American Journal of Transplantation xxx (xxxx) xxx

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

Risk factors, management, and clinical outcomes of invasive *Mycoplasma* and *Ureaplasma* infections after lung transplantation

Patrick C.K. Tam [1,*], Rochelle Hardie [2], Barbara D. Alexander [1,3], Michael E. Yarrington [1,4], Mark J. Lee [3], Chris R. Polage [3], Julia A. Messina [1], Eileen K. Maziarz [1], Jennifer L. Saullo [1], Rachel Miller [1], Cameron R. Wolfe [1], Sana Arif [1], John M. Reynolds [5], John C. Haney [6], John R. Perfect [1], Arthur W. Baker [1,4,**]

[1] *Division of Infectious Diseases, Duke University School of Medicine, Durham, North Carolina, USA*
[2] *Division of Infectious Diseases, College of Medicine, University of Florida, Gainesville, Florida, USA*
[3] *Duke University Clinical Microbiology Laboratory, Durham, North Carolina, USA*
[4] *Duke Center for Antimicrobial Stewardship and Infection Prevention, Durham, North Carolina, USA*
[5] *Department of Medicine, Transplant Pulmonology, Duke University School of Medicine, Durham, North Carolina, USA*
[6] *Division of Cardiovascular and Thoracic Surgery, Duke University School of Medicine, Durham, North Carolina, USA*

ARTICLE INFO

Keywords:
mollicute infection
Mycoplasma species
Ureaplasma species
lung transplantation

ABSTRACT

Mollicute infections, caused by *Mycoplasma* and *Ureaplasma* species, are serious complications after lung transplantation; however, understanding of the epidemiology and outcomes of these infections remains limited. We conducted a single-center retrospective study of 1156 consecutive lung transplants performed from 2010-2019. We used log-binomial regression to identify risk factors for infection and analyzed clinical management and outcomes. In total, 27 (2.3%) recipients developed mollicute infection. Donor characteristics independently associated with recipient infection were age ≤40 years (prevalence rate ratio [PRR] 2.6, 95% CI 1.0-6.9), White race (PRR 3.1, 95% CI 1.1-8.8), and purulent secretions on donor bronchoscopy (PRR 2.3, 95% CI 1.1-5.0). Median time to diagnosis was 16 days posttransplant (IQR: 11-26 days). Mollicute-infected recipients were significantly more likely to require prolonged ventilatory support (66.7% vs 21.4%), undergo

Abbreviations: BAL, bronchoalveolar lavage; CI, confidence intervals; DUH, Duke University Hospital; HS, hyperammonemia syndrome; IQR, interquartile range; OPTN, organ procurement and transplant network; PCR, polymerase chain reaction; PRR, prevalence rate ratios.

* Corresponding author. Patrick C.K. Tam, Division of Infectious Diseases, Duke University School of Medicine, Durham, NC, USA .
** Corresponding author. Arthur W. Baker, Division of Infectious Diseases, Duke University School of Medicine, Durham, NC, USA .
E-mail addresses: Patrick.Tam@duke.edu (P.C.K. Tam), Arthur.Baker@duke.edu (A.W. Baker).

https://doi.org/10.1016/j.ajt.2023.08.019
Received 6 March 2023; Received in revised form 8 August 2023; Accepted 24 August 2023
Available online xxxx

dialysis (44.4% vs 6.3%), and remain hospitalized ≥30 days (70.4% vs 27.4%) after transplant. One-year posttransplant mortality in mollicute-infected recipients was 12/27 (44%), compared to 148/1129 (13%) in those without infection (P <0001). Hyperammonemia syndrome occurred in 5/27 (19%) mollicute-infected recipients, of whom 3 (60%) died within 10 weeks posttransplant. This study highlights the morbidity and mortality associated with mollicute infection after lung transplantation and the need for better screening and management protocols.

1. Introduction

Mollicutes, such as *Mycoplasma* species (spp.) and *Ureaplasma* spp., are a class of bacteria that commonly colonize the urogenital tract.[1,2] Lacking a cell wall, these bacteria are not identifiable on traditional Gram-stain methods and are intrinsically resistant to beta-lactams. Their small size and limited biosynthetic function further complicate culture recovery. Excluding *M. pneumoniae*, infections associated with these bacteria are limited largely to urogenital conditions in immunocompetent patients, although extragenital infections can occur, particularly in the immunocompromised host.[3] Extragenital mollicute infection after lung transplantation is well described, predominantly for *M. hominis*, *U. parvum*, and *U. urealyticum*.[4-6] Donor transmission of mollicute infection after lung transplantation was first proposed in a report of 2 single orthotopic lung transplant recipients who developed *M. hominis* pneumonia after receiving lungs procured from the same donor.[5] Subsequent studies using molecular diagnostics further support donor acquisition of mollicute infection among lung transplant recipients.[6,7]

Clinical syndromes associated with mollicute infection in lung transplant recipients include pneumonia, superficial and deep surgical site infections including empyema and anastomotic dehiscence.[8-13] Hyperammonemia syndrome (HS) is a posttransplant complication strongly associated with mollicute infection that results from the metabolism of arginine and urea by *Mycoplasma* spp. and *Ureaplasma* spp., respectively.[14-16] Increased ammonium production may lead to accumulation and subsequent encephalopathy, coma, seizures, and death.[17] HS, irrespective of concurrent mollicute infection, can affect up to 4% of lung transplant recipients with an associated mortality of up to 75%.[14,15,18]

While mollicute infections after lung transplantation can cause substantial morbidity and mortality, data on the epidemiology, management, and outcomes of these infections remain sparse. Single-center studies have reported donor characteristics, including younger age,[19-21] sexual activity,[20,21] and aspiration preceding death[19] as potential risk factors for recipient mollicute infections; however, most transplant centers lack policies for donor screening. Similarly, no consensus exists for recipient management, and clinical outcomes of mollicute-infected recipients without HS are largely unknown. The prevalence of recipient mollicute infection is similarly uncertain due to the technical challenges with standard culture methods[22] and the nonspecific clinical features associated with infection.

We performed this single-center retrospective cohort study to better understand mollicute infections occurring after lung transplantation, including risk factors for infection, clinical presentation, management, and outcomes.

2. Materials and methods

2.1. Setting and transplant protocols

Duke University Hospital (DUH) is a 957-bed academic hospital and transplant center located in North Carolina. This study included all lung transplant surgeries performed from January 2010 through December 2019 and 2 years of posttransplant follow-up. Mollicute-selective cultures or polymerase chain reaction (PCR) testing of transplant recipient specimens was performed only if clinicians suspected mollicute infection. When mollicute cultures were ordered, specimens were incubated on mollicute-selective media at DUH for up to 5 days. Standard bacterial cultures performed on routine media were incubated for up to 14 days. Upon the clinician's request, specimens were sent to the University of Alabama at Birmingham Diagnostic Mycoplasma Laboratory or the Mayo Clinic Laboratories for PCR identification of *M. hominis*, *U. urealyticum*, and *U. parvum,* and antimicrobial susceptibility testing via microbroth dilution. Lung transplant donor samples were not tested for mollicutes.

Lung transplant recipients received induction immunosuppression with basiliximab, followed by maintenance immunosuppression consisting of a calcineurin inhibitor (eg, tacrolimus or cyclosporine), steroids, and an antimetabolite (eg, mycophenolate mofetil or azathioprine). Standard early posttransplant antibacterial prophylaxis included intravenous vancomycin and either cefepime or ceftazidime. No patients received additional antibacterial prophylaxis intended to prevent mollicute infection. Surveillance bronchoscopies for bronchoalveolar lavage (BAL) bacterial cultures, fungal cultures, mycobacterial cultures, and transbronchial biopsies were routinely performed 1, 3, 6, and 12 months after transplant. Diagnostic bronchoscopies were performed based on the clinician's judgment.

Over the course of this study, 2 clinical practice changes occurred that affected posttransplant mollicute diagnostic approaches. First, DUH clinicians began to utilize external laboratory PCR diagnostic mollicute testing in 2016. Second, beginning

in 2019, we provided education to lung transplant clinicians regarding donor-derived mollicute infections and encouraged a low threshold for posttransplant diagnostic testing, including serum ammonia levels for patients with posttransplant encephalopathy.

2.2. Analysis plan

We analyzed data on all consecutive lung transplant donors and their recipients transplanted at DUH from January 2010 through December 2019, including patients undergoing retransplantation and multiorgan recipients. Discrete donor and recipient demographics and clinical data prospectively submitted to the Organ Procurement and Transplantation Network (OPTN) per standard procedure were subsequently analyzed via the OPTN Thoracic Standard Transplant Analysis and Research datasets. Donors were classified as Public Health Service (PHS) increased-risk donors based on criteria established by the Centers for Disease Control and Prevention for viral bloodborne pathogen transmission.[23] Detailed donor sexual histories were not available.

The mollicute cohort in this study included all patients who had positive *Mycoplasma* spp. or *Ureaplasma* spp. cultures after transplant, or had a positive PCR test for *M. hominis*, *U. urealyticum*, or *U. parvum*. Date of diagnosis was defined as the collection date of the first positive mollicute test. For patients who underwent multiple lung transplants, mollicute infection was attributed to the transplant surgery that immediately preceded the diagnosis date. Transplant infectious diseases physicians retrospectively collected additional clinical data from the DUH electronic medical record on patients with mollicute infection. These data included presenting symptoms and signs of mollicute infection, microbiological studies, extent of infection, the development of HS, and characteristics of concurrent infections. Specific aspects of clinical management including modifications to immunosuppression, antimicrobial therapy, and procedural interventions were also collected. Finally, we analyzed clinical outcomes, including comorbidities experienced during the index transplant hospitalization, rejection up to 180 days posttransplant, and 2-year survival.

Beginning in 2015, data were collected on all lung recipients with mollicute-specific diagnostics (Mollicute-selective cultures or PCR) performed within the first 90 days after transplant, serum ammonia levels collected within 30 days posttransplant, and exposure to mollicute-active antibiotics within the first 30 days posttransplant. Antibiotics considered to have activity against mollicutes included doxycycline, minocycline, tigecycline, levofloxacin, moxifloxacin, azithromycin, and clindamycin.

At least 2 transplant infectious diseases physicians reviewed data on all patients in the mollicute cohort to adjudicate the diagnosis of mollicute infection and assess for HS. Definite mollicute infections included all cases of culture-proven infection outside of the pulmonary parenchyma, and respiratory isolation of mollicutes with evidence of clinical pneumonia or definite HS (Supplemental Table 1). Possible/probable infection occurred when patients had positive microbiologic studies for mollicutes from the respiratory tract alone without clearly attributable clinical infection. Clinical pneumonia was defined as the presence of new pulmonary infiltrates or changes in respiratory status resulting in an alteration to antimicrobial therapy. Definite HS required the presence of positive microbiologic studies for mollicutes, altered mentation, and a corresponding serum ammonia level $\geq$100 μmol/L. Patients with positive microbiologic studies, altered mentation, and ammonia levels of 51 to 99 μmol/L were categorized as having possible HS.

We used unadjusted log-binomial regression to compare clinical characteristics and outcomes of transplant recipients who developed mollicute infection with recipients without microbiologically proven mollicute infection. We then constructed a multivariate log-binomial regression model to identify independent predictors of posttransplant mollicute infection. We initially included all donor and recipient characteristics in the multivariate model that were epidemiologically plausible risk factors and had statistically significant univariate associations (P <05) with mollicute infection. After assessing for collinearity, we used a backward elimination strategy and included risk factors in the final model that were statistically significant predictors (P <05) of mollicute infection. Potential for confounding was evaluated by calculating the percent change in point estimates when variables were removed from the model. Prevalence rate ratios (PRR) were estimated using maximum likelihood. Wald 95% confidence intervals (CI) were calculated, and likelihood ratio Chi-square tests were used to compare prevalence rates. Chi-square tests were used to compare 1-year survival among recipients with mollicute infection that occurred after transplants performed in 2019 versus 2010-2018, as well as to compare donor characteristics for patients who underwent transplants in 2019 versus prior years. Two-year survival for recipients stratified by development of mollicute infection was analyzed using the Kaplan-Meier method. Calculations were performed in SAS, version 9.4 (SAS Institute).

The Duke University Institutional Review Board approved this research (Reference Number: Pro00105729).

3. Results

3.1. Recipient and donor characteristics

From 2010-2019, our center performed 1156 lung transplant surgeries. Of this cohort, 27 (2.3%) patients developed microbiologically proven posttransplant mollicute infection. The median age, sex, indications for transplantation, and perioperative characteristics between patients with and without mollicute infection posttransplant were similar (Table 1). Donor characteristics associated with a statistically significant increased risk of recipient infection upon univariate analysis included age $\leq$40 years (81.5% vs 59.8%; P =.03), White race, (85.2% vs 64.0%; P = .03), and PHS increased risk for viral bloodborne pathogen transmission (40.7% vs 21.1%; P = .02) (Table 2).[23] A lung transplant recipient was also more likely to develop mollicute infection if the donor's cause of death was due to anoxia (48.1% vs 24.4%; P = .01) or if the donor had purulent secretions

Table 1

Recipient characteristics and outcomes for 1156 patients who underwent lung transplantation surgery from 2010-2019. Results are stratified by development of mollicute infection after transplant. Univariate associations between each variable and prevalence of mollicute infection were assessed with log-binomial regression.

Recipient characteristic	Recipient mollicute infection (N = 27)		No recipient mollicute infection (N = 1129)		PRR for recipient mollicute infection (95% CI)		*P* value
Preoperative characteristics							
Age at transplant, median (IQR), y[a]	59	(49-68)	60	(47-67)	1.0	(0.8-1.3)	.89
Male sex	14	(51.9)	683	(60.5)	0.7	(0.3-1.5)	.37
Race/ethnicity							
White	23	(85.2)	1019	(90.3)	0.6	(0.2-1.8)	.38
Black	3	(11.1)	84	(7.4)	1.5	(0.5-5.0)	.48
Hispanic	1	(3.7)	18	(1.6)	2.3	(0.3-16.1)	.40
Other[b]	0	(0)	8	(0.7)	0	N/A	1.0
Underlying pulmonary disease							
Idiopathic pulmonary fibrosis	14	(51.9)	467	(41.4)	1.5	(0.7-3.2)	.28
Chronic obstructive pulmonary disease	2	(7.4)	177	(15.7)	0.4	(0.1-1.8)	.26
Cystic fibrosis	1	(3.7)	172	(15.2)	0.2	(0.0-1.6)	.13
Other disease	10	(37.0)	313	(27.7)	1.5	(0.7-3.3)	.29
Prior lung transplant	2	(7.4)	69	(6.1)	1.2	(0.3-5.1)	.78
Obese (BMI $>$ 30 kg/m^2)	1	(3.7)	21	(1.9)	2.0	(0.3-14.0)	.49
Underweight (BMI $<$ 20 kg/m^2)	1	(3.7)	219	(19.4)	0.2	(0.0-1.2)	.07
Diabetes mellitus	3	(11.1)	281	(24.9)	0.4	(0.1-1.3)	.12
Renal insufficiency (creatinine $\geq$ 1.3mg/dL)	4	(14.8)	100	(8.9)	1.8	(0.6-5.0)	.29
Karnofsky Performance Status Score $\leq$ 30%[c]	6	(22.2)	159	(14.1)	1.7	(0.7-4.2)	.24
Lung allocation score, median (IQR)[d]	42.4	(36.9-62.7)	43.4	(36.8-54.4)	1.0	(0.8-1.3)	.73
Perioperative characteristics							
Hospitalized at time of transplant	4	(14.8)	165	(14.6)	1.0	(0.4-2.9)	.98
Ventilator at time of transplant	1	(3.7)	62	(5.5)	0.7	(0.1-4.8)	.69
ECMO at time of transplant	2	(7.4)	53	(4.7)	1.6	(0.4-6.6)	.51
Ischemic time, median (IQR), h[a]	6.2	(5.2-7.7)	6.6	(5.6-7.9)	1.0	(0.8-1.1)	.61
Bilateral lung transplantation[d]	22	(81.5)	859	(76.1)	1.4	(0.5-3.6)	.52
CMV mismatch (recipient CMV negative)	7	(25.9)	277	(24.5)	1.1	(0.5-2.5)	.87
Clinical outcomes							
Posttransplant ventilator support >5 d[e]	**18**	**(66.7)**	**236**	**(21.4)**	**6.9**	**(3.1-15.2)**	**<.0001**
Dialysis between transplant and discharge	**12**	**(44.4)**	**71**	**(6.3)**	**10.3**	**(5.0-21.4)**	**<.0001**
Transplant hospitalization ≥30 d	**19**	**(70.4)**	**309**	**(27.4)**	**6.0**	**(2.7-13.6)**	**<.0001**
Death ≤180 d after transplant	**7**	**(25.9)**	**80**	**(7.1)**	**4.3**	**(1.9-9.9)**	**.0006**
Death ≤365 d after transplant	**12**	**(44.4)**	**148**	**(13.1)**	**5.0**	**(2.4-10.4)**	**<.0001**

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

Abbreviations: BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; LAS, lung allocation score; N/A, not applicable; PRR, prevalence rate ratio.

[a] Prevalence rate ratios and confidence intervals are given for 10-year increase in age, 10-point increase in lung allocation score,[24] and 1-h increase in ischemic time, respectively.

[b] Other race/ethnicity for recipients without mollicute infection was reported as Asian (n = 6) or American Indian/Alaska Native (n = 2).

[c] Missing data on performance status[25] were excluded for 1 (0.1%) recipient who did not develop mollicute infection.

[d] One patient who developed mollicute infection underwent combined bilateral lung and heart transplantation.

[e] Missing data on duration of ventilator support were excluded for 25 (2.2%) recipients who did not develop mollicute infection.

identified on bronchoscopy at the time of procurement (37.0% vs 19.2%; $P = .02$).

Multivariate analysis demonstrated that donor characteristics of age ≤40 years (PRR, 2.6; 95% CI, 1.0-6.9), White race (PRR, 3.1; 95% CI, 1.1-8.8), and purulent secretions on bronchoscopy (PRR, 2.3; 95% CI, 1.1-5.0) were independent risk factors for recipient mollicute infection (Table 3). Donor PHS increased risk status and death due to anoxia were not independent predictors of recipient infection and did not suggest notable confounding when removed from the multivariate model, changing point estimates of remaining variables by less than 15%. Of the 27 patients with mollicute infection, 22 (81%) had donors with at least 2 of the 3 independent risk factors, whereas only 543 (48%) donors not associated with recipient mollicute infection had 2 or more risk factors. However, 4 of the 5 mollicute infections linked to donors with fewer than 2 risk factors had invasive extrapulmonary infections.

Table 2

Donor characteristics for 1156 patients who underwent lung transplantation surgery from 2010-2019. Results are stratified by recipient development of mollicute infection after transplant. Univariate associations between each variable and prevalence of recipient mollicute infection were assessed with log-binomial regression.

Donor characteristic, n (%)	Recipient mollicute infection (N = 27)		No recipient mollicute infection (N = 1129)		PRR for recipient mollicute infection (95% CI)		*P* value
Age ≤40 y	**22**	**(81.5)**	**675**	**(59.8)**	**2.9**	**(1.1-7.6)**	**.03**
Male sex	20	(74.1)	696	(61.6)	1.8	(0.7-4.1)	.20
Race/ethnicity							
White	**23**	**(85.2)**	**722**	**(64.0)**	**3.2**	**(1.1-9.1)**	**.03**
Black	2	(7.4)	256	(22.7)	0.3	(0.1-1.2)	.08
Hispanic	1	(3.7)	83	(7.4)	0.5	(0.1-3.6)	.48
Other[a]	1	(3.7)	68	(6.0)	0.6	(0.1-4.4)	.62
Obese (BMI > 30 kg/m^2)	5	(18.5)	269	(23.8)	0.7	(0.3-1.9)	.52
Underweight (BMI < 20 kg/m^2)	1	(3.7)	87	(7.7)	0.5	(0.1-3.4)	.45
Diabetes mellitus[b]	2	(7.4)	101	(8.9)	0.8	(0.2-3.4)	.78
Renal insufficiency (creatinine ≥ 1.3)	10	(37.0)	368	(32.6)	1.2	(0.6-2.6)	.63
PHS increased risk donor[c]	**11**	**(40.7)**	**239**	**(21.2)**	**2.5**	**(1.2-5.3)**	**.02**
Heavy alcohol use[d]	5	(19.2)	168	(15.2)	1.3	(0.5-3.4)	.57
Death due to anoxia	**13**	**(48.1)**	**275**	**(24.4)**	**2.8**	**(1.3-5.9)**	**.01**
Abnormal chest X-ray[e]	18	(66.7)	762	(67.7)	1.0	(0.4-2.1)	.91
Purulent secretions on bronchoscopy[f]	**10**	**(37.0)**	**217**	**(19.2)**	**2.4**	**(1.1-5.2)**	**.02**

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

Abbreviations: BMI, body mass index; CI, confidence interval; N/A, not applicable; PHS, Public Health Service; PRR, prevalence rate ratio.

[a] Other race/ethnicity for donor associated with recipient mollicute infection was reported as multiracial. Other race/ethnicity for donors not associated with recipient mollicute infection was reported as multiracial (n = 45), Asian (n = 22), or American Indian/Alaska Native (n = 1).

[b] Diabetes mellitus was considered not to be present for 9 (0.8%) donors for whom diabetes status was not documented. These donors were not associated with recipient mollicute infection.

[c] Donor at increased risk for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus transmission to recipient, according to the United States Public Health Service guideline recommendations.[23]

[d] Data on heavy alcohol use were excluded for 25 (2.2%) donors with unknown alcohol use histories. These donors included 1 donor associated with recipient mollicute infection and 24 donors not associated with recipient mollicute infection.

[e] Data on chest X-ray findings were excluded for 4 (0.3%) donors without reported chest X-ray findings. These donors were not associated with recipient mollicute infection.

[f] As documented at time of procurement. Secretions were considered not to be purulent for 43 (3.7%) donors for whom bronchoscopy findings were not documented. These donors included 2 donors associated with recipient mollicute infection and 41 donors not associated with recipient mollicute infection.

Table 3
Characteristics of lung transplantation donors that were independent predictors of recipient mollicute infection after transplant performed from 2010-2019. Multivariate analysis was performed with log-binomial regression.

Donor characteristic[a]	Prevalence rate (95% CI)	*P* value
Age ≤40	2.6 (1.0-6.9)	.05
White race	3.1 (1.1-8.8)	.04
Purulent secretions on bronchoscopy	2.3 (1.1-5.0)	.03

[a] Other donor characteristics included in the multivariable model prior to backward elimination were Public Health Service increased infection risk donor status and death due to anoxia.

3.2. Diagnostics and microbiology

Among the 27 patients with mollicute infection, 15 (56%) patients had isolated extrapulmonary disease, 11 (41%) patients had isolated pulmonary disease, and 1 (4%) patient had both pulmonary and extrapulmonary disease (Table 4). Of the 11 patients with isolated pulmonary disease, 6 patients had clinical pneumonia or definite HS. No patients developed urogenital infection. Most infections were caused by *M. hominis* or *U. urealyticum* (22/27; 81%). *Ureaplasma* spp. were identified in 10 (83%) of 12 infections with pulmonary involvement, whereas *Mycoplasma* spp. were identified in 11 (69%) of 16 extrapulmonary infections (Fig. 1).

Median time to mollicute diagnosis was 16 days posttransplant (interquartile range [IQR]:11-26 days), and most infections (22/27; 81%) were detected during the index transplant admission (Table 4). Isolated pulmonary infections trended toward an earlier diagnosis at a median of 13 days posttransplant (IQR, 5-21 days), compared to extrapulmonary infections at a median of 20 days (IQR, 13-32 days; $P = .12$). Initial diagnosis occurred from culture growth on mollicute-selective media in 19 (70%) patients. The remaining patients were diagnosed via standard bacterial cultures (6/27; 22%) or PCR of BAL fluid (2/27; 7.4%). All standard bacterial cultures detecting mollicute infection isolated *M. hominis*; culture diagnosis of *Ureaplasma* spp. infections uniformly required use of mollicute-selective media. Antimicrobial susceptibility testing was performed on 12 isolates. All isolates were susceptible to tetracycline; 2 isolates were levofloxacin resistant; and 1 isolate was erythromycin-resistant (Supplemental Table 2).

3.3. Clinical syndrome and management

The most common clinical characteristics associated with mollicute infection were leukocytosis and pleural effusion, occurring in 17 (63%) and 16 (59%) patients, respectively (Table 4). All 16 patients with extrapulmonary infection underwent invasive procedural or surgical intervention, including thoracentesis (4/16; 25%), chest tube insertion (6/16; 38%), and surgical site wound debridement (13/16; 81%). Patients with

Table 4
Clinical characteristics and antimicrobial treatment of 27 lung transplant recipients with mollicute infection.

Characteristic		
Median time from transplant to diagnosis, d (IQR)	16	(11-26)
Extent of infection, n (%)		
Isolated extrapulmonary disease[a]	15	(56)
Isolated pulmonary infection	11	(41)
Definite pulmonary infection	6	(19)
Possible/probable pulmonary infection	5	(22)
Extrapulmonary and pulmonary disease	1	(4)
Species identified causing infection[b], n (%)		
Mycoplasma hominis	11	(41)
Mycoplasma species. not further identified	1	(4)
Ureaplasma parvum	1	(4)
Ureaplasma urealyticum	12	(44)
Ureaplasma species. not further identified	3	(11)
Initial diagnostic test identifying infection, n (%)		
Standard bacterial media culture[c]	6	(22)
Selective mollicute media culture[d]	19	(70)
Polymerase chain reaction	2	(7)
Signs and symptoms at time of infection, n (%)		
Encephalopathy	10	(37)
Clinical pneumonia[e]	11	(41)
Fever	10	(37)
Leukocytosis (peripheral white blood cell count ≥ 12 × 10^9cells/L)	17	(63)
Pulmonary effusion	16	(59)
Unilateral	7	(26)
Bilateral	9	(33)
Peak serum ammonia level, n (%)		
≤50 μmol/L	5	(19)
51-99 μmol/L	5	(19)
≥100 μmol/L	6	(22)
Not performed	11	(41)
Hyperammonemia syndrome, n (%)		
Definite	5	(19)
Possible	4	(15)
Median duration of antimicrobial treatment, weeks (IQR)	6	(4-8)
Antimicrobial regimen, n (%)		
Doxycycline and levofloxacin	18	(67)

(*continued on next page*)

Table 4 (*continued*)

Characteristic		
Doxycycline and azithromycin	2	(7)
Doxycycline	2	(7)
Other[f]	5	(19)

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

[a] Defined as infection outside of the lung parenchyma including pleural infections.

[b] One patient had infection with both *Mycoplasma* and *Ureaplasma* species.

[c] Bacterial media consisting of horse-blood agar.

[d] Mycoplasma media consisting of A8 Agar and 10B broth tube.

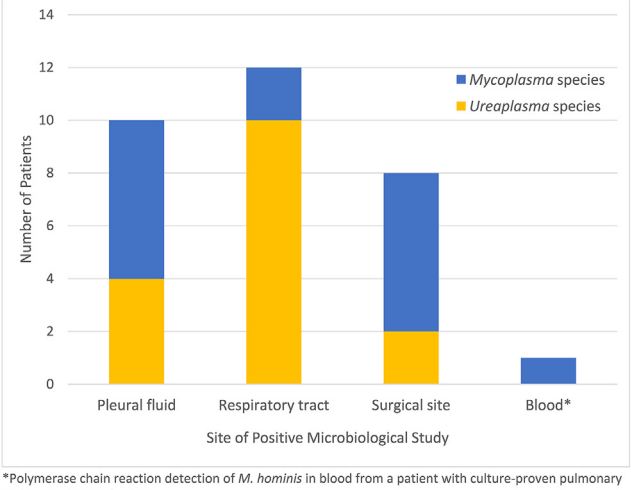
[e] Defined as the presence of new pulmonary infiltrates or changes in respiratory status resulting in an alteration to antimicrobial therapy.

[f] Doxycycline + azithromycin + ciprofloxacin (n = 1); doxycycline + ciprofloxacin (n = 1); doxycycline + moxifloxacin (n=1); moxifloxacin + azithromycin (n = 1); moxifloxacin (n = 1).

mollicute infection universally received antimicrobial therapy with antimollicute activity (Fig. 2 and Supplemental Table 3).

Most patients (18/27; 67%) were treated with dual doxycycline and levofloxacin for the duration of their antibiotic course; median total duration of therapy was 6 weeks (IQR: 4-8 weeks). Immunosuppression was not changed in 13/27 (48%) patients, and antimetabolite therapy was suspended in 12/27 (44%) patients. Calcineurin inhibition was modified from tacrolimus to cyclosporine in 2/27 (7%) due to concerns of altered mentation. Biopsy-proven acute cellular rejection (ACR) within 180 days of transplantation occurred in 10/27 (37%) patients, and most rejection episodes (8/10; 80%) were diagnosed after the diagnosis of mollicute infection.

In total, 5/27 (19%) mollicute-infected patients met criteria for definite HS (Table 5). HS was diagnosed with a median time of 16 days (range, 4-26 days) after transplant. *Ureaplasma* spp. were the causative pathogens in 4/5 (80%) patients and *M. hominis*-associated HS was identified in 1 patient. At the time of HS diagnosis, 3 (60%) patients were on dialysis for renal replacement therapy, and the other 2 (40%) patients were commenced on dialysis to facilitate ammonia removal. Most patients (4/5; 80%) additionally received bowel decontaminants for hyperammonemia.



*Polymerase chain reaction detection of *M. hominis* in blood from a patient with culture-proven pulmonary and surgical site infections.

Figure 1. Sites of infection among 27 lung transplant recipients who developed *Mycoplasma* spp. or *Ureaplasma* spp. Infection.

3.4. Outcomes

Compared to patients without mollicute infection, patients who developed mollicute infection were more likely to require ventilatory support beyond 5 days posttransplant (66.7% vs 21.4%; $P < .0001$), undergo dialysis during their index hospitalization (44.4% vs 6.3%; $P < .0001$), and remain hospitalized ≥30 days after transplant (70.4% vs 27.4%; $P < .0001$) (Table 1). In the first year after transplant, 12 (44%) patients in the mollicute cohort died compared to 148 (13%) deaths among patients without infection ($P < .0001$) (Table 1). Only 1 additional mollicute-infected patient died in the second posttransplant year (Fig. 3). In the mollicute cohort, 9 (69%) of 13 total deaths were deemed at least possibly attributable to mollicute infection (Fig. 2). Of patients with HS, 3 (60%) of 5 patients died within the first 10 weeks after transplant, and all deaths within the HS cohort were at least possibly attributable to mollicute infection (Table 5 and Supplemental Table 4).

3.5. Longitudinal trends

Mollicute diagnoses in 2019, the final year of the study, accounted for 10/27 (37%) cases identified in this 10-year cohort. Among those diagnosed with mollicute infection in 2019, only 2/10 (20%) patients died within 1 year of transplant, compared to 10/17 (59%) patients with mollicute infection who underwent transplant over the previous 9 years ($P = .05$).

In 2015, only 4 (4%) of 107 lung transplant recipients had a mollicute-specific culture performed within the first 90 days after transplant (Supplemental Fig. 1) and only 15 (14%) recipients underwent serum ammonia within 30 days after transplant (Supplemental Fig. 2). Use of mollicute-specific cultures and serum ammonia testing increased over time, and in 2019, 46 (36%) of 128 recipients had a mollicute culture performed, and 50 (39%) recipients had a serum ammonia level tested. Mollicute PCR testing was first used in 2016 but was utilized in only 14 patients throughout the full study period. Early posttransplant use of antibiotics with antimollicute activity among recipients without known mollicute acquisition remained stable until a modest decrease in antibiotic utilization occurred in 2018-2019 (Supplemental Fig. 3).

For transplant surgeries performed in 2019, most donor characteristics were similar to those of donors for transplants performed from 2010-2018 (Supplemental Table 6); however, donors from 2019 were significantly more likely to be White (75.0% vs 63.1%; $P = .01$ for White vs. non-White race) and have PHS increased risk status (35.2% vs 19.9%; $P < .0001$). The 2019 donors were also more likely to be younger than 40 years of age (68.0% vs 59.3%; $P = .06$) and have died from anoxia (31.3%

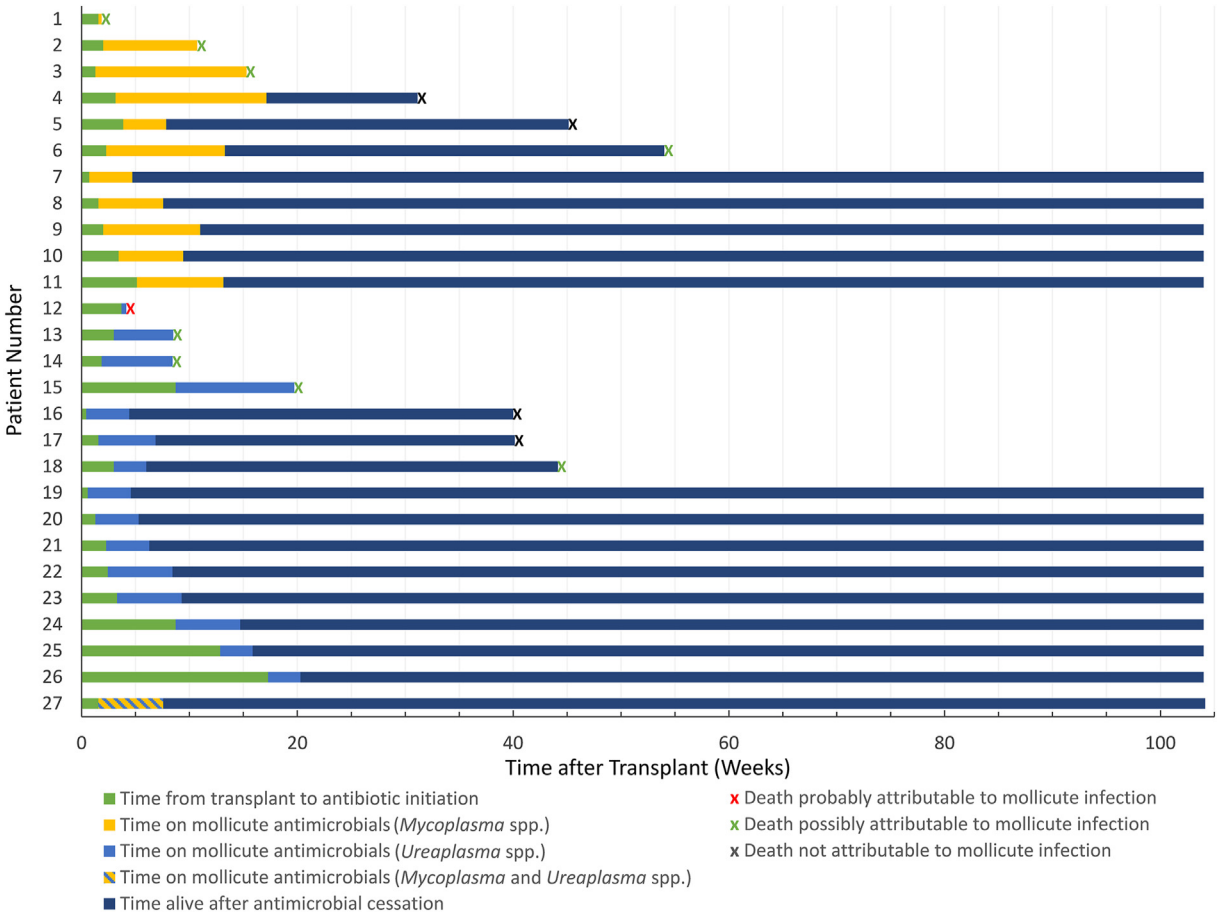


Figure 2. Clinical courses of 27 lung transplant recipients who acquired posttransplant *Mycoplasma hominis* or *Ureaplasma species*.

vs 24.1%; $P = .08$), though these trends did not reach statistical significance.

3. Discussion

We analyzed the epidemiology, risk factors, clinical characteristics, and outcomes associated with mollicute infections that occurred after lung transplantation at a large transplant center. To our knowledge, this study includes the largest published cohort of culture-proven mollicute infections post–lung transplantation. Donor-related factors that increased risk of recipient infection included young age, White race, and purulent secretions in the donor's lungs at the time of procurement. In contrast, no key recipient risk factors were identified, suggesting a risk for these donor-derived infections in all recipients. Recipients with mollicute infection had longer index hospitalizations, increased time on mechanical ventilation, and increased mortality. Morbidity and mortality were further magnified in those with HS.

Clinical signs and symptoms characterizing mollicute infection were nonspecific, and disease severity was highly variable. *Ureaplasma* spp. were more common in pulmonary specimens whereas *Mycoplasma* spp. were more common in extrapulmonary cultures. Notably, mollicute-selective media for extrapulmonary specimens was rarely used, potentially limiting the detection of small *Ureaplasma* spp. colonies[1]; this practice contrasts with the near-universal use of mollicute-selective cultures in respiratory samples that showed pulmonary mollicute infection. Nonspecific clinical signs highlight the need for maintained hypervigilance for mollicute infection posttransplant and the potential for improved detection through use of mollicute-specific diagnostics.

Nearly all patients with mollicute infection received several weeks of combination antimicrobial therapy. Dual antibiotic therapy use was based on proposed synergistic benefits, and the potential for antibiotic resistance to macrolides, tetracyclines, and fluoroquinolones.[26-28] Notably, no isolate in our study was tetracycline-resistant, and *in vitro* resistance to macrolides and fluoroquinolones was uncommon. Our data suggest that doxycycline monotherapy could be appropriate in some scenarios (eg, early respiratory colonization or mild pulmonary infection). In addition to receiving antimicrobial therapy, nearly half of patients had antimetabolite immunosuppression held during acute infections. The rate of ACR in the mollicute-infected cohort did not exceed historical rates at our center.[29] Additional studies are needed to better instruct antimicrobial treatment and immunosuppressive management as demonstrated by the heterogeneity in management shown in this cohort.

Patients with extrapulmonary infections or HS required adjuncts to antimicrobials. In all cases of extrapulmonary infection, patients underwent invasive procedures, such as drainage of pleural effusions or surgical debridement of infected tissue. In cases of HS, all patients received dialysis, either as renal

Table 5
Patient characteristics, management, and outcomes of 5 lung transplant recipients with definite hyperammonemia syndrome.

Patient number	Age, sex (y of transplant)	Indication for transplant	Time from transplant to mollicute diagnosis (d)	Pathogen	Site of infection	Peak ammonia level[a] (μmol/L)	Antibiotic duration (wk)	Dialysis performed at the time of HS diagnosis	Bowel decontaminants given at the time of HS diagnosis[b]	Clinical outcome (wk of follow-up after transplant)
6	69 yo, F (2016)	IPF	16	*Mycoplasma hominis*	Pulmonary and Extrapulmonary	114	11	Yes	Lactulose Rifaximin	Death, possible contribution from mollicute infection (54)
12	49 yo, F (2019)	pHTN	26	*Ureaplasma urealyticum*	Pulmonary	>1000	3	Yes[c]	Lactulose Rifaximin	Death, probably attributable to mollicute infection (4)
13	50 yo, F (2017)	PM-ILD	21	*Ureaplasma urealyticum*	Pulmonary	199	6	Yes[c]	Lactulose Rifaximin	Death, possibly attributable to mollicute infection (9)
14	67 yo, M (2018)	IPF	13	*Ureaplasma* species	Pulmonary	102	7	Yes[c]	None	Death, possible contribution from mollicute infection (9)
19	53 yo, M (2019)	IPF	4	*Ureaplasma urealyticum*	Pulmonary	100	4	Yes	Lactulose Rifaximin Metronidazole	Cure (104)

Abbreviations: HS, hyperammonemia syndrome; IPF, idiopathic pulmonary fibrosis; pHTN, pulmonary hypertension; PM-ILD, polymyositis associated interstitial lung disease; yo, year old.

[a] Measured 2-weeks before or after mollicute diagnosis.

[b] Bowel decontaminant agents used specifically to treat hyperammonemia syndrome.

[c] Dialysis initiated prior to diagnosis of mollicute infection for management of renal failure.

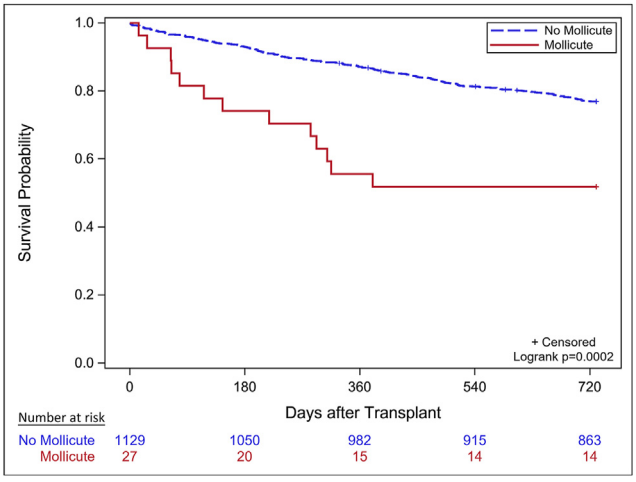


Figure 3. Kaplan-Meier curve of lung transplant recipients with and without mollicute infection over a 2-year posttransplant period.

replacement therapy or to facilitate ammonia removal; nearly all patients received bowel decontaminating agents to further promote ammonia reduction, though the benefit of these practices is unclear.[14,18] One patient with HS had disseminated infection from *M. hominis* detected on multiple mollicute-specific cultures without concurrent growth of *Ureaplasma* spp., adding to the evidence of *M. hominis* as a potential cause of HS,[30] despite the stronger link between *Ureaplasma* spp. and HS.[15]

Our data affirm the findings of other studies demonstrating mollicute infection post–lung transplant as a donor-derived infection.[4-6,21,31] Also consistent with prior studies, young donor age increased the risk of mollicute infection in our cohort,[19-21] and male donors were associated with an increased risk of infection that did not reach statistical significance.[19,21] Our analysis also revealed novel risk factors for mollicute infection, including the presence of purulent secretions on donor bronchoscopy and White donor race. The association between purulent donor secretions and mollicute infection supports donor aspiration as a means of inoculation with urogenital *Mycoplasma* and *Ureaplasma* spp. colonizing the oropharynx, presumably acquired through oropharyngeal sex.[19,32] The association between White race and risk of infection has not been previously reported. Rather than a genetic predisposition to mollicute colonization, this association likely reflects other unmeasured factors associated with donor race, possibly related to social behaviors or sexual practices.[33] The potential utility of including donor secretions and race in predictive models of donor respiratory mollicute colonization and recipient infection merits further study.

This study highlights the significant adverse outcomes associated with posttransplant mollicute infection and the need for pre-emptive screening or earlier disease detection. At present, most centers do not employ protocolized donor or recipient screening, nor is there an accepted standard for recipient antimicrobial prophylaxis or monitoring for posttransplant infection. At least 1 transplant center screens donor lungs via BAL with mollicute-selective cultures and *Ureaplasma* spp. PCR, administering dual antimicrobial prophylaxis to recipients until a negative screen result or 14 days of therapy in cases of a positive result.[21] Investigators at 2 other centers reported their experience with screening recipient serum ammonia levels and either donor[31] or early postoperative recipient[20] BAL with *Mycoplasma* and *Ureaplasma* PCRs; results of these studies instructed recipient management.

Near the end of our study, we began providing education to clinicians regarding posttransplant mollicute infections and promoted a low threshold for diagnostic testing, including serum ammonia testing for patients with posttransplant encephalopathy. Following this intervention, utilization of mollicute-specific cultures and serum ammonia levels increased. An apparent increase in the prevalence of mollicute infections also occurred at the end of the study, likely reflecting increased awareness and diagnostic testing, which may have contributed to improved survival. Independent of testing practices, characteristics of the 2019 donor cohort may have increased risk of recipient mollicute infection at the end of the study. The 2% prevalence of recipient mollicute infection reported for the full study cohort likely underestimates the true prevalence due to incomplete diagnostic testing and frequent use of antibiotics active against mollicutes that may have successfully treated occult infections.

Variability in screening and management practices emphasizes the need for carefully designed studies to ascertain the value of donor respiratory tract mollicute screening and protocolized management of recipients. While selective donor screening would reduce diagnostic resources compared to universal donor screening, use of a selective strategy in our cohort would have excluded several donors linked to important extrapulmonary recipient infections. Future studies could also elucidate whether prophylactic recipient antimicrobial therapy targeting mollicutes could be avoided in recipients of donors who screen negative. Finally, uncertainties remain about the relative performance of culture and PCR methods for both screening and diagnosis of clinical infection. Moreover, a lack of FDA-approved molecular tests for urogenital mollicutes impacts the ability to routinely test donors with a standardized assay. In our study, diagnostic PCR was rarely utilized but may lead to earlier detection if available locally.[2,34] Conversely, PCR could detect airway colonization and lead to antibiotic overuse among recipients who may not progress to clinical infection.[20]

This study had 3 primary limitations, largely due to its retrospective nature. First, some mollicute infections may not have been captured, particularly early in the study due to

potential underuse of mollicute-specific diagnostics. Consequently, the true prevalence of mollicute infection may be underestimated. Second, 5 patients were classified as having possible/probable infection when microbiological confirmation was limited to pulmonary specimens. Some of these patients may have had respiratory colonization without invasive infection. Distinguishing between colonization and infection was difficult due to our practice of administering prompt antimollicute therapy for all lung transplant recipients with positive mollicute microbiologic studies. Third, our experience with mollicute infections may not be fully generalizable to other institutions due to

differences in donor selection and recipient management, including immunosuppression, antimicrobial prescribing practices, and the threshold for performing mollicute-specific diagnostic studies.

Mollicute infection after lung transplantation is difficult to diagnose and is associated with substantial morbidity and mortality, particularly for recipients who develop HS. Keys to early diagnosis include a high index of clinical suspicion and specific microbiological testing. This study identified donor risk factors associated with the development of infection, and screening for mollicutes in the donor's lungs prior to transplantation may prevent recipient infections and improve outcomes; however, the best protocols for donor screening and recipient prophylaxis remain unknown. The management of recipient mollicute infection remains heterogeneous and depends on site of infection, disease severity, and presence of HS. Further studies are needed to improve our understanding of donor-derived infections caused by *Mycoplasma* and *Ureaplasma* spp. and promote strategies to best mitigate the complications they cause.

Author contributions

A.B., E.M., and C.W. conceptualized the study; P.T., R.H., M.Y., J.M., E.M, J.S., R.M., C.W., S.A., and A.B. collected data; P.T. and A.B. drafted the manuscript and analyzed the data; all authors contributed to the interpretation of results and critically appraised the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Julia A. Messina receives royalties from UpToDate. Dr Barbara D. Alexander receives royalties from UpToDate

Funding

AWB was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (grant no. K08-AI163462).

Data availability

Deidentified data from this study will be made available to investigators after approval of a data use proposal. Proposals may be submitted to Arthur.Baker@duke.edu.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2023.08.019.

ORCiD

Patrick C.K. Tam https://orcid.org/0000-0003-4602-1889
Barbara D. Alexander https://orcid.org/0000-0001-5868-0529
Michael E. Yarrington https://orcid.org/0000-0003-3186-1519
Chris R. Polage https://orcid.org/0000-0003-1433-6886
Julia A. Messina https://orcid.org/0000-0001-6411-198X
Eileen K. Maziarz https://orcid.org/0000-0001-7779-9605
Jennifer L. Saullo https://orcid.org/0000-0002-7684-431X
Rachel Miller https://orcid.org/0000-0001-7387-1171
John M. Reynolds https://orcid.org/0000-0003-4766-8852
John R. Perfect https://orcid.org/0000-0003-0019-8638
Arthur W. Baker https://orcid.org/0000-0002-0914-0291

References

1. Taylor-Robinson D, McCormack WM. The Genital mycoplasmas. *N Engl J Med*. 1980;302(18):1003–1010. https://doi.org/10.1056/NEJM198005013021805.
2. Waites KB, Xiao L, Paralanov V, Viscardi RM, Glass JI. Molecular methods for the detection of *Mycoplasma* and *Ureaplasma* infections in humans: a paper from the 2011 William Beaumont Hospital Symposium on molecular pathology. *J Mol Diagn*. 2012;14(5):437–450. https://doi.org/10.1016/j.jmoldx.2012.06.001.
3. Meyer RD, Clough W. Extragenital *Mycoplasma hominis* infections in adults: emphasis on immunosuppression. *Clin Infect Dis*. 1993;17(suppl 1):S243–S249. https://doi.org/10.1093/clinids/17.supplement_1.s243.
4. Fernandez R, Ratliff A, Crabb D, Waites KB, Bharat A. Ureaplasma transmitted from donor lungs is pathogenic after lung transplantation. *Ann Thorac Surg*. 2017;103(2):670–671. https://doi.org/10.1016/j.athoracsur.2016.09.026.
5. Gass R, Fisher J, Badesch D, et al. Donor-to-host transmission of *Mycoplasma hominis* in lung allograft recipients. *Clin Infect Dis*. 1996; 22(3):567–568. https://doi.org/10.1093/clinids/22.3.567.
6. Smibert OC, Wilson HL, Sohail A, et al. Donor-derived *Mycoplasma hominis* and an apparent cluster of *M. hominis* cases in solid organ transplant recipients. *Clin Infect Dis*. 2017;65(9):1504–1508. https://doi.org/10.1093/cid/cix601.
7. Sampath R, Patel R, Cunningham SA, et al. Cardiothoracic transplant recipient *Mycoplasma hominis*: an uncommon infection with probable donor transmission. *EBioMedicine*. 2017;19:84–90. https://doi.org/10.1016/j.ebiom.2017.04.026.
8. Vecchio M, Koutsokera A, Touilloux B, et al. Bronchial anastomosis dehiscence and stenosis caused by donor-transmitted *Mycoplasma hominis* infection in a lung transplant recipient: case report and literature review. *Transpl Infect Dis*. 2021;23(2):e13475. https://doi.org/10.1111/tid.13475.
9. Lyon GM, Alspaugh JA, Meredith FT, et al. *Mycoplasma hominis* pneumonia complicating bilateral lung transplantation: case report and review of the literature. *Chest*. 1997;112(5):1428–1432. https://doi.org/10.1378/chest.112.5.1428.
10. Hopkins P. A cluster of *Mycoplasma hominis* infection in heart-lung transplantation. *J Heart Lung Transplant*. 2001;20(2):223–224. https://doi.org/10.1016/s1053-2498(00)00492-7.
11. Hagiya H, Yoshida H, Yamamoto N, et al. *Mycoplasma hominis* periaortic abscess following heart-lung transplantation. *Transpl Infect Dis*. 2017;19(3). https://doi.org/10.1111/tid.12697.
12. Boyle Jr EM, Burdine J, Bolman III RM. Successful treatment of *Mycoplasma* mediastinitis after heart-lung transplantation. *J Heart Lung Transplant*. 1993;12(3):508–512.
13. Dixit A, Alexandrescu S, Boyer D, Graf EH, Vargas SO, Silverman M. *Mycoplasma hominis* empyema in an 18-year-old stem cell and lung transplant recipient: case report and review of the literature. *J Pediatr Infect Dis Soc*. 2017;6(4):e173–e176. https://doi.org/10.1093/jpids/pix049.
14. Leger RF, Silverman MS, Hauck ES, Guvakova KD. Hyperammonemia post lung transplantation: a review. *Clin Med Insights Circ Respir Pulm*

Med. 2020;14:1179548420966234. https://doi.org/10.1177/1179548420966234.

15. Bharat A, Cunningham SA, Scott Budinger GR, et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. *Sci Transl Med*. 2015;7(284). https://doi.org/10.1126/scitranslmed.aaa8419, 284re283:284re3.
16. Wylam ME, Kennedy CC, Hernandez NM, et al. Fatal hyperammonaemia caused by *Mycoplasma hominis*. *Lancet*. 2013; 382(9908):1956. https://doi.org/10.1016/S0140-6736(13)62115-7.
17. McLaughlin DC, Mallea JM, Ng LK. Hyperammonemia presenting as refractory status epilepticus after lung transplant in a patient positive for *Ureaplasma parvum*. *Indian J Crit Care Med*. 2018;22(6):463–465. https://doi.org/10.4103/ijccm.IJCCM_356_17.
18. Chen C, Bain KB, Iuppa JA, et al. Hyperammonemia syndrome after lung transplantation: A Single Center experience. *Transplantation*. 2016; 100(3):678–684. https://doi.org/10.1097/TP.0000000000000868.
19. Fernandez R, Chi M, Ison MG, et al. Sequelae of donor-derived Mollicutes transmission in lung recipients. *Am J Respir Crit Care Med*. 2017;195(5):687–689. https://doi.org/10.1164/rccm.201607-1377LE.
20. Buzo BF, Preiksaitis JK, Halloran K, et al. Association between *Mycoplasma* and *Ureaplasma* airway positivity, ammonia levels, and outcomes post-lung transplantation: A prospective surveillance study. *Am J Transplant*. 2021;21(6):2123–2131. https://doi.org/10.1111/ajt.16394.
21. Roberts SC, Bharat A, Kurihara C, Tomic R, Ison MG. Impact of screening and treatment of *Ureaplasma* species on hyperammonemia syndrome in lung transplant recipients: A Single Center experience. *Clin Infect Dis*. 2021;73(9):e2531–e2537. https://doi.org/10.1093/cid/ciaa1570.
22. Spiller OB. Emerging pathogenic respiratory *Mycoplasma hominis* infections in lung transplant patients: time to reassesses it's role as a pathogen? *EBioMedicine*. 2017;19:8–9. https://doi.org/10.1016/j.ebiom.2017.05.002.
23. Jones JM, Kracalik I, Levi ME, et al. Assessing solid organ donors and monitoring transplant recipients for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection – U.S. Public Health Service guideline, 2020. *MMWR Recomm Rep*. 2020;69(4):1–16. https://doi.org/10.15585/mmwr.rr6904a1.
24. United Network for Organ Sharing. A guide to calculating the lung allocation score. https://www.unos.org/wpcontent/uploads/unos/lung-allocation-score.pdf. Accessed April 21, 2022.
25. Snyder J, Salkowski N, Lamb K, et al. Karnofsky performance score and its use in risk adjustment of transplant outcomes in the United States. Scientific Registry of Transplant Recipients. Accessed April 21, 2022. https://www.srtr.org/media/1111/atc2012_kasiske_snyder_part_ii.pdf.
26. Ahmadi MH. Resistance to tetracyclines among clinical isolates of *Mycoplasma hominis* and *Ureaplasma* species: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2021;76(4):865–875. https://doi.org/10.1093/jac/dkaa538.
27. Meygret A, Le Roy C, Renaudin H, Bébéar C, Pereyre S. Tetracycline and fluoroquinolone resistance in clinical *Ureaplasma* spp. and *Mycoplasma hominis* isolates in France between 2010 and 2015. *J Antimicrob Chemother*. 2018;73(10):2696–2703. https://doi.org/10.1093/jac/dky238.
28. Palù G, Valisena S, Barile MF, Meloni GA. Mechanisms of macrolide resistance in *Ureaplasma urealyticum*: a study on collection and clinical strains. *Eur J Epidemiol*. 1989;5(2):146–153. https://doi.org/10.1007/BF00156820.
29. Baker AW, Maziarz EK, Arnold CJ, et al. Invasive fungal infection after lung transplantation: epidemiology in the setting of antifungal prophylaxis. *Clin Infect Dis*. 2020;70(1):30–39. https://doi.org/10.1093/cid/ciz156.
30. Nowbakht C, Edwards AR, Rodriguez-Buritica DF, et al. Two cases of fatal hyperammonemia syndrome due to Mycoplasma hominis and Ureaplasma urealyticum in immunocompromised patients outside lung transplant recipients. *Open Forum Infect Dis*. 2019;6(3):ofz033. https://doi.org/10.1093/ofid/ofz033.
31. Vijayvargiya P, Esquer Garrigos Z, Kennedy CC, et al. Routine donor and recipient screening for *Mycoplasma hominis* and *Ureaplasma* species in lung transplant recipients. *Open Forum Infect Dis*. 2022; 9(11):ofac607. https://doi.org/10.1093/ofid/ofac607.
32. Sackel SG, Alpert S, Fiumara NJ, Donner A, Laughlin CA, McCormack WM. Orogenital contact and the isolation of *Neisseria gonorrhoeae, Mycoplasma hominis*, and *Ureaplasma urealyticum* from the pharynx. *Sex Transm Dis*. 1979;6(2):64–68. https://doi.org/10.1097/00007435-197904000-00004.
33. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLOS ONE*. 2014;9(1):e86023. https://doi.org/10.1371/journal.pone.0086023.
34. Xiao L, Glass JI, Paralanov V, et al. Detection and characterization of human *Ureaplasma* species and serovars by real-time PCR. *J Clin Microbiol*. 2010;48(8):2715–2723. https://doi.org/10.1128/JCM.01877-09.