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MAJOR ARTICLE

Risk Factors for and Outcomes Following Early Acquisition of *Mycobacterium abscessus* Complex After Lung Transplantation

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Background. Lung transplant recipients are at increased risk of *Mycobacterium abscessus* complex (MABC) acquisition and invasive infection. We analyzed risk factors and outcomes of early post–lung transplant MABC acquisition.

Methods. We conducted a retrospective matched case–control study of patients who underwent lung transplant from 1/1/2012 to 12/31/2021 at a single large tertiary care facility. Cases had de novo MABC isolation within 90 days post-transplant. Controls had no positive MABC cultures and were matched 3:1 with cases based on age and transplant date. Recipient demographics and pre-/peri-operative characteristics were analyzed, and a regression model was used to determine independent risk factors for MABC acquisition. We also assessed 1-year post-transplant outcomes, including mortality.

Results. Among 1145 lung transplants, we identified 79 cases and 237 matched controls. Post-transplant mechanical ventilation for >48 hours was independently associated with MABC acquisition (adjusted odds ratio, 2.46; 95% CI, 1.29–4.72; $P = .007$). Compared with controls, cases required more days of hospitalization after the MABC index date (28 vs 12 days; $P = .01$) and had decreased 1-year post-transplant survival (78% vs 89%; log-rank $P = .02$). One-year mortality appeared highest for cases who acquired *M. abscessus* subsp. *abscessus* (31% mortality) or had extrapulmonary infections (43% mortality).

Conclusions. In this large case–control study, prolonged post-transplant ventilator duration was associated with early post–lung transplant MABC acquisition, which in turn was associated with increased hospital-days and mortality. Further studies are needed to determine the best strategies for MABC prevention, surveillance, and management.

Keywords. case–control study; hospital-associated infections; infection prevention; lung transplantation; nontuberculous mycobacteria.

Nontuberculous mycobacteria (NTM) are opportunistic aerobic bacteria that are ubiquitous in the environment [1]. Acquisition traditionally occurs through exposure to contaminated water, dust, and soil in the community setting. However, numerous NTM outbreaks have occurred at health care facilities due to patient exposure to colonized hospital water and aerosols [2–5]. Clinical syndromes of NTM infection include pulmonary disease, skin and soft tissue infections, disseminated disease, and lymphadenitis [6].

Known patient risk factors for NTM pulmonary infection include underlying structural and inflammatory lung disease, ciliary dysfunction, low body weight, malignancy, female sex, older age, and immunosuppression [6]. Solid organ transplant (SOT) recipients are at particularly increased risk of infection, with lung transplant recipients having up to 11-fold increased odds for NTM infection compared with other SOT recipients [7]. Risk factors previously identified for NTM infection after lung transplant include single lung transplant [8], biopsy-proven acute rejection [7], recently augmented immunosuppression [9], Black race [10], and cytomegalovirus (CMV) mismatch [10]. In 1 study, azithromycin prophylaxis was associated with reduced odds of NTM isolation [9]. However, the application of these risk factors is limited because most prior studies did not stratify risk by NTM species, site of infection, or an explicit post-transplant time frame. Therefore, few prior studies have evaluated risk factors and outcomes specific to *Mycobacterium abscessus* complex (MABC) [11–14], extrapulmonary disease [13, 15], or the early post-transplant period [8].

MABC is one of the most difficult to treat NTM and includes 3 subspecies (*M. abscessus* subsp. *abscessus*, *massiliense*, and *bolletii*) [16]. MABC is intrinsically resistant to many antibiotics, and despite aggressive medical and surgical management, many individuals do not achieve cure [17]. Patients with

Received 28 January 2024; editorial decision 4 April 2024; accepted 10 April 2024; published online 12 April 2024

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https://doi.org/10.1093/ofid/ofae209

MABC infections are often burdened with significant antibiotic-related toxicities, accelerated decline in lung function, and increased mortality [18, 19]. Despite potential for poor outcomes related to MABC infection after lung transplant [11, 14], prior studies have not sufficiently identified risk factors for de novo acquisition and infection.

One of the largest hospital-associated outbreaks of MABC occurred at our hospital from 2013 to 2015 and was related to a plumbing system colonized with NTM [2, 3]. Over 100 cases of MABC were identified, including more than 35 lung transplant patients. In the context of this outbreak and numerous cases of endemic MABC unrelated to the outbreak, we sought to identify patient and clinical risk factors associated with early post-transplant MABC acquisition. We also analyzed the effect of MABC acquisition on morbidity and mortality.

METHODS

Study Design and Patient Population

This retrospective matched case–control study was conducted at Duke University Hospital (DUH), a tertiary-care, 1048-bed academic hospital and transplant center located in central North Carolina. Included patients underwent lung transplant at DUH from January 1, 2012, to December 31, 2021.

Cases were defined as lung transplant recipients who had a first-time positive culture for MABC from any clinical specimen within 90 days post-transplant. Patients with positive cultures for MABC obtained before transplant or during the transplant surgery were excluded. Controls were lung transplant recipients who had no positive cultures for MABC before transplant or for 1 year after transplant. For patients who underwent 2 transplants within the 90-day period before a first positive culture, only the transplant most closely preceding the positive culture was included. Potential cases were identified by cross-referencing clinical culture data with the Organ Procurement and Transplant Network (OPTN) database [20].

Cases were matched 1:3 with controls based on date of lung transplantation (+/− 1 year) and age (+/− 5 years). An index date was determined for control patients based on the number of days between transplantation and MABC isolation for their matched case. Control patients who met criteria but did not survive to this index date were excluded. Data from all patients were reviewed from the date of transplantation to 1 year after that date.

Patient Consent

The study was approved by the Duke University Health System institutional review board (Pro00111883). A waiver of informed consent was issued.

Laboratory Methods

Standard mycobacterial culture methods were utilized [21, 22]. Subspecies identification of selected MABC isolates was performed at the Mycobacteria/Nocardia Research Laboratory at the University of Texas Health Science Center at Tyler, Texas, according to previously described methods [2].

Standard Care of Lung Transplant Recipients

Post-transplant immunosuppression and antimicrobial prophylaxis were administered according to the protocols of the Duke Lung Transplant Program [23]. Standard immunosuppression included basiliximab induction, followed by maintenance therapy with a calcineurin inhibitor, corticosteroids, and an antimetabolite. Standard bacterial intravenous (IV) peri-operative prophylaxis consisted of cefepime (7–10 days) and vancomycin (variable duration). Additional post-transplant prophylaxis included aerosolized amphotericin B lipid complex (duration of transplant hospitalization), fluconazole (90 days post-transplant, beginning in 2015), trimethoprim/sulfamethoxazole, nystatin swish and swallow, and antiviral prophylaxis dependent on CMV serostatus. If the donor or recipient had CMV-positive serostatus, the recipient received at least 1 year of post-transplant IV ganciclovir/oral valganciclovir.

At the time of transplant, native lung specimens from either the bronchial cuff or bronchoalveolar lavage (BAL) were obtained for bacterial, fungal, and mycobacterial cultures. Bronchoscopy for these 3 BAL cultures and transbronchial biopsy were additionally performed at 1, 3, 6, and 12 months after transplant and as clinically indicated.

Lung transplant recipients were primarily affected by the pulmonary phase of the DUH MABC outbreak, which occurred from August 2013 to May 2014 [2]. In response to the outbreak, some aspects of post-transplantation care were changed. In May 2014, a tap water avoidance protocol was implemented for all hospitalized lung transplant recipients [3]. Sterile water was used for all patient care activities, and tap water was also avoided in the community in the early post-transplant period. This protocol remained in place for the duration of the study period. From June 2014 to November 2015, the perioperative antibiotic prophylaxis regimen changed to include IV imipenem, instead of cefepime, and inhaled amikacin. After November 2015, imipenem and inhaled amikacin prophylaxis were stopped, and cefepime was resumed.

Data Collection

Data were collected from the electronic health record (EHR), DUH clinical transplant database, DUH clinical microbiology database, and OPTN database. For each identified case and control, extracted data included demographics, pretransplant health condition and status, Karnofsky Performance Status Score [24], lung allocation score [25], details of the transplant surgery and post-transplant care, and outcomes over the first post-transplant year. Race and ethnicity were sourced from a DUH clinical transplant database where data were extracted from the EHR and OPTN database; race and ethnicity were self-reported by the patient.

Definitions

The date of diagnosis was considered to be the date that the first positive culture for MABC was performed. Pulmonary cultures included specimens from the respiratory tract, excluding the pleural space. Cases with positive pulmonary cultures were considered to have obtained culture clearance if the final mycobacterial pulmonary culture obtained during 1-year study follow-up was negative. For case patients who died in the first year after transplant, 2 investigators reviewed detailed clinical data to adjudicate if death was attributable to MABC infection.

The case definition did not differentiate pulmonary infection from colonization because the primary objective of the study was to characterize risk factors and outcomes related to post-transplant MABC acquisition, independent of progression to invasive infection. Furthermore, standardized definitions for NTM pulmonary disease [26] have not been validated for lung transplant recipients [27]. In secondary analysis, we stratified outcomes for cases with isolated pulmonary MABC involvement. These patients were considered to have suspected infection if they were treated with antibiotics targeting MABC. Pulmonary cases were presumed to be colonized if antibiotics targeting MABC were not prescribed due to a clinical diagnosis of pulmonary colonization.

Statistical Analysis

Descriptive statistical comparisons were reported as medians and interquartile ranges (IQRs) for continuous variables, and percentages were used to report event rates and nominal data.

Characteristics of cases and controls were compared using conditional logistic regression that controlled for matching. The reference model included all variables with a P value $\leq .2$ in univariate analysis after accounting for collinearity and epidemiologic plausibility (Supplementary Data). A backward selection procedure was used to select variables for inclusion in the final model. Confounding variables and variables with an adjusted P value $\leq .05$ were included in the final model. Confounding variables were identified as variables that, once removed, changed β coefficients by more than 10%. Single variable conditional logistic regression was also performed to evaluate the potential impact of MABC subspecies and site of positive cultures on MABC acquisition.

Outcomes of cases and controls were compared using univariate conditional logistic regression. Survival probabilities at 1 year were calculated using the Kaplan-Meier method. Log-rank tests estimated the association between MABC acquisition and survival. In secondary analyses, Kaplan-Meier survival analysis and other outcomes were stratified by subspecies, site of positive cultures (pulmonary vs extrapulmonary), presence of suspected pulmonary infection vs colonization, and time period of diagnosis (during the MABC pulmonary outbreak vs before or after the outbreak). Outcomes were compared for stratified groups of cases using the Fisher exact or chi-square test for dichotomous variables and the Wilcoxon rank-sum test for continuous variables.

Statistical analyses were performed using R, version 4.2.1 [28].

RESULTS

Patient Characteristics

A total of 1110 unique patients underwent lung or heart–lung transplant between January 1, 2012, and December 31, 2021. Of this cohort, 79 (7%) met the case inclusion criteria and were matched with 237 controls. Relative to the pulmonary phase of the MABC outbreak (August 2013 to May 2014), 17 (22%) cases were diagnosed before the outbreak, 36 (46%) were diagnosed during this outbreak period, and 26 (33%) were diagnosed afterwards [2]. Demographics of case and control patients were similar (Table 1).

MABC Cases

The median time to early MABC isolation after transplant was 33 (IQR 11–59) days (Table 2). For the majority of cases (n = 70; 89%), the first positive culture was pulmonary. Of the 74 (94%) cases with any positive pulmonary cultures, 68 (92%) demonstrated pulmonary culture clearance within 1 year. A total of 23 (29%) patients had positive extrapulmonary cultures. Of the 56 (71%) cases with only positive pulmonary cultures, all patients had at least 1 positive BAL culture. The majority of cases (n = 59; 75%) received antibiotics targeting MABC. Of the 20 (25%) who did not, treating clinicians nearly always suspected pulmonary colonization rather than invasive infection (n = 18; 90%). The remaining 2 patients who did not receive antibiotics had extrapulmonary infections diagnosed postmortem. Subspecies identification was performed for 55 (70%) cases, and the most common subspecies was *M. abscessus* subsp. *abscessus* (n = 36; 46%), followed by *M. abscessus* subsp. *massiliense* (n = 18; 23%) and M. *abscessus* subsp. *bolletii* (n = 1; 1%).

Risk Factors for MABC Isolation

In univariate analysis, case patients were significantly more likely to have a Karnofsky Performance Status Score ≤30% ($P = .04$) and to require mechanical ventilation ($P = .02$) or extracorporeal membrane oxygenation ($P = .03$) immediately before transplant (Table 1). Cases were less likely to have idiopathic pulmonary fibrosis (IPF; $P = .04$). Perioperatively, case patients were more likely to have CMV mismatch ($P = .05$), receive a bilateral transplant ($P = .04$), and spend more days in the hospital ($P = .009$) or be on the ventilator for >48 hours ($P < .001$) between transplant and index date.

Multivariable analysis demonstrated that only post-transplant ventilation for >48 hours was independently associated with MABC acquisition in the first 90 days after transplant

Table 1. Lung Transplant Recipient Characteristics and Odds of *Mycobacterium abscessus* Complex Acquisition

	MABC Cases (n = 79)	Matched Controls (n = 237)	Statistical Analysis[a]	
			Unadjusted Odds Ratio (95% CI)	*P* Value
Demographics				
Age at transplant, median (IQR), y	63 (51–68)	63 (51–68)	1.15 (0.38–3.46)[b]	.81
Female sex	25 (32)	87 (37)	0.78 (0.44–1.38)	.39
Hispanic ethnicity[c]	0 (0)	2 (<1)	0.00 (0–0)	1.00
Race				
White	74 (94)	212 (89)	1.76 (0.65–4.78)	.27
Black	3 (4)	17 (7)	0.49 (0.14–1.77)	.28
Other[d]	2 (3)	8 (3)	0.75 (0.16–3.53)	.72
Preoperative characteristics				
Underlying pulmonary disease				
Idiopathic pulmonary fibrosis	32 (41)	124 (52)	0.54 (0.30–0.97)	.04
Cystic fibrosis	8 (10)	21 (9)	1.27 (0.42–3.80)	.68
COPD	16 (20)	37 (16)	1.41 (0.72–2.76)	.32
Pulmonary hypertension	5 (6)	4 (2)	4.46 (1.05–18.95)	.04
Graft failure	4 (5)	9 (4)	1.38 (0.39–4.86)	.61
Other	14 (18)	42 (18)	1.00 (0.51–1.96)	1.00
BMI, median (IQR), kg/m^2	25.1 (21.9–26.4)	24.8 (21.5–26.5)	1.00 (0.93–1.08)[e]	.99
Diabetes mellitus	16 (20)	51 (22)	0.92 (0.48–1.76)	.81
Renal insufficiency (creatinine ≥1.3)	10 (13)	24 (10)	1.29 (0.58–2.85)	.53
Prior lung transplant[f]	5 (6)	17 (7)	0.86 (0.29–2.54)	.79
End-match lung allocation score, median (IQR)	44.8 (36.7–52.7)	42.8 (36.4–50.3)	1.16 (0.97–1.39)[g]	.10
Karnofsky Performance Status score ≤30%	13 (16)	20 (8)	2.39 (1.05–5.42)	.04
Pretransplant immunosuppression[h]	31 (39)	104 (44)	0.82 (0.49–1.39)	.47
Hospitalized (not ICU) immediately before transplant	6 (8)	13 (5)	1.45 (0.51–4.07)	.49
ICU immediately before transplant	7 (9)	10 (4)	2.18 (0.81–5.91)	.13
Ventilator immediately before transplant	7 (9)	6 (3)	4.43 (1.27–15.44)	.02
ECMO immediately before transplant	6 (8)	5 (2)	4.10 (1.14–14.70)	.03
Perioperative characteristics				
CMV mismatch (donor + /recipient - serology)	22 (28)	42 (18)	1.84 (1.00–3.39)	.05
Ischemic time, median (IQR), h	6.7 (5.6–7.8)	6.6 (5.5–8.2)	0.92 (0.82–1.03)[i]	.17
Multiple solid organ transplant[j]	4 (5)	8 (3)	1.59 (0.44–5.82)	.48
Bilateral lung transplantation	64 (81)	167 (70)	2.05 (1.03–4.06)	.04
Post-transplant ventilator >48 h[k]	36 (47)	50 (22)	3.07 (1.77–5.34)	<.001
≥14 d of antibiotic therapy with in vitro *M. abscessus* activity before index date	6 (8)	29 (12)	0.57 (0.22–1.46)	.24
Inhalational amikacin	5 (6)	17 (7)	0.86 (0.29–2.53)	.79
Azithromycin	2 (3)	16 (7)	0.33 (0.07–1.53)	.16
Other[l]	5 (6)	16 (7)	0.93 (0.32–2.71)	.89
Immunosuppression from transplant to index date with rituximab, antithymocyte globulin, or alemtuzumab	4 (5)	11 (5)	1.10 (0.34–3.54)	.88
Rejection between transplant and index date[m]	16 (20)	48 (20)	1.00 (0.5–1.99)	1.00
No. of days in hospital between transplant and index date, median (IQR)	17 (10–31)	13 (8–21)	1.21 (1.05–1.40)[n]	.009

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; MABC, *Mycobacterium abscessus* complex.

[a]MABC cases and controls were compared using univariate conditional logistic regression.

[b]Per 10 years.

[c]Data were excluded for 2 cases and 4 controls where ethnicity was unknown.

[d]For cases, other race included Asian (n = 1) and unknown (n = 1). For controls, other race included Asian (n = 2), American Indian (n = 1), and other (not specified; n = 5).

[e]Per 1-point increase.

[f]Prior lung transplant included those with graft failure and staged single lung transplants.

[g]Per 10-point increase.

[h]Defined as chronic steroid use at the time of transplant (not otherwise specified by the Organ Procurement and Transplant Network database); rituximab or antithymocyte globulin in the 6 months before transplant; or alemtuzumab in the 12 months before transplant.

[i]Per 1-hour increase in ischemic time.

[j]For cases, multiple organ transplant included lung and heart (n = 2), lung and liver (n = 1), and lung and kidney (n = 1). For controls, multiple organ transplant included lung and heart (n = 2), lung and liver (n = 5), and lung and kidney (n = 1).

[k]Data were excluded for 2 cases and 6 matched controls with days between transplant and index date <48 hours.

[l]For cases, other included imipenem (n = 4) and linezolid (n = 1). For controls, other included imipenem (n = 11) and linezolid (n = 5).

[m]Rejection defined by International Classification of Diseases, Ninth Revision, diagnosis and chart review.

[n]Per 7 days.

Table 2. Characteristics of *Mycobacterium abscessus* Complex cases

	All MABC Cases (n = 79)
Time to isolation post-transplant, median (IQR), d	33 (11–59)
Total No. of positive cultures, median (IQR)	3 (1–6)
First positive culture was pulmonary	70 (89)
BAL	67/70 (96)
Sputum	2/70 (3)
ETS/ETA	1/70 (1)
First positive culture was extrapulmonary	9 (11)
Blood	5/9 (56)
Pleura	4/9 (44)
Any positive pulmonary culture	74 (94)
BAL	73/74 (99)
Sputum	12/74 (16)
ETS/ETA	4/74 (5)
Other site[a]	3/74 (4)
Pulmonary culture clearance within 1 y post-transplant	68/74 (92)
Any positive extrapulmonary culture	23 (29)
Blood	14/23 (61)
Pleura	11/23 (48)
Transverse sternotomy incision	6/23 (26)
Other site[b]	13/23 (57)
Only positive pulmonary cultures	56 (71)
At least 1 positive BAL culture	56/56 (100)
Positive pulmonary and extrapulmonary culture	18 (23)
Received antibiotics targeting MABC	59 (75)
Did not receive antibiotics targeting MABC	20 (25)
MABC thought to represent pulmonary colonization	18/20 (90)
Extrapulmonary infection diagnosed postmortem	2/20 (10)
Subspecies *abscessus*	36 (46)
Subspecies *massiliense*	18 (23)
Subspecies *bolletii*	1 (1)
Subspecies unknown	24 (30)

Data are presented as No. (%) or n/N (%).

Abbreviations: BAL, broncheoalveolar lavage; ETA, endotracheal aspiration; ETS, endotracheal suction; IQR, interquartile range; MABC, *Mycobacterium abscessus* complex.

[a]Other sites of pulmonary positive cultures included: sinus, n = 2; bronchial biopsy, n = 1.

[b]Other sites of extrapulmonary positive cultures included: abdominal wall abscess, n = 3; unspecified drainage, n = 3; chest wall abscess, n = 2; breast abscess, n = 1; groin abscess, n = 1; sternal tissue, n = 1; thigh abscess, n = 1; unspecified wound, n = 1.

(adjusted odds ratio [AOR], 2.46; 95% CI, 1.29–4.72; $P = .007$) (Table 3). Six other variables were retained in the model as potentially important confounders. For the variable of post-transplant ventilation for >48 hours, single variable analysis on odds of MABC acquisition was done for stratified groups of cases compared with their matched controls. The odds ratio (OR) increased from 3.07 (95% CI, 1.77–5.34; $P < .001$) for the entire cohort to 3.92 (95% CI, 1.66–9.26; $P = .002$) for cases known to represent *M. abscessus* subsp. *abscessus* and to 31.43 (95% CI, 4.10–241.21; $P < .001$) for cases with extrapulmonary involvement (Supplementary Table 1).

Twelve-Month Outcomes

Compared with controls, case patients required more days of hospitalization between the MABC index date and the end of the first post-transplant year (median, 28 vs 12 days; $P = .01$) (Table 4). Kaplan-Meier survival probability 1 year after transplant was 78% for cases vs 89% for controls (log-rank $P = .02$) (Figure 1). Of the 17 cases who died in the year after transplant, 11 (65%) deaths were directly (n = 4) or in part (n = 7) attributable to MABC infection. All patients whose death was directly attributed to MABC were infected with *M. abscessus* subsp. *abscessus* and had extrapulmonary involvement.

Compared with cases who acquired *M. abscessus* subsp. *massiliense*, cases with *M. abscessus* subsp. *abscessus* required more days of hospitalization, but this difference was not statistically significant (median, 39 vs 25 days; $P = .15$) (Table 5). Kaplan-Meier survival probability 1 year after transplant was 69% for *M. abscessus* subsp. *abscessus* vs 89% for *M. abscessus* subsp. *massiliense* (log-rank $P = .10$) (Figure 1). Compared with cases with isolated pulmonary involvement, cases with any positive extrapulmonary cultures accrued more days of hospitalization (median, 52 vs 25 days; $P = .004$). Kaplan-Meier survival probability 1 year after transplant was 57% for cases with any positive extrapulmonary cultures vs 88% for cases with positive pulmonary cultures only (log-rank $P = .001$) (Figure 1). For cases with isolated pulmonary involvement, there were no significant differences in 12-month outcomes for those with suspected infection compared with those deemed to be colonized (Supplementary Table 2). Time from transplant to initial isolation of MABC was shorter for cases that occurred during the pulmonary MABC outbreak in comparison to cases that occurred before or after the outbreak; however, diagnosis during the outbreak was not significantly associated with days of hospitalization or survival.

Table 3. Conditional Logistic Regression Model of *Mycobacterium abscessus* Complex Acquisition[a]

	Adjusted Odds Ratio (95% CI)	*P* Value
Independent predictors		
Post-transplant ventilator >48 h	2.46 (1.29–4.72)	.007
Confounding variables		
Ventilator immediately before transplant	3.24 (0.64–16.48)	.16
CMV mismatch (donor + /recipient - serology)	1.53 (0.76–3.08)	.24
No. of days in hospital between transplant and index date	1.02 (0.99–1.05)	.20
End-match lung allocation score	1.00 (0.98–1.03)	.73
Idiopathic pulmonary fibrosis	0.52 (0.26–1.05)	.07
≥14 d of azithromycin between transplant and index date	0.21 (0.04–1.07)	.06

Abbreviations: CMV, cytomegalovirus; MABC, *Mycobacterium abscessus* complex.

[a]The variable bilateral lung transplant was eliminated during backward elimination.

DISCUSSION

This retrospective matched case–control study provides the largest analysis of early post–lung transplant MABC acquisition and outcomes to date. Our analysis determined

Table 4. Comparison of Outcomes Between *Mycobacterium abscessus* Complex Cases and Matched Controls

	MABC Cases (n = 79)	Matched Controls (n = 237)	*P* Value[a]
Augmented immunosuppression between index date and 1 y after transplant	19 (24)	75 (32)	.21
Rituximab	7 (9)	34 (14)	.21
ATG	14 (18)	51 (22)	.47
Alemtuzumab	4 (5)	7 (3)	.38
Rejection between index date and 1 y after transplant[b]	40 (51)	151 (64)	.04
No. of hospital-days between index date and 1 y after transplant, median (IQR)	28 (12–54)	12 (4–34)	.01
Death ≤1 y after transplant	17 (22)	27 (11)	.03

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; MABC, *Mycobacterium abscessus* complex.

[a]MABC cases and controls were compared using univariate conditional logistic regression.

[b]Rejection defined by International Classification of Diseases, Ninth Revision, diagnosis and chart review.

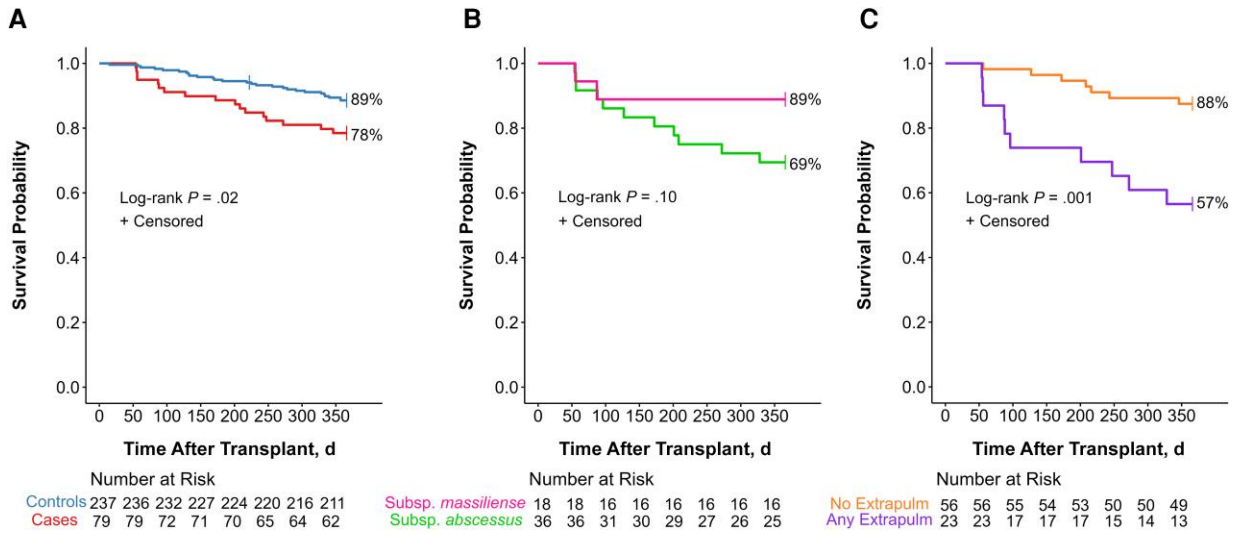

Figure 1. Kaplan-Meier survival curve for 1 year after lung transplant. *A*, Comparing MABC cases and controls. *B*, Comparing cases stratified by acquisition of *M. abscessus* subspecies *abscessus* and subspecies *massiliense*. *C*, Comparing cases stratified by any extrapulmonary MABC involvement and no extrapulmonary involvement. Abbreviations: Extrapulm, extrapulmonary; MABC, *Mycobacterium abscessus* complex.

that >48 hours of post-transplant mechanical ventilation was an independent predictor of MABC acquisition in the first 90 days after transplant. We also found that cases had decreased 1 year post–transplant survival, especially for patients with *M. abscessus* subsp. *abscessus* or extrapulmonary disease.

Prolonged mechanical ventilation has numerous risks after lung transplant [29]. We suspect the association between duration of ventilatory support and MABC acquisition identified in this study indicates that patients who required extended mechanical ventilation had more complex postoperative courses with increased exposure to water and aerosols colonized with MABC. For example, these patients likely had increased risk of oropharyngeal MABC inoculation during routine oral and respiratory care performed while on ventilators and in intensive care units (ICUs) [3], higher risk of micro-aspiration events [30], and ultimately increased risk of pulmonary MABC acquisition. Similarly, recipients with difficult early postoperative courses who required increased lines, devices, and surgeries likely had increased risk of extrapulmonary MABC inoculation via water or aerosols present in operating rooms and ICUs. By focusing only on acquisition in the first 90 days after transplant, we were able to investigate risks specific to this vulnerable period.

Prior studies identified potential risk factors that were not independent predictors of MABC acquisition in our analysis. Grimes et al. found that receipt of azithromycin protected against NTM acquisition [9]. Increased statistical significance of this relationship in their study may be secondary to longer time allowed to post-transplant NTM isolation (median, 10.7 months) and their center's routine use of indefinite post-transplant azithromycin prophylaxis. Contrary to previous studies, our study did not find single lung transplant, a history of biopsy-proven rejection, or recent augmented immunosuppression to be associated with

Table 5. Outcomes for Cases Stratified by *Mycobacterium abscessus* Complex Subspecies and Site of Positive Cultures

Stratified by Subspecies[a]	Subspecies *abscessus*[b] (n = 36)	Subspecies *massiliense*[c] (n = 18)	*P* Value[b]
Any positive pulmonary culture	34 (94)	15 (83)	.32
MABC culture clearance within 1 y post-transplant	28/34 (82)	15/15 (100)	.16
Any positive extrapulmonary culture	14 (39)	7 (39)	1.00
No. of hospital-days between index date and 1 y after transplant, median (IQR)	39 (19–71)	25 (9–39)	.15
Death <1 y after transplant	11 (31)	2 (11)	.18
Stratified by Site of Positive Cultures	**Any Extrapulmonary (n = 23)**	**No Extrapulmonary (n = 56)**	***P* Value[d]**
Time to initial isolation of MABC post-transplant, median (IQR), d	44 (29–55)	26 (6–68)	.09
Received antibiotics targeting MABC	21 (91)	38 (68)	.04
Did not receive antibiotics targeting MABC	2 (9)	18 (32)	.04
MABC thought to represent pulmonary colonization	0/2 (0)	18/18 (100)	<.001
Diagnosed postmortem	2/2 (100)	0/0 (0)	.08
No. of hospital-days between index date and 1 y after transplant, median (IQR)	52 (22–111)	25 (9–42)	.003
Death <1 y after transplant	10 (43)	7 (13)	.005

Data are presented as No. (%) or n/N (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; MABC, *Mycobacterium abscessus* complex.

[a]Isolates were excluded from subspecies analysis when subspecies identification was not performed (n = 24) and for *Mycobacterium abscessus* subsp. *bolletii* (n = 1).

[b]Of the 36 subspecies *abscessus* isolates, 32 (89%) represented the primary outbreak clone [2].

[c]Of the 18 subspecies *massiliense* isolates, 15 (83%) represented the secondary outbreak clone [2].

[d]Comparisons between subspecies and sites of positives cultures were performed with chi-square or Fisher exact tests for dichotomous variables and Wilcoxon rank-sum tests for continuous variables.

increased risk [8, 9, 27]. Our study excluded patients with a pre-transplant history of MABC, which may have diminished apparent risks of a single lung transplant, such as graft inoculation from a colonized native lung [8]. In addition, our study did not capture MABC cases associated with rejection and augmented immunosuppression that occurred after the early post-transplant period.

Compared with controls, MABC cases had worse outcomes with increased days of hospitalization and decreased 1-year post-transplant survival. Moreover, patients who acquired *M. abscessus* subsp. *abscessus* or had extrapulmonary involvement appeared to have increased mortality. *M. abscessus* subsp. *abscessus* is typically macrolide resistant and has worse treatment outcomes than *M. abscessus* subsp. *massiliense* [31, 32]. Furthermore, the majority of patients in our cohort with extrapulmonary involvement also had positive pulmonary cultures, consistent with reports of worse outcomes in patients with disseminated disease [33]. In other analyses, the direct effect of NTM infection on patient survival continues to be debated. While several studies have reported higher all-cause mortality among patients with NTM, increased risk of death has not conclusively been deemed a result of NTM infection [8, 9, 11, 19]. While we observed worse outcomes in cases, our study was not designed to fully assess these associations. Further study in the lung transplant population is needed to better understand factors associated with progression from MABC acquisition to invasive infection, as well as factors that increase morbidity and mortality of proven infections. More effective MABC therapies represent an emerging need, particularly for macrolide-resistant and extrapulmonary infections [34].

The difficulty in treating MABC infections, combined with poor outcomes, underscores the importance of preventing MABC acquisition and performing detailed NTM surveillance. At our center, the implementation of a hospital and community tap water avoidance protocol both mitigated the pulmonary phase of the MABC outbreak and decreased the risk of NTM acquisition after outbreak cessation [2, 3]. Hospitals with endemic NTM or vulnerable immunosuppressed patients should ensure effective water management programs and consider tap water avoidance, use of highly filtered tap water, and water engineering strategies designed to decrease the burden of NTM in the hospital water supply [2, 35, 36]. We also decreased risk of extrapulmonary MABC infection after lung transplant at our hospital by replacing colonized heater-cooler units (HCUs) used in cardiopulmonary bypass surgeries and implementing a careful HCU maintenance and disinfection protocol. Regardless of the HCU model used, hospitals that perform cardiothoracic surgery should carefully adhere to HCU protocols to reduce risk of NTM aerosolization in the operating room and invasive postoperative infections [37]. Despite these interventions and successful outbreak mitigation, our center has subsequently identified sporadic hospital-associated MABC infections, which have led to additional safeguards [38, 39]. Therefore, careful clinical surveillance for MABC and other NTM is critical to identify infections and potential outbreaks, promoting timely interventions [40].

The primary limitations of this study are related to the single-center cohort, which may limit generalizability to other lung transplant recipients and hospitals. First, nearly half of cases occurred during the pulmonary phase of the MABC

outbreak at our hospital. While diagnosis during the outbreak period did not appear to affect clinical outcomes, this outbreak likely still influenced study findings. Second, most cases, even if not contemporaneous with the outbreak, were caused by 2 primary MABC clones; other MABC clones may have different risks of acquisition and outcomes [2]. Third, varying transplant practices at other centers, such as donor and recipient selection, immunosuppression, and antibiotic prophylaxis, could also affect generalizability.

In conclusion, in this large case–control study, prolonged post-transplant ventilator duration was associated with early post–lung transplant MABC acquisition, which in turn was linked to increased hospital-days and decreased survival. The risk of adverse events appeared higher for patients who acquired *M. abscessus* subspecies *abscessus* or developed extrapulmonary infection. Given these poor outcomes, further studies are needed to determine the best strategies for MABC prevention, surveillance, and management.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author contributions. S.E.N. was responsible for study design, data collection, analysis, and interpretation, literature search, and manuscript writing and editing. M.E.Y. performed data collection and manuscript editing. J.M.R. was responsible for manuscript editing. D.J.A. and A.W.B. were responsible for study design, data collection, analysis, and interpretation, and manuscript editing.

Data availability. Deidentified data will be made available to investigators after approval of a data use proposal. Proposals may be submitted to arthur.baker@duke.edu.

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases (K08 AI163462 to A.W.B.) and the Stead Program of the Duke University Department of Medicine (to S.E.N.). The remaining authors have no funding source to disclose.

Potential conflicts of interest. A.W.B. served as an investigator for 2 clinical trials of amikacin liposome inhalation suspension for patients with *Mycobacterium avium* complex pulmonary disease, sponsored by Insmed (payments to the institution, outside of submitted work). A.W.B. and D.J.A. have participated in the Centers for Disease Control and Prevention's Prevention Epicenter Program (grant to the institution, outside of submitted work). D.J.A. received royalties from UpToDate Online, LLC, and is the owner of Infection Control Education for Major Sports, LLC. All other authors report no potential conflicts.

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