Lung Transplant Outcomes in Patients with Chronic Respiratory Disease and Pre-Operative Nontuberculous Mycobacterial Disease

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BACKGROUND

Nontuberculous mycobacteria (NTM) are a ubiquitous and diverse group of nearly 200 mycobacteria species not in the Mycobacterium tuberculosis complex and other than Mycobacterium leprae.[1,2] These represent a diverse and emerging group of pathogens that cause disease in both immunocompromised and immunocompetent individuals.

Pulmonary infection secondary to NTM is associated with significant morbidity and mortality, especially in individuals with underlying structural lung disease. Such infections are challenging to treat due to high virulence, antibiotic resistance, and the lack of effective and tolerable therapies. At many transplant centers, the isolation of NTM may be considered a contraindication for lung transplantation.[3,4,5] In this retrospective study, we analyzed the epidemiology of NTM infections in lung transplant candidates and assessed risk factors for post-transplant infection and association with post-transplant outcomes in this population.

METHODS

We conducted a retrospective chart review of 445 patients who underwent lung transplantation at a large tertiary hospital between 1/200 6-2/2020. Institutional and referral medical records, microbiology, radiology, and pathology databases were reviewed for information regarding demographics, medical history, clinical findings, treatment, and outcome. American Thoracic Society/Infectious Diseases Society of America criteria were used to define pulmonary NTM infection.[6] The institutional review board at the University of Washington approved this study. Sample processing and mycobacterial cultures were performed using standard techniques and mycobacterial species were identified from culture by biochemical or molecular methods.[7-10] Demographic and clinical information, including age, sex, ethnicity, primary lung disease, comorbidities, microbiology cultures, and antimicrobial regimens were obtained from chart review of data submitted by patients and providers during the relevant clinical time period. Comorbidities were identified based on review of pre-transplant inpatient and outpatient chart notes. Cardiovascular disease was defined as chart documentation of heart failure, arrhythmias, or coronary artery disease; renal disease was defined as GFR < 60 mL/min per 1.73 m^2; and gastroesophageal reflux disease (GERD) was defined based on documentation of GERD as a comorbidity or inferred based on outpatient medications and/or surgical history. Patients were documented as taking pre-transplant outpatient antimicrobials if they were taking oral, inhaled, or intravenous antibiotics for suppressive or prophylactic purposes at the time of transplant.

Standard peri-operative antibiotics and post-operative antibiotics were defined based on institutional guidelines. Additional antimicrobials were administered based on an individual patient's microbiologic history and sensitivity profile. Death was considered potentially related to the NTM infection if it was documented as a possible contributing factor or if a patient was being treated for mycobacterial disease at the time of death.

Results

Among 445 lung transplant recipients, 15 subjects met criteria for NTM pulmonary infection prior to being listed for lung transplantation and 23 subjects had positive sputum culture for NTM but did not meet criteria for NTM disease.

Demographics of the subjects are presented in Table 1 and Figure 1.

Detailed microbiology, antibiotic regimens, and post-transplant clinical outcomes for the subjects infected with NTM are presented in Table 2. In the 17 patients with NTM disease, 6 (35%) patients had two unique species isolated prior to transplant. In comparison, in the 21 patients with a history of a positive AFB culture but without clinical disease, 2 (10%) patients had two unique species identified as shown in Figure 2.

Patients with NTM disease continued antimycobacterial therapy pre- and post-operatively as outlined in Table 2.

In the cohort with NTM-disease, 3 patients (17.6 %) died within a year of transplantation, 4 (23.5 %) died within 1-5 years, 1 (6%) died more than 5 years post-transplant, 6 (35.3%) are still alive 1-5 years post-transplant, and 3 (17.6%) are alive more than 5 years post-transplant. Only one patient clearly died as a direct cause of the NTM infection, and this occurred early post-transplantation due to disseminated *M abscessus* infection.

In the cohort without NTM disease, but with positive mycobacterial cultures, 2 (9.5%) died within one year of transplantation, 2 (9.5%) died within 1-5 years, 1 (4.8%) died more than 5 years post-transplant, 2 (9.5%) are alive and less than one year post-transplantation, 10 (47.6%) are alive more than 1 year post-transplant, and 4 (19%) are alive more than 5 years post-transplant. These outcomes are compared to patients without any history of positive mycobacterial cultures as shown in Table 3.

The probability of survival more than 1 year and more than 5 years post-transplant was 82% and 24% in patients with NTM-disease, and 83% and 32% in patients without NTM disease.

Table 1. Demographics and clinical characteristics of transplant recipients

	All patients (N = 445)	Patients without NTM (N = 406)	Patients with positive culture but no disease (N = 21)	Patients with NTM disease (N = 17)
Male, N (%)	246 (55%)	223 (55%)	14 (67%)	9 (53%)
Median age, years (range)	58 (14, 71)	59 (14,71)	43 (20, 65)	35 (17, 67)
Average age, years (std dev)	52.8 (14.6)	54.0 (14.0)	42.4 (14.7)	38.4 (16.7)
Ethnicity				
Caucasian	398 (89%)	364 (89.4%)	17 (81%)	17 (100%)
Black/African American	11 (2.5%)	10 (2.5%)	1 (4.7%)	0
Unknown/declined to answer	8 (1.8%)	6 (1.5%)	2 (10%)	0
Asian	9 (2.0%)	8 (2.0%)	1 (4.7%)	0
Hispanic	6 (1.3%)	6 (1.5%)	0	0
Multiracial	6 (1.3%)	6 (1.5%)	0	0
American Indian/Alaska Native	5 (1.1%)	5 (1.2%)	0	0
Native Hawaiian/Pacific Islander	2 (0.5%)	2 (0.5%)	0	0
Primary lung disease				
Obstructive lung disease	120 (27%)	116 (29%)	1 (5%)	3 (18%)
Cystic Fibrosis	80 (18%)	57 (14%)	13 (62%)	10 (59%)
Interstitial Lung Disease	206 (46%)	196 (47%)	6 (29%)	4 (24%)
Alpha-1 antitrypsin deficiency	22 (5%)	21 (5%)	1 (4%)	0 (0%)
Pulmonary hypertension	15 (3%)	15 (4%)	0 (0%)	0 (0%)
Other	15 (3%)	15 (4%)	0 (0%)	0 (0%)
Comorbidities				
DM	112 (25%)	97 (24%)	12 (57%)	3 (17%)
Renal	61 (14%)	54 (13%)	5 (24%)	2 (12%)
Hypertension	149 (33%)	142 (35%)	6 (29%)	3 (18%)
Hyperlipidemia	111 (25%)	106 (26%)	5 (24%)	2 (11%)
GERD*	238 (54%)	214 (53%)	14 (67%)	11 (65%)
Cardiovascular	128 (29%)	124 (30%)	4 (19%)	1 (6%)
BMI (lbs/in²), Average (SD)	24.37 (3.88)	24.64 (3.77)	21.47 (3.49)	21.54 (3.82)
Albumin (g/dL), Average (SD)	3.74 (0.51)	3.76 (0.49)	4.03 (0.66)	3.82 (0.60)
Taking outpatient antibiotic regimen immediately prior to transplant	140 (31%)	109 (27%)	15 (71%)	16 (94%)

Figure 1. Geographic distribution of transplant recipients by state of primary residence.

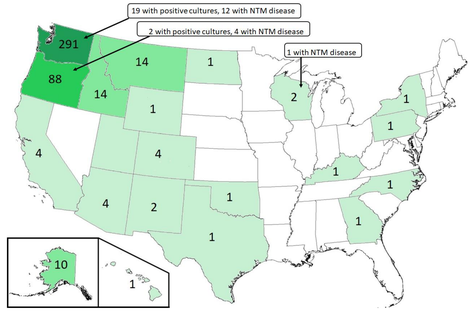

Figure 2. Relative proportions of the isolated NTM

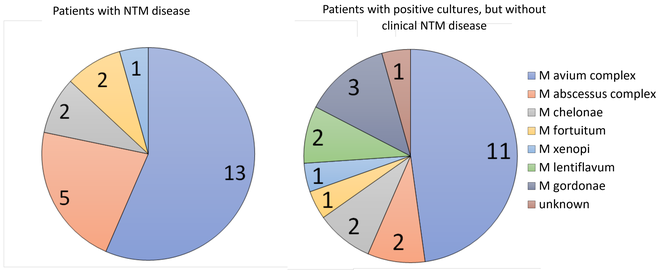

Table 2. Clinical course for patients with NTM infections

Patient	NTM organism	NTM regimen immediately prior to transplant	Obtained negative cultures prior to transplant	NTM regimen post-transplant	Positive NTM cultures post-transplant	Survival	Cause of death
1	*M avium complex*	PO ethambutol, clofazimine, moxifloxacin; Nebulized amikacin	No	Completed 3-month oral regimen of rifabutin, clofazimine, and ethambutol	No	Alive, 1-5 years post-transplant	n/a
2	*M abscessus complex*	No (completed regimen previously)	Yes, for approx. 6 years prior to transplant	None	No	Alive, 1-5 years post-transplant	n/a
3	*M avium complex* and *M abscessus complex*[1]	Azithromycin, ethambutol, clofazimine	Cleared *M abscessus complex* 2 years prior to transplant, but not *M avium*	Completed 12-month oral regimen of bedaquiline, clofazimine, ethambutol, rifabutin, and tedizolid	Yes, for 4 months post-transplant	Alive, 1-5 years post-transplant	n/a
4	*M avium complex* and *M chelonae*	No (completed regimen previously)	Yes, for approx. 4 years prior to transplant	None	No	Deceased < 1 year post-transplant	Shock, bacteriemia, bacterial pneumonia and heart failure
5	*M avium complex* and *M fortuitum*[1]	Azithromycin, Levofloxacin	Cleared *M fortuitum* 9 months prior to transplant, but not *M avium complex*	Completed 3-month oral regimen of azithromycin, moxifloxacin, and ethambutol.	No	Alive, 1-5 years post-transplant	
6	*M avium complex*	Azithromycin, ethambutol, rifampin	Yes, for approx. 6 months prior to transplant	PO azithromycin and ethambutol until time of death	No	Deceased < 1 year post-transplant	Cardiac arrest and renal failure.
7	*M avium complex*	No (completed regimen previously)	Yes, for approx. 10 years prior to transplant	None	No	Alive, 1-5 years post-transplant	n/a
8	*M avium complex*	PA clofazimine, ethambutol, and rifabutin; Nebulized amikacin	No	Completed 5-month regimen of inhaled amikacin, PO clofazimine, PO ethambutol, and PO rifabutin	No	Alive, > 5 years post-transplant	n/a
9	*M avium complex*	No (completed regimen previously)	Yes, for approx. 10 years prior to transplant	None	No	Deceased 1-5 years post-transplant	Chronic allograft rejection
10	*M abscessus complex, M chelonae*	No (completed regimen previously)	Yes, for approx. 10 years prior to transplant	None	No	Deceased 1-5 years post-transplant	Chronic allograft rejection
11	*M avium complex* and *M abscessus complex*[1]	PO azithromycin, rifabutin, clofazimine, and ethambutol; Nebulized amikacin	Cleared *M abscessus complex* 2 years prior to transplant but not *M avium complex*	Completed 6-month regimen of inhaled amikacin, PO clofazimine, PO azithromycin, PO ethambutol	No	Deceased 1-5 years post-transplant	Chronic allograft rejection, pulmonary fungal infection, renal failure
12	*M abscessus complex*	IV tigecycline, PO linezolid	No	IV aztreonam, IV linezolid, IV tigecycline	Yes (disseminated)	Deceased < 1 year post-transplant	Disseminated NTM infection
13	*M avium complex*	PO rifampin, ethambutol, azithromycin, clofazimine; Nebulized amikacin	No	Completed 3-month oral regimen of clofazimine, moxifloxacin, ethambutol, rifabutin.	No	Alive, 1-5 years post-transplant	n/a
14	*M fortuitum*	None[2]	No	Completed 3-month course of inhaled amikacin, PO imipenem, PO azithromycin	No	Alive, > 5 years post-transplant	n/a
15	*M avium complex*	PO azithromycin, ethambutol, rifampin; Nebulized amikacin	No	Completed 6-month regimen of inhaled amikacin, PO azithromycin, PO ethambutol	No	Deceased 1-5 years post-transplant	Chronic allograft rejection, pulmonary fungal infection, renal failure
16	*M avium complex*	PO azithromycin, ethambutol, rifampin	Yes	PO azithromycin, PO ethambutol, PO rifampin	No	Alive, > 5 years post-transplant	n/a
17	*M avium complex* and *M kansasii*[2]	PO azithromycin and ethambutol	Yes	Completed 6-month course of PO azithromycin and ethambutol with brief use of isoniazid and rifampin	No	Deceased 1-5 years post-transplant	Chronic allograft rejection

Table 3. Outcomes post-transplant

	Status and survival post-transplantation, n (%)							Probability survive	
	Deceased			Alive			Unknown		
Cohort, n	< 1 year	1-5 years	> 5 years	< 1 year	1-5 years	> 5 years		> 1 year	> 5 years
NTM disease, 17	3 (17.6%)	4 (23.5%)	1 (5.9%)	0 (0%)	6 (35.3%)	3 (17.6%)	0	0.82	0.24
Positive cultures with no clinical disease, 21	2 (9.5%)	2 (9.5%)	1 (4.8%)	2 (9.5%)	10 (47.6%)	4 (19.0%)	0	0.81	0.24
No NTM, 407	43 (10.6%)	67 (16.5%)	58 (14.3%)	26 (6.4%)	138 (34.0%)	74 (18.1%)	1 (0.02%)	0.83	0.32

Conclusions

NTM infection in the lung transplant candidate is uncommon and challenging, however successful treatment can occur in some settings. To gain further insight into the relative risk of lung-transplantation in a candidate with NTM colonization or infection, additional studies and data analysis will need to be executed. This includes review of approximately 300 other lung-transplant recipients at our institution, and evaluation of other risk factors and potential confounders such as baseline pulmonary function, nutrition, comorbidities, NTM organism, etc.

References

1. Parte AC, et al. *Int J Syst Evol Microbiol.* 2020, DOI: 10.1099/ijsem.0.004332
2. Rivero-Lezcano OM, González-Cortés C, Mirsaeidi M. *Int J Mycobacteriol.* 2019 8:1.
3. Lobo LJ, et al. *Clin Transplant.* 2013. 27: 523–529 DOI: 10.1111/ctr.12140
4. Orens JB, Merlo CA. *Semin Respir Crit Care Med.* 2018; 39:117.
5. Weill D. *J Thorac Dis.* 2018. 10:4574.
6. Daley CL, et al. *Clin Infect Dis.* 2020. 71:905
7. Ford ES, et al. *Ann Am Thorac Soc.* 2017. 14:1129
8. Bloch KC, et al. *Ann Intern Med.* 1998. 129:698
9. Selvarangan R, et al. *J Clin Microbiol.* 2004. 42:52.
10. Metchcock B, Nolte F, Wallace R. Mycobacterium. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. Manual of clinical microbiology. 7th ed. Washington, DC: ASM Press; 1999. p. 399–437