Antifungal Prophylaxis after T-lymphocyte Depletion in Lung Transplant Patients at Vancouver General Hospital

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Background

- Lung transplant recipients are at high risk of developing invasive fungal infections (IFIs). Risk factors include:[1,2]
  - airway ischemia
  - pre/post-transplant airway colonization with Aspergillus
  - increased donor age
  - single lung transplant
  - CMV infection
  - augmented immunosuppression within last 3 months
- Annual incidence of IFIs is 8.6% despite antifungal prophylaxis[2]
- Most common pathogens for IFIs in lung transplant patients are Aspergillus (44%) and Candida (23%)[2]
- Guidelines recommend consideration of antifungal prophylaxis in patients receiving t-lymphocyte depletion

Objectives

- Describe prescribing patterns and costs associated with antifungal prophylaxis in lung transplant patients receiving T-lymphocyte depleting therapy at VGH
- Describe efficacy and safety outcomes of mold active antifungal prophylaxis in this patient population

Methods

- **Design:** Retrospective chart review of inpatient and outpatient data
- Study period: September 1, 2012 – September 30, 2019
- **Follow-up period**: 1 year*
- **Inclusion criteria**:
  - Patients followed by VGH Lung Transplant Clinic
  - Receipt of rATG or alemtuzumab
- There are no exclusion criteria
- **Analysis:** Descriptive statistics

* Incidence of SCC followed until present day or death

Results

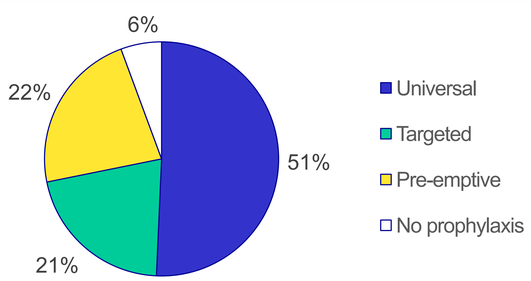


Figure 1: Antifungal Prophylaxis

Results

Table 1 : Baseline Characteristics at Time of Transplant

	All Transplant Patients (N=59) No. (%)
Age at time of transplant (median), IQR	56.8 (46.2-61.5)
Female	32 (56.1)
Weight (kg)	68.6
Double lung transplant	52 (88.1)
Single lung transplant	7 (11.9)
Pre-transplant Aspergillus colonization	6 (10.2)
Post-transplant Aspergillus colonization	8 (13.6)
CMV recipient IgG (+)	40 (67.8)
EBV recipient IgG (+)	53 (89.8)
EBV IgG mismatch R(-)/D(+)	3 (5.1)
T-lymphocyte Depletion	
Induction	25 (42.4)
Augmentation	34 (57.6)
Single course	51 (86.4)
rATG	50 (98)
alemtuzumab	1 (2)
Multiple courses	8 (13.6)
rATG	3 (37.5)
rATG followed by alemtuzumab	5 (62.5)
Total no. of courses	71

Table 2: Antifungal Prophylaxis Prescribing Trends

	Initial Course of T-lymphocyte Depleting Therapy (N=59) No. (%)	Subsequent Courses of T-lymphocyte Depleting Therapy (N=12) No. (%)
Antifungal Prophylaxis Received	55 (93.2)	12 (100)
Initial Antifungal Therapy		
Voriconazole	43 (78.2)	7 (58.3)
Posaconazole	6 (10.9)	2 (16.7)
Amphotericin B	6 (10.9)	3 (25)
Daily Dose (mg), median (IQR)		
Voriconazole	400 (400-600)	400 (400-500)
Posaconazole DR (range)	300 (300-400)	300
Posaconazole susp. (range)	800 (800-1000)	N/A
Amphotericin B	30 (30-50)	26.78 (3.57-50)
Subtherapeutic Trough Level		
Voriconazole	6 (14)	0
Posaconazole DR	1 (33.3)	0
Posaconazole suspension	1 (33.3)	N/A
No level done	4 (11.8)	2 (20)
Switched to Alternate Antifungal	24 (43.6)	3 (25)
Adverse Event	18 (75)	1 (33.3)
Active treatment	3 (12.5)	1 (33.3)
Concomitant antifungal	3 (12.5)	1 (33.3)
Switched to:		
Voriconazole	0	0
Posaconazole	7 (29.2)	2 (66.7)
Amphotericin B	16 (66.7)	1 (33.3)
Other	1 (4.1)	0
Duration of prophylaxis (days), median (IQR)		
rATG	44 (32-93)	26 (16-41)
Alemtuzumab	88	90 (48-174)

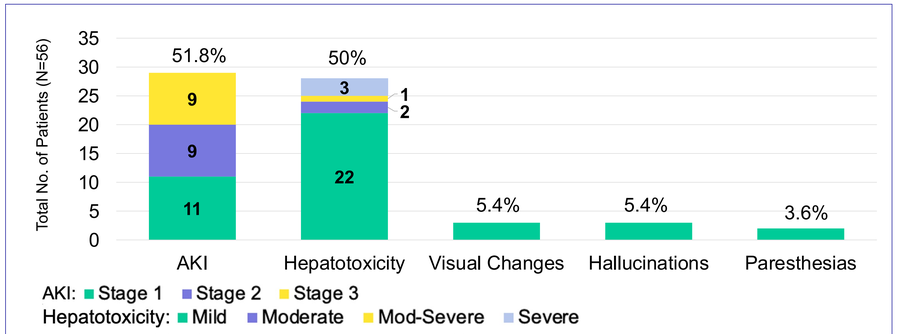
- Median cost ranges $2,086 - $11,808 depending on agent and duration

Table 3: Fungal Infection Outcomes

	3 months post t-lymphocyte depletion (N=61) No. (%)	1 year post t-lymphocyte depletion (N=50) No. (%)
No fungal growth	54 (88.5)	39 (78)
Fungal growth	7 (11.5)	13* (N=11, 22%)
Aspergillus	4 (57.1)	7 (53.8)
Candida	1 (14.3)	1 (7.7)
Penicillium	1 (14.3)	3 (23.1)
Cryptococcus	1 (14.3)	1 (7.7)
Pseudallescheria boydii	0	1 (7.7)
Invasive Aspergillosis	4 (6.6)	6 (12)
Invasive Candidiasis	1 (1.6)	1 (2.0)

*Cumulative incidence up to 1 yr post t–lymphocyte depletion. 11 pts. experienced a total of 13 types of fungal growth

- Breakthrough fungal infections accounted for 15.4% (n=2) of all infections
- Patients who experienced fungal infections 3 months post t-lymphocyte depletion received:
  - Universal prophylaxis=5 (71.4%), targeted prophylaxis=1 (14.3%), no prophylaxis=1 (14.3%)
- All patients who experienced fungal infections received rATG



- Incidence of SCC and bronchospasm was 0%

Figure 2: Adverse Effects Associated with Antifungal Prophylaxis

Limitations

- Retrospective chart review with small sample size
- Possible underreporting of CNS side effects
- Cost analysis – assumed prescription was filled, unable to differentiate between cost incurred by patient vs. hospital
- Safety outcomes may be influenced by concomitant medications and disease states

Conclusions

- Approximately 50% of patients received universal antifungal prophylaxis
- Voriconazole was poorly tolerated with 37% of pts. requiring alternate therapy
- Median duration of antifungal prophylaxis: rATG:43 days, alemtuzumab:82 days
- Rate of IFIs 3 months post t-lymphocyte depletion was 8.2% and 14% 1 yr post t-lymphocyte depletion
- AKI and hepatotoxicity occurred in approx. 50% of all patients
- Guideline concordant practice will significantly reduce cost and toxicity

References

1. Husain S, Camargo J. Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9)
2. Patel T, Eschenauer G, Stuckey L, Carver P. Antifungal Prophylaxis in Lung Transplant Recipients. Transplantation. 2016;100(9):1815-1826