Azithromycin Prophylaxis after Lung Transplantation is associated with Improved Overall Survival and Graft Function

David Li BSc, Justin Weinkauf MD, Alim Hirji MD MSc, Ali Kapasi MD, Dale Lien MD, Kieran Halloran MD MSc

Department of Medicine, University of Alberta, Edmonton, Canada

Introduction

Chronic lung allograft dysfunction (CLAD) is the most significant limiter of long-term survival after lung transplant with approximately 50% of recipients developing CLAD at 5 years post-transplant (1). Despite its prevalence and implications, therapies for CLAD remain elusive so prevention is critical (2).

Azithromycin is a macrolide antibiotic known to have anti-inflammatory properties particularly in the context of airway diseases. In a clinical trial, azithromycin prophylaxis (AP) was shown to improve lung function and CLAD-free survival in a small cohort of lung transplant recipients (3). However, there is no long-term data on this strategy in larger cohorts.

Our program implemented AP in 2010. Our objective was to evaluate the association between routine use of AP and overall survival in a large cohort of lung transplant recipients, as well as CLAD and baseline lung allograft dysfunction (BLAD).

We hypothesized that patients receiving AP would show equivalent survival but reduced rates of CLAD and BLAD.

Methods

We studied all double lung transplant recipients at the University of Alberta Hospital transplanted between 2004 and 2016. We defined AP as azithromycin (250 mg every other day) initiated prior to CLAD onset [typically very soon after transplant] and maintained thereafter. The primary endpoint was death or re-transplant.

We defined CLAD status, grade and subtype according to the 2019 ISHLT consensus criteria (2) and BLAD in accordance with our previously published definition (failure to achieve both FEV1 and FVC ≥80% predicted on 2 consecutive tests ≥3 weeks apart) (4).

We analyzed survival using proportional hazards regression with AP as a time-varying covariate, adjusting for recipient age, gender, underlying diagnosis, year of transplant and induction immunosuppression. We ran unadjusted proportional hazards and logistic models for CLAD and BLAD respectively.

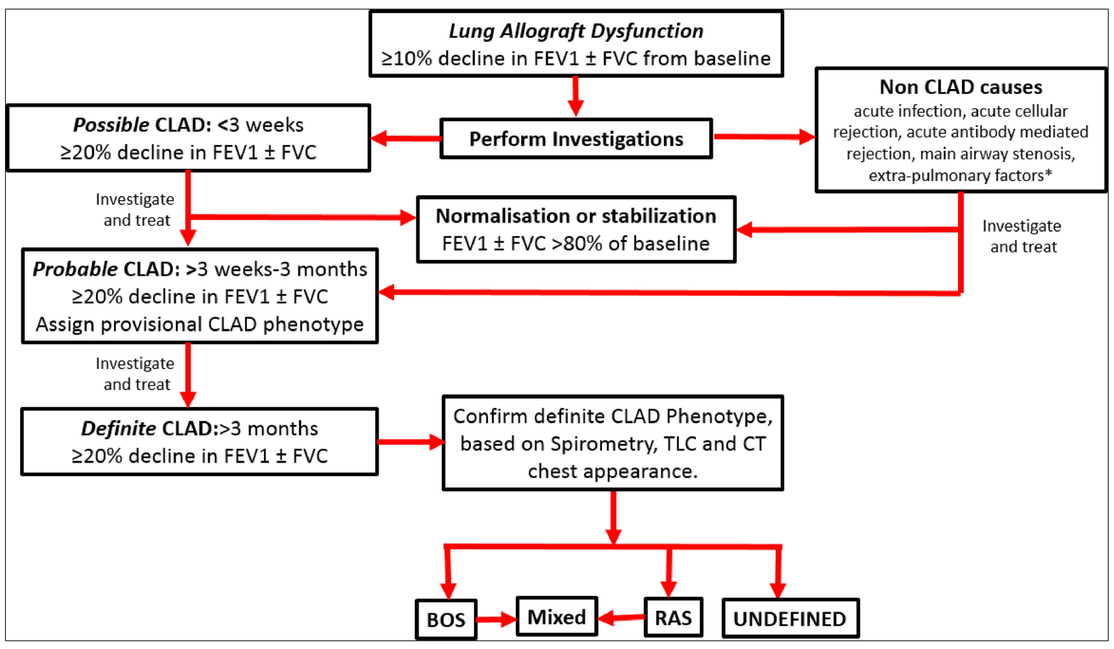

Figure 1. *Flowchart of CLAD diagnosis (Verleden et al. 2019).*

Results

445 patients met inclusion criteria and 344 (77%) were given AP with median time to azithromycin of 51 days [25th-75th quartile 20-211].

Patients receiving AP were more likely to have received induction with IL-2 receptor antagonists (57% vs. 35%; p<0.001), had shorter duration of mechanical ventilation (54 [29-150] vs. 96 [48-245] hours; p<0.001) and shorter hospital stay (23 [18-36] vs. 29 [19-44] days; p=0.016).

There were 170 deaths and one retransplant during the study timeframe. As such, study models primarily reflect risk of death.

AP was associated with improved survival (**HR 0.60** [95% confidence interval [CI] 0.41-0.81]; **p=0.002**) in our adjusted model, as well as a reduced unadjusted risks of CLAD onset (**HR 0.64** [95% CI 0.44-0.94]; **p=0.025**) and BLAD (**OR 0.55** [95% CI 0.35-0.86]; **p=0.009**).

Results

Table 1. *Patient characteristics*

Characteristic	Overall (n=445)	Azithromycin prior to CLAD (n=344)	No azithromycin prior to CLAD (n=101)	p-value
Donor				
Age in years, mean (SD)	39 (17)	39 (17)	37 (16)	0.223
Female sex, n (%)	206 (46)	163 (47)	43 (43)	0.428
BMI, mean (SD)	25.4 (5.4)	25.5 (5.4)	24.9 (5.2)	0.281
Smoking >20 pack years, n (%)	60 (13)	47 (14)	13 (13)	1.000
Ischemic time in minutes, mean (SD)	352 (119)	347 (119)	365 (115)	0.188
Recipient				
Age in years, mean (SD)	52 ± 13	51 ± 14	53 ± 12	0.413
Female sex, n (%)	154 (35)	120 (35)	34 (34)	0.905
BMI, mean (SD)	24.6 (5.0)	24.5 (5.0)	25.3 (5.0)	0.156
Diagnosis, n (%)				
Bronchiectasis	69 (16)	58 (17)	11 (11)	0.196
Interstitial lung disease	166 (37)	120 (35)	46 (46)	
Obstructive lung disease	184 (41)	143 (42)	41 (41)	
Pulmonary vascular disease	17 (4)	15 (4)	2 (2)	
Other	9 (2)	8 (2)	1 (1)	
Induction therapy, n (%)				
IL-2 receptor antagonists	232 (52)	197 (57)	35 (35)	**<0.001**
ATG	199 (45)	137 (40)	62 (61)	
None	14 (3)	10 (3)	4 (4)	
Recipient post-operative course				
Intubation time in hours, median (IQR)	63 (33-171)	54 (29-150)	96 (48-245)	**<0.001**
Hospital LOS in days, median (IQR)	23 (18-38)	23 (18-36)	29 (19-44)	**0.016**
Grade 3 PGD, n (%)	76 (17)	63 (18)	23 (23)	0.312
BLAD, n (%)	179 (40)	127 (37)	52 (51)	**0.011**
CLAD, n (%)	129 (29)	91 (26)	38 (38)	**0.038**
Time to CLAD in days, mean (SD)	1397 (959)	1485 (1015)	1187 (782)	0.108
Max FEV1 % predicted, mean (SD)	92 (21)	93 (20)	87 (23)	**0.006**
Time to azithromycin in days, median (IQR)	57 (20-283) (n=360)	51 (20-211) (n=344)	1290 (1003-1804) (n=16)	**<0.001**
Year of transplant, mean (SD)	2011 ± 4	2012 ± 4	2008 ± 3	**<0.001**

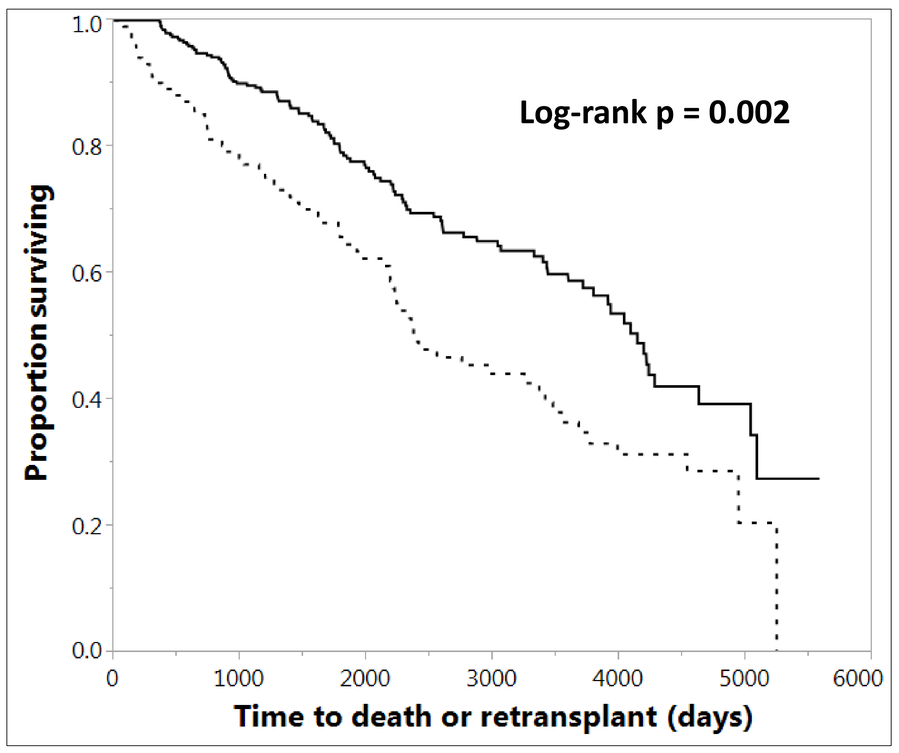

Figure 2. *Kaplan-Meier estimate of overall survival (170 deaths, one retransplant)*

Conclusions

1. **Azithromycin prophylaxis is associated with improved overall survival after lung transplantation** in this large cohort
2. This is possibly mediated through improved baseline function and a reduced risk of CLAD onset
3. Our findings are in keeping with prior trial results but with a substantially larger cohort. Taken together, this suggests AP is a beneficial therapy for lung transplant recipients.

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Acknowledgements

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The authors of this work have no relevant conflicts of interest to disclose.

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