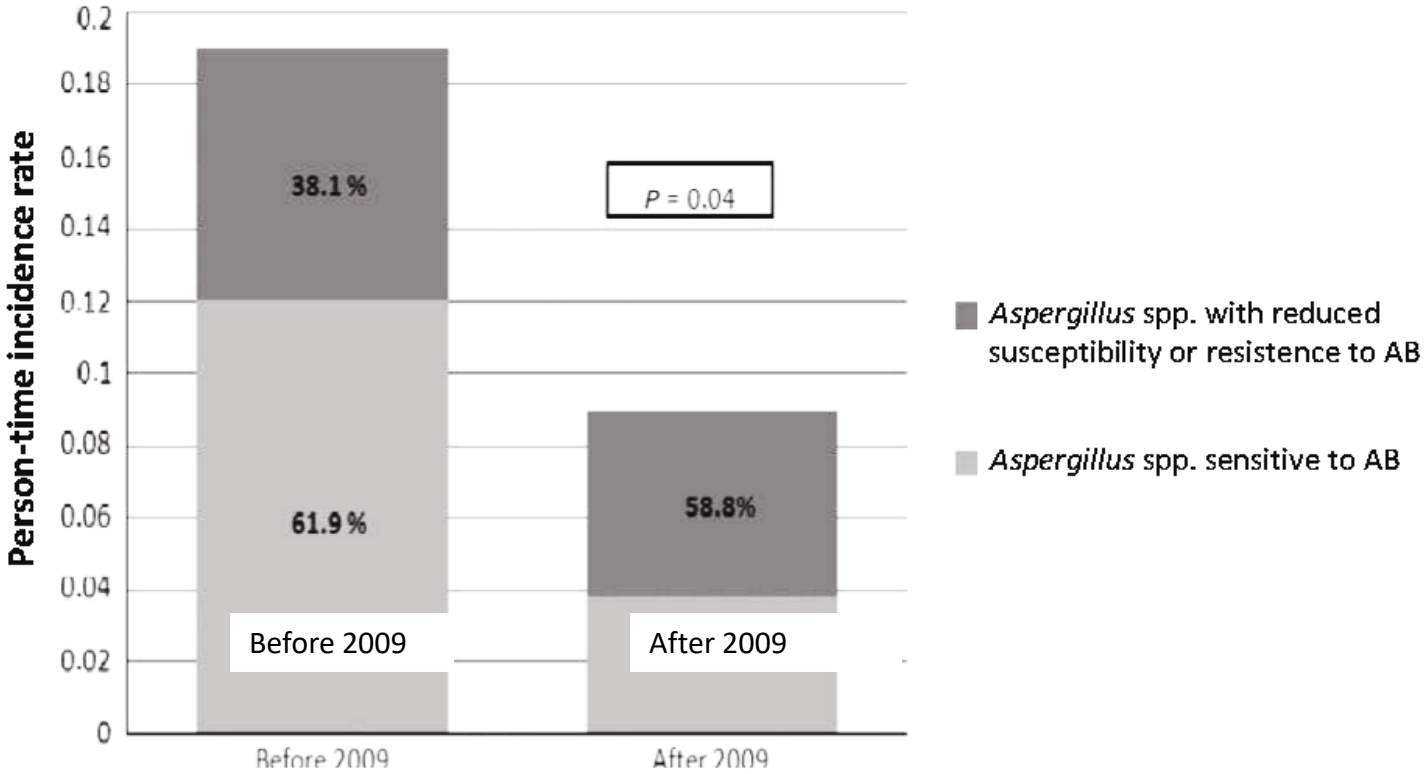
1. Monforte V et al. J Heart Lung Transplant 2001;20:1274-1281
2. Calvo V Chest. 1999 May;115(5):1301-4.doi:10.1378/chest.115.5.1301.
3. Reichenspurner H et el. Transplant Proc 1997;29:627-628
4. S M Palmer, R H Drew et al. Transplantation.2001 Aug 15;72(3):545-8.
5. Baker AW Clinical Infectious Diseases® 2020;70(1):30–9

Comparative Side Effect Profile of Inhaled Amphotericin Preparations

Adverse Event	Liposomal AMB (n=118)	Lipid Complex AMB (n=51)	Amphotericin B (n=49)
Wheezing	5/118 (4%)	2/48 (4.2%)	3/47(6.4%)
Cough	12 (10%)	1/47 (2.1%)	5/47 (10.6%)
Shortness of Breath	NR	1/47 (2.1%)	9/47 (19.9)
Nausea	8/118(7%)	1/47 (2.1%)	4/47 (8.5%)
Decline in FEV1	None	5/45 (11.1%)	5/47 (10.6%)
Decline in FVC	None	5/45 (11.1%)	5/47 (10.6%)
More than one adverse event	NR	14/51 (27.5%)	21/49(42.9%)
Discontinuation due to intolerance	3/118(2.5%)	3/51(5.9%)	6/49 (12.2%)

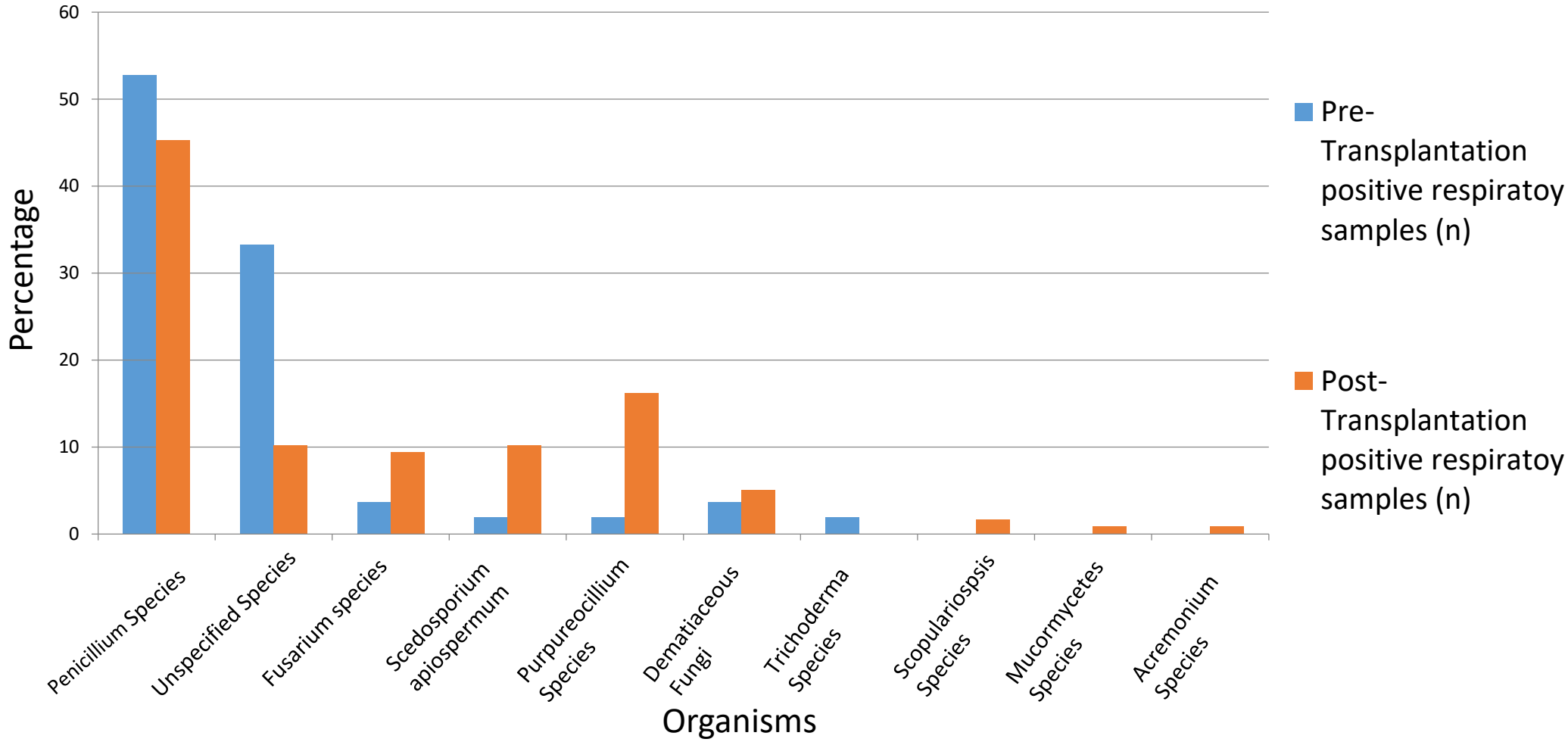
Roman A 2005, Drew RH Transpl 2004

Evolution of *Aspergillus* spp. Infection and Colonization



Peghin M *Transpl Int.* 2016 Jan;29(1):51-62.

Emergence of Resistance: non-*Aspergillus* Molds



- Pre-transplantation non-aspergillus molds isolated in 55 different respiratory samples from 49 lung transplant recipients
- Post-transplantation non-aspergillus species molds isolated in 117 different respiratory samples from 70 lung transplant recipients

Peghin M et al., *Transplant Infect Dis*. 2016 Feb;18(1):70-8.

Some Definitions Regarding Colonization

- **Eradication of fungal colonization**
  - Was defined by negative fungal culture of respiratory specimens (e.g. a single negative culture from BAL or 2 negative sputum cultures) at the end-points.
- **Recurrent colonization**
  - Was defined as the isolation of the same fungal species repeatedly during the follow-up period, with the recurrent isolation occurring at least 1 month after completion of the first course of prophylaxis.
- **New colonization**
  - Was defined as colonization by a different fungal species from the baseline colonization during the follow-up period, occurring at least 1 month after completion of the first course of prophylaxis.
- **Persistent colonization**
  - Was defined as ongoing isolation of the same fungal species as that identified at baseline despite prophylaxis.

Neoh, C. F. Transplant Infectious Disease, 15(4), 344–353. doi:10.1111/tid.12071

What is Different for Mold Infection in SOT

- **Risk period is longer**
  - Until a year in lung transplantation
  - 3 months in heart transplantation
- **Unique clinical presentation**
  - Mold colonization, tracheobronchitis, bronchial anastomotic infections (BAI)
- **Clinical risk factors for mold are not well defined**
  - Lack of robust data in Heart Transplant
- **Differential characteristics of biomarkers**
  - Lack of sensitivity of serum Galactomannan, higher false positivity with BAL
- **Long term safety of inhaled drugs are not known. Concerns related to graft**
  - Lung transplantation

Universal Prophylaxis in Lung Transplantation

- **Recommended duration first 4-6 months post transplantation**
- **Primary End Points**
  - Proportion of patients with probable or proven fungal infection (Tracheobronchitis , bronchial anastomosis infection , Pulmonary or systemic fungal infection) at 6 months post transplant
  - Proportion of patients with mold colonization at 6 months post transplant
- **Secondary End Points (Safety)**
  - Rate of prevalence of side effects during therapy or within 30 days of cessation:
    - Headache
    - Dizziness and fatigue
    - Fever
    - Nausea
    - Vomiting
    - Wheezing
    - Cough
    - Shortness of Breath
    - Taste preservation
    - Decline in FEV1
    - Decline in FVC
    - Elevation of serum creatinine>50% of baseline elevation of liver enzymes (≥ 3 times)
    - Neutropenia (absolute neutrophil count ≤ 1000) during the treatment
  - Pulmonary Function Test at baseline (2 weeks), 3, 6, 9, 12 months
  - Tolerance – need to discontinue for side-effects

Universal Prophylaxis in Lung Transplantation (Cont'd)

- **Secondary End Points (Efficacy)**
  - Proportion of patients with probable or proven fungal infection (Tracheobronchitis , bronchial anastomosis infection , Pulmonary or systemic fungal infection) at 1 year post transplant
  - Proportion of patients with mold colonization at 1 year post transplant.
  - Rate of breakthrough fungal infection during prophylaxis (at least one week into treatment or in a week post cessation of therapy)
  - Quality of Life at the baseline 3, 6, 9, 12 months post transplant
  - Time to development of mold colonization, tracheobronchitis/bronchial anastomotic infection, or invasive pulmonary infection at 1 year post transplant.
  - Mortality – all-cause and fungal infection-related mortality (all types) at 1 year post transplant
  - Use of empiric antifungals at 1 year post transplant
  - Time to diagnosis of CLAD
  - *Aspergillus* resistance rates and rates of resistant organisms – e.g. *L. prolificans*

Pre-emptive Therapy in Lung Transplantation

- Directed by positive BAL GM (>1.0) or *Aspergillus* culture/PCR in BAL without radiological or bronchoscopic evidence of disease during first year of transplantation
- Recommended duration 3-4 months
- **Primary End Points**
  - Negative BAL for GM or Aspergillus culture/PCR at the end of therapy
  - Proportion of patients with mold colonization,probable or proven fungal infection (Tracheobronchitis, bronchial anastomosis infection, pulmonary or systemic fungal infection) at 6 months post cessation of therapy
- **Secondary End Points (Safety)**
  - Rate of prevalence of side effects during therapy or within 30 days of cessation
    - Headache
    - Dizziness and fatigue
    - Fever
    - Nausea
    - Vomiting
    - Wheezing
    - Cough
    - Shortness of Breath
    - Taste preservation
    - Decline in FEV1
    - Decline in FVC
    - Elevation of serum creatinine>50% of baseline elevation of liver enzymes (≥ 3 times)
    - Neutropenia (absolute neutrophil count ≤ 1000) during the treatment.
  - Pulmonary function Test at baseline, 3, 6, 9, 12 months
  - Tolerance – need to discontinue for side-effects

Pre-emptive Therapy in Lung Transplantation (Cont'd)

- **Secondary End Points (Efficacy)**
  - Proportion of patients with fungal infection (mold colonization, probable or proven Tracheobronchitis, bronchial anastomosis infection, pulmonary or systemic fungal infection at 1 year post transplant *
  - Rate of breakthrough fungal infection during treatment (at least one week into treatment or in a week post cessation of therapy)
  - QOL at the baseline, 3, 6, 9, 12 months post transplant
  - Time to development of colonization(non candida), probable or proven tracheobronchitis/bronchial anastomotic infection, or invasive pulmonary infection at
  - Mortality – all-cause and fungal infection-related mortality (all types) at 1 year post transplant
  - Use of empiric antifungals at 1 year post transplant
  - Time to diagnosis of CLAD
  - *Aspergillus* resistance rates and rates of resistant organisms – e.g. *L. prolificans*

*In cases of comparison between two preemptive arms outcome should be 1 year post initiation of therapy

Heart Transplantation

- No need for routine prophylaxis
- May Consider prophylaxis
  - Episode of IA in the heart transplant program
  - Isolation of Aspergillus in the BAL of heart transplant

Heart Transplant Prophylaxis

- Prophylaxis in the setting of outbreak in the program
- Recommended duration 6 weeks - 3 months
- **Primary End Points**
  - Negative BAL GM or *Aspergillus* culture/ PCR four weeks post cessation of therapy
  - Proportion of patients with probable or proven fungal infection (Pulmonary or systemic fungal infection) at 3 months post cessation of therapy
- **Secondary End Points (Safety)**
  - Rate of prevalence of side effects during therapy or within 30 days of cessation
    - Headache
    - dizziness and fatigue
    - Fever
    - Wheezing
    - Cough
    - Shortness of Breath
    - Taste preservation
    - Nausea
    - Vomiting
    - Decline in FEV1
    - Decline in FVC
    - elevation of serum creatinine>50% of baseline elevation of liver enzymes (≥ 3 times)
    - neutropenia (absolute neutrophil count ≤ 1000) during the treatment
  - Pulmonary Function Test at baseline weeks 2, 4, 6 and 12 wks.
  - Tolerance – need to discontinue for side-effects

Heart Transplant Prophylaxis
(Cont'd)

- **Secondary End Points (Efficacy)**
  - Proportion of patients with probable or proven fungal infection (Pulmonary or systemic fungal infection) at 6 months post cessation
  - Rate of breakthrough fungal infection during treatment (at least one week into treatment or within 7 days post cessation)
  - QOL at the baseline, 3, 12 months
  - Time to development of probable or proven invasive pulmonary infection at 1 year post transplant
  - Mortality – all-cause and fungal infection-related mortality (all types) at 1 year post transplant
  - Use of empiric anti mold antifungals at 1 year post transplant

Treatment of IFI with Inhaled Antifungal

- Not recommended with nebulized drugs ALONE due to the lack of existing data and possible systemic fungal disease
- Potential clinical syndromes it can be used in include
  - Tracheobronchitis
  - Bronchial anastomotic infection
- **Endpoints**
  - Microbiological cure at the end of therapy {*Aspergillus* culture/PCR or GM negative}
  - Normal looking airways or a bronchial anastomosis during bronchoscopy at the end of therapy
  - Used inhaled antifungals in conjunction with systemic antifungals


THANK YOU!
Contact: shahid.husain@uhn.ca