Routine Donor and Recipient Screening for *Mycoplasma hominis* and *Ureaplasma* Species in Lung Transplant Recipients

Prakhar Vijayvargiya,1,2 Zerelda Esquer Garrigos,1,2 Cassie C. Kennedy,3 Richard C. Daly,4 Mark E. Wylam,3 Robin Patel,1,5 and Elena Bean1,6

1Division of Infectious Diseases, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA, 2Division of Infectious Diseases, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA, 3Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA, 4Cardiovascular Surgery, Department of Surgery, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA, and 5Division of Clinical Microbiology, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA

**Background.** *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum* may cause post-transplant infections in lung transplant recipients. We evaluated routine pretransplant screening for these Mollicutes.

**Methods.** We retrospectively reviewed records of lung transplant recipients at our tri-site institution from 01/01/2015 to 11/15/2019. *M. hominis* and/or *Ureaplasma* polymerase chain reaction (PCR) was performed on pretransplant recipient urine specimens and donor bronchial swabs at the time of transplantation. Development of Mollicute infection and hyperammonemia syndrome (HS) was recorded.

**Results.** A total of 268 patients underwent lung transplantation during the study period, of whom 105 were screened with at least 1 Mollicute PCR. Twelve (11%) screened positive; 10 donors, 1 recipient, and 1 both. Among positive donors, 3 were positive for *M. hominis*, 5 for *U. urealyticum*, and 4 for *U. parvum*. Preemptive therapy included doxycycline, levofloxacin, and/or azithromycin administered for 1–12 weeks. Despite therapy, 1 case of *M. hominis* mediastinitis and 1 case of HS associated with *Ureaplasma* infection occurred, both donor-derived. Of those screened before transplant, cases with positive screening were more likely (*P < 0.05*) to develop Mollicute infection despite treatment (2/12, 17%) than those who screened negative (1/93, 1%).

**Conclusions.** Pretransplant recipient urine screening had a low yield and was not correlated with post-transplant Mollicute infection, likely because most *M. hominis* and *U. parvum/urealyticum* infections in lung transplant recipients are donor-derived. Routine donor bronchus swab PCR for *M. hominis*, *U. urealyticum*, and *U. parvum* followed by preemptive therapy did not obviously impact the overall incidence of Mollicute infection or HS in this cohort.

**Keywords.** *Mycoplasma*; lung transplantation; Mollicutes; pretransplant screening; *Ureaplasma*.

Pre-/peritransplant screening for *Mycoplasma hominis* and *Ureaplasma* species was incorporated by several institutions after fatal cases of hyperammonemia syndrome (HS) attributed to *Ureaplasma parvum* or *urealyticum* and *M. hominis*-associated mediastinitis, surgical site infection, and pleural space infections were reported post–lung transplant [1–3]. Hyperammonemia is well described in patients with liver failure, and a condition called hyperammonemia syndrome (HS) had been recognized following lung transplantation absent hepatic dysfunction, with no apparent etiology, until a sentinel case observation in 2011 [4]. Subsequently, we and others have linked Mollicute infection with HS following lung transplantation [2, 5]. Post-transplant infections with *M. hominis* more typically present as mediastinitis, surgical site infection, or pleuritis [6, 7]. As not all empiric post-transplant antibiotics cover Mollicutes, the reported mortality of HS in lung transplant recipients has been as high as 67% [8, 9]. Both *U. parvum* and *U. urealyticum* alongside *M. hominis* have been shown to be donor-transmitted and can be part of normal genitourinary microbiota [10]. We previously reported the absence of Mollicute colonization in bronchoalveolar lavage (BAL) specimens from immunosuppressed nontransplant patients [10].

Our institution initiated a PCR-based Mollicute screening protocol for donor colonization via donor bronchial swab and pretransplant urine testing of lung transplant candidates in 2015. A laboratory-developed PCR test was used as culture requires specialized media, technical skill for interpretation of microscopic colonies, and can take 2–5 days for results [11]. Positive screening triggered preemptive therapy, with

Received 21 July 2022; editorial decision 01 November 2022; accepted 03 November 2022; published online 7 November 2022.

Correspondence: Prakhar Vijayvargiya, MBBS, Division of Infectious Diseases, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216 (pvijayvargiya@umc.edu).

Open Forum Infectious Diseases®

© The Author(s) 2022. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

https://doi.org/10.1093/ofid/ofac607

Pretransplant Screening for Mollicutes • OFID • 1
antimicrobial choice and duration not protocolized. Data to support recipient and donor screening and preemptive therapy are currently lacking. In this study, we retrospectively evaluated the effectiveness of routine screening in preventing future *M. hominis* and *U. parvum/urealyticum* infections, including HS, in lung transplant recipients.

**METHODS**

**Study Population**

We retrospectively evaluated patients who underwent lung transplantation at our tri-site institution (Arizona, Florida, Minnesota) between 1/1/2015 and 11/15/2019. All patients who had undergone *M. hominis* or *U. urealyticum/parvum* PCR screening were included. This included donor bronchus testing at the time of transplant and candidate urine testing pre-transplant. In addition, we assessed any patient who underwent *M. hominis* or *U. urealyticum/parvum* PCR or culture testing post-transplant for diagnosis of infection or HS. Post-transplant ammonia levels in all lung transplant recipients were obtained using institutional Advanced Cohort Explorer software and individually reviewed by the study team. Patients with elevated ammonia levels were assessed for attribution to Mollicute infection. The study was approved by the Mayo Clinic Institutional Review Board (ID: 19-011956). The routine antibiotic prophylaxis protocol used in this patient population is available in the Supplementary Data.

The primary outcome was development of HS or infection from *M. hominis* or *U. urealyticum/parvum*. Demographic data, clinical presentation, microbiological data, and management details were recorded.

**Specimens and Sample Collection**

*M. hominis* or *U. urealyticum/parvum* PCR was performed on urine of recipients as part of pretransplant screening. *M. hominis* or *U. urealyticum/parvum* PCR was also performed on donor bronchus swabs at the time of transplantation. *M. hominis* or *U. urealyticum/parvum* PCR on plasma, bronchoalveolar lavage fluid, or tissue specimens was performed in the post-transplant period when infection was suspected, as clinically indicated. Laboratory-developed real-time PCRs targeting the tuf gene for *M. hominis* and the ureC gene for *U. urealyticum* and *U. parvum*, as described by Cunningham et al. [11], were used.

**Definitions**

Hyperammonemia was defined as an ammonia level above the upper limit of normal (reference range, \( \leq 30 \mu \text{moL/L} \)) and HS as the development of new or worsening altered mental status (AMS) in the context of hyperammonemia absent liver disease and leading to treatment. For patients receiving sedation, inability to wean sedatives in the setting of rising ammonia levels was considered evidence of HS.

**Statistical Analysis**

Continuous variables are reported as medians and interquartile ranges (IQRs) and categorical variables as frequencies and percentages. The \( \chi^2 \) test was used to compare categorical variables and the Kruskal-Wallis test to analyze continuous variables among PCR-positive and PCR-negative cases. Statistical tests were 2-tailed, with \( P \leq 0.05 \) considered statistically significant. All analyses were performed using JMP software (SAS Institute, Cary, NC, USA).

**RESULTS**

**Demographic Characteristics**

A total of 268 patients (58 Minnesota, 5 Arizona, and 205 Florida) underwent lung transplantation during the study.
period. In cases of retransplantation, only the most recent transplant course was reviewed. Screening was incorporated at different times at the 3 sites and was variably used even after adoption. Screening PCR was performed in 105 cases (Figure 1). Positive PCR was observed in 12/105 (11%) patients, of whom 11 results were from donor bronchus swabs and 2 were from recipient urines (in 1 case both donor and recipient specimens were positive). Of the 12 cases with a positive screening PCR, the majority of donors were female (8/12, 67%) (Table 1). The median age (IQR) of donors in the PCR-positive group (22 [18–29] years) was lower (P = .01) than the PCR-negative group (27 [21–37] years) and those who did not undergo PCR testing (37 [22–45] years). Among the 11 positive donor PCR-positive cases, 3 were positive for M. hominis, 5 for U. urealyticum, and 4 for U. parvum (Figure 2). In 1 case, screening was positive for U. urealyticum with M. hominis detected by post-transplant testing. In another case, both U. urealyticum and M. hominis were detected in the donor sample, and a third Mollicute, U. parvum, was detected in the recipient pretransplant urine sample. The only other positive pretransplant candidate urine sample was positive for U. urealyticum.

Overall, Mollicute infection was seen in 3/105 (3%) cases who underwent screening compared with 4/163 (3%) cases

| Characteristic                     | PCR Positive, No. (%) (n = 12) | PCR Negative, No. (%) (n = 93) | No PCR Testing, No. (%) (n = 163) | P Value |
|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|---------|
| Donor characteristics             |                                |                                |                                   |         |
| Sex, female                       | 8 (66.67)                      | 47 (52.22)*                    | 62 (42.18)*                       | .04     |
| Age, median (IQR), y              | 22 (18–29)                     | 27 (21–37)*                    | 37 (22–45)*                       | .01     |
| Race                              |                                |                                |                                   | .74     |
| White                             | 8 (67)                         | 54 (58)                        | 81 (49.69)                        |         |
| Hispanic                          | 1 (8)                          | 5 (5)                          | 13 (7.98)                         |         |
| Black                             | 0                              | 14 (15)                        | 34 (20.86)                        |         |
| Asian                             | 0                              | 3 (3)                          | 3 (1.84)                          |         |
| Other                             | 3 (25)                         | 17 (18)                        | 32 (19.63)                        |         |
| PHS increased risk                | 4 (33)                         | 28 (30)                        | 24 (14.72)                        | .01     |
| Recipient characteristics         |                                |                                |                                   |         |
| Sex, female                       | 5 (42)                         | 38 (41)                        | 58 (35.58)                        | .68     |
| Age, median (IQR), y              | 55 (42–63)                     | 59 (47–63)                     | 59 (53–67)                        | .05     |
| Race                              |                                |                                |                                   | .14     |
| White                             | 11 (92)                        | 70 (75)                        | 114 (69.94)                       |         |
| Hispanic                          | 0                              | 2 (2)                          | 2 (1.23)                          |         |
| Black                             | 0                              | 3 (3)                          | 24 (14.72)                        |         |
| Asian                             | 0                              | 2 (2)                          | 22 (13.5)                         |         |
| Other                             | 1 (8)                          | 16 (17)                        | 24 (14.72)                        |         |
| Indication for lung transplant    |                                |                                |                                   | .01     |
| ILD                               | 6 (50)                         | 52 (56)                        | 76 (46.63)                        |         |
| COPD                              | 1 (8)                          | 9 (10)                         | 22 (13.5)                         |         |
| Cystic fibrosis                   | 1 (8)                          | 8 (9)                          | 12 (7.36)                         |         |
| Pulmonary hypertension            | 3 (25)                         | 6 (7)                          | 1 (0.61)                          |         |
| Alpha-1 antitrypsin deficiency    | 1 (8)                          | 3 (3)                          | 1 (0.61)                          |         |
| Other                             | 0                              | 26 (28)                        | 51 (31.29)                        |         |
| LOS, median (IQR), d              | 21 (16–28)                     | 19 (14–30)                     | 17.5 (12–31)                      | .50     |
| Lung transplant site              |                                |                                |                                   | .01     |
| Bilateral sequential              | 7 (58)                         | 68 (73)                        | 105 (64.42)                       |         |
| En-block double                   | 4 (33)                         | 6 (7)                          | 1 (0.61)                          |         |
| Left                              | 1 (8)                          | 14 (15)                        | 34 (20.86)                        |         |
| Right                             | 0                              | 5 (6)                          | 21 (12.89)                        |         |
| Graft status                      |                                |                                |                                   | .38     |
| Functioning                       | 11 (92)                        | 84 (90)                        | 138 (84.67)                       |         |
| Failed                            | 1 (8)                          | 9 (10)                         | 25 (15.34)                        |         |

Abbreviations: COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IQR, interquartile range; LOS, length of stay; PCR, polymerase chain reaction; PHS, Public Health Service.

*Data are shown as No. (%), unless otherwise indicated.

*bData only available for 90 cases.

cData only available for 147 cases.

dData only available for 92 cases.
not screened before transplant. Cases with positive screening were more likely ($P \leq 0.05$) to develop Mollicute infection despite treatment (2/12, 17%) than those who screened negative (1/93, 1%). In the positive screening group, 1 patient died unrelated to a Mollicute infection. The choice of antibiotic therapy for positive cases was made by treating physicians and included doxycycline ($n = 6$), levofloxacin ($n = 6$), or azithromycin ($n = 3$) administered for durations ranging from 1 to 12 weeks (Table 2). Monotherapy was used in all patients except 2, where a combination of doxycycline and levofloxacin was prescribed. Interestingly, 1 of these 2 patients developed $M. hominis$ mediastinitis and the other HS.

**Test of Cure**

PCR was repeated in 8 patients. PCR returned negative as soon as 2 days and as long as 68 days after an initial positive result (Table 2).

**$M. hominis$ Mediastinitis and Empyema**

In the positive screening group, the patient who developed $M. hominis$ mediastinitis was a 63-year-old man who underwent bilateral lung transplantation for combined pulmonary fibrosis and emphysema. The donor was a 19-year-old female. The recipient did not undergo pretransplant urine screening, but the donor bronchial swab obtained at the time of transplantation returned PCR positive for $M. hominis$ and negative for $U. parvum/urealyticum$. Bronchial cultures obtained at transplantation grew $M. hominis$ in specimens from the right and left sides. The recipient was started on doxycycline 100 mg twice daily and levofloxacin 500 mg once daily. Levofloxacin was increased to 750 mg daily when the donor bronchus swab had growth of *Enterobacter cloacae* complex. Levofloxacin was stopped after 14 days, with doxycycline continued for a month. Five weeks after transplantation, the patient developed lower sternal site osteomyelitis and mediastinitis requiring incision and debridement and removal of sternal wires. $M. hominis$ PCR was positive from 2 bronchial washing specimens and sputum and negative from a sternal incision swab. The bronchial culture $M. hominis$ isolate from the time of transplantation was susceptible to clindamycin (minimum inhibitory concentration [MIC], 0.125 µg/mL), tetracycline (MIC, 0.125 µg/mL), and levofloxacin (MIC, 0.5 µg/mL). The patient was prescribed lifelong doxycycline.

Of the patients who tested with negative results, 1 developed $M. hominis$ mediastinitis 2 weeks after transplantation; screening of the donor bronchus swab was negative for $M. hominis$ and $U. parvum/urealyticum$, and recipient urine screening was not done. Two other patients developed empyema from $M. hominis$ but had no screening for Mollicutes.

**Hyperammonemia Syndrome**

Three patients developed HS during the study period; 2 did not have screening for Mollicutes. The one who had undergone screening was a 64-year-old male with idiopathic pulmonary fibrosis. He received lung transplantation from a 21-year-old male donor. *Ureaplasma* PCR was positive for $U. urealyticum$ from the donor bronchus swab. Donor $M. hominis$ and recipient pretransplant screening were not pursued. Three days after transplantation, the patient was started on levofloxacin 750 mg daily because of the positive PCR for $U. urealyticum$. The same day, he was confused and disoriented and required mechanical intubation. His ammonia level was 90 µmol/L, peaking at 114 µmol/L a couple of days later. Five days after transplantation, doxycycline 100 mg twice daily was added to levofloxacin, and Mollicute PCR testing was repeated on the bronchus swab, returning positive for $U. urealyticum$ and $M. hominis$. The recipient also received lactulose, rifaximin, and zinc. A week later, his mental status had returned to baseline, and his ammonia levels were within normal limits. Both

---

**Figure 2.** Distribution of screening PCR assays for Mollicutes in lung transplant recipients. Abbreviations: PCR, polymerase chain reaction; UP, *Ureaplasma parvum*; UU, *Ureaplasma urealyticum*. 4 • OFID • Vijayvargiya et al
| No. | Patient | Organism Detected | Source of PCR | Donor | Recipient | Donor | Recipient | Developed Infection | Ammonia Level, mg/L (Ref ≤ 20) | Preemptive Therapy | Preemptive Therapy Duration | Was PCR Repeated as Test of Cure? | Recipient Age, y | Recipient Race | Recipient Gender | Died | Donor Age, y | Donor Gender |
|-----|---------|-------------------|---------------|-------|-----------|-------|-----------|-------------------|-----------------------------|-------------------|-----------------------------|-----------------------------|---------------|--------------|----------------|-------|------------|------------|
| 1   | U. urealyticum | Bronchus swab | Positive | Negative | Negative | No | <10 | Levofloxacin | 1 wk | No | 40 | White | F | N | 29 | F |
| 2   | U. urealyticum | Bronchus swab | Positive | Negative | Negative | No | 17 | Doxycycline | 4 wk | Yes-negative after 2 d | 57 | White | M | Y | 30 | M |
| 3   | U. parvum | Bronchus swab | Positive | Negative | No | 42 | Doxycycline | 4 wk | Yes-positive 3 d later, negative 9 d later | 34 | White | M | N | 23 | M |
| 4   | U. parvum | Bronchus swab | Negative | Positive | No | 15 | Azithromycin | 12 wk | Yes-negative 9 d later | 47 | White | F | N | 18 | F |
| 5   | U. parvum | Bronchus swab | Positive | Negative | No | 13 | Levofloxacin | 3 wk | Yes-negative 13 d later | 51 | White | F | N | 22 | F |
| 6   | U. parvum | Bronchus swab | Positive | Negative | No | 20 | Doxycycline | 4 wk | Yes-positive for 21 d negative after 30 d | 24 | White | F | N | 16 | F |
| 7   | U. parvum | Bronchus swab | Positive | Negative | No | 39 | Doxycycline | 6 wk | Yes-negative 6 d later | 63 | White | M | N | 18 | F |
| 8   | U. parvum | Bronchus swab | Positive | Negative | No | 32 | Azithromycin | 3 wk | No | 53 | White | M | N | 32 | F |
| 9   | U. parvum | Bronchus swab | Positive | Negative | No | 114 | Doxycycline | 2 wk | Yes-positive 2, 4, and 5 d later, negative M. hominis 20 d later | 64 | White | M | N | 21 | M |
| 10  | U. parvum | Bronchus swab | Positive | Negative | No | 25 | Levofloxacin | 1 wk | No | 98 | White | M | N | 28 | M |
| 11  | U. parvum | Bronchus swab | Positive | Negative | No | 74 | Azithromycin | 2 wk | No | 62 | White | F | N | 22 | F |

**Table 2. Characteristics of Peritransplant PCR-Positive Cases**

**Abbreviations:** BAL, bronchoalveolar lavage; PCR, polymerase chain reaction.
antibiotics were stopped after 14 days. There was no relapse of Mollicute infection a year into follow-up.

The other 2 patients, who had not undergone Mollicute screening, developed HS early in the post-transplant period. One of these patients developed HS 10 days after transplantation from a 20-year-old donor with a peak ammonia level of 275 µmol/L. Subsequently, Ureaplasma PCR on BAL resulted positive for *U. urealyticum*. He was treated with 7 days of azithromycin and levofloxacin, with normalization of ammonia levels. Another patient developed HS 4 days after transplantation from a 19-year-old donor with a peak ammonia level of 1242 µmol/L. *Ureaplasma* PCR from BAL was positive for *U. parvum*. The patient developed multi-organ failure in the subsequent days and died of cerebral edema and herniation.

**Ammonia Level for the Cohort**

Overall, 135 lung transplant patients had ammonia levels assessed in the post-transplant setting. All 12 patients with any positive screening had ammonia levels followed. Of these 12 patients, in addition to the patient with HS, 3 lung transplant recipients had ammonia levels slightly higher than the reference range, but none developed HS. Of those with negative screening (n = 93) or no screening (n = 163), 59 and 64 patients, respectively, had ammonia levels followed in the post-transplant setting. The median ammonia level (IQR) was 32 (16–45) µmol/L in patients with positive screening, 35 (25–50) µmol/L in patients with negative screening, and 48 (35–64) µmol/L in patients with no screening. The median peak ammonia level (IQR) was 24 (17–35) µmol/L in patients with positive screening, 34 (15–65) µmol/L in patients with negative screening, and 47 (27–73) µmol/L in patients with no screening (Figure 3).

Of the patients with negative or no screening, 70 had ammonia levels above the reference range (Supplementary Table 1). Based on chart review, 25 developed HS in the post-transplant setting but were either not tested for a Mollicute or were found to be negative (4 had negative screening but did not have Mollicute PCR when they developed hyperammonemia, 4 had both screening and post-transplant testing, 11 had no screening but post-transplant testing was negative, and 6 had neither screening nor post-transplant testing). Despite the lack of confirmed Mollicute infection, 16 of these patients were treated with at least 1 of levofloxacin, azithromycin, or doxycycline.

**DISCUSSION**

Optimal screening and treatment for Mollicute infections in solid organ transplant patients lacks evidence-based practices. In this retrospective study, we observed that donor bronchus *M. hominis* and *U. urealyticum/parvum* positivity was more likely to be associated with Mollicute infection than candidate urine testing. In a cohort of 105 lung transplant cases screened for *M. hominis* and *U. urealyticum/parvum*, 12 (11%) were colonized with Mollicutes, and this colonization was associated with 1 *M. hominis*-related mediastinitis case and 1 HS case; both were donor-derived infections. Of these 105 cases, 93 (89%) had a negative screening test, of which only 1 developed *M. hominis*-related mediastinitis. The study findings suggest that despite treatment after a positive PCR screen for a Mollicute, local infection and HS may still occur. Patients who did not undergo screening and, hence, did not receive antibiotic treatment, developed Mollicute-related infections and HS at similar rates (3%) as patients who underwent screening (3%). Prognostically, patients with a negative screen were at lower risk of developing HS (0/93) compared with patients with a positive screen (1/12, 8%) and patients who did not undergo screening (2/163, 1%). In this cohort, prophylactic antimicrobial therapy following a positive Mollicute screen was initiated after receipt of the positive PCR result; the delay associated with administration of antibiotics may have affected outcomes.

Mollicutes are normal microbiota of the genitourinary tract with higher colonization rates in women (20%–80%) than men (<10%) [12, 13]. Genitourinary colonization, however, does not appear to be associated with post-transplant infections.

---

**Figure 3.** Distribution of peak ammonia levels in patients with positive screening, negative screening, and no screening. Abbreviation: PCR, polymerase chain reaction.
In this study, only 2 candidates were colonized with a Mollicute on urine testing, and none developed infection in the posttransplant period. Candidate screening with urine PCR was not beneficial, however; only 21 candidates underwent urine screening. This finding is similar to the results reported in a single-center study on 60 lung transplant patients by Roberts et al. [14]. In another study, Gerber et al. evaluated positive urine cultures for *U. urealyticum* and *M. hominis* in 10 renal allograft recipients with complications due to Mollicute infections limited to the genitourinary tract [15]. None of the cases developed HS.

Colonization of the respiratory tract with Mollicutes occurs in 1%–3% of healthy adults and 8% of individuals with chronic respiratory illness [16–18]. However, these data preceded the development of PCR technology and may underestimate colonization rates. In this cohort, 11% of donor lungs were found to be colonized with Mollicutes, which is similar to the 13.3% donor lung colonization previously reported [14]. Higher rates of respiratory colonization of donor lung also explain cases of mediastinitis and empyema, likely related to anatomical proximity to the location of transplantation. In our cohort, both *U. urealyticum* and *U. parvum* were more common in donor bronchus samples (4 *U. parvum* and 5 *U. urealyticum*). In contrast, in the study by Roberts et al., *U. urealyticum* was predominantly isolated from donor bronchoalveolar lavage samples (7/8 donor-positive samples were *U. urealyticum*) and *U. parvum* from recipient urine samples (4/5 recipient-positive samples were *U. parvum*) [14]. The mechanism of bronchial colonization by Mollicutes is not known, but unproven speculations include routine colonization, aspiration, oropharyngeal colonization during orogenital sexual activity, or distant colonization after introduction of Mollicutes in the bloodstream at the time of placement of the urinary catheter [14, 19]. Colonization with Mollicutes has been reported to be more common in individuals who are young and those with multiple sexual partners [20]. Similarly, in this cohort, donors who tested positive for Mollicutes were younger compared with donors who tested negative or did not undergo testing.

In our series, in one of the patients who developed HS, the donor bronchus swab was found to be colonized with both *M. hominis* and *Ureaplasma* species. This was similar to the initial case reported by Wy lam et al., where *M. hominis* was initially considered the culprit pathogen for HS, with subsequent analysis of residual BAL fluid and blood samples revealing that the patient harbored *Ureaplasma* species in addition to *M. hominis* [2, 21]. While the association between *Ureaplasma* infection and HS has been confirmed in vitro and in animal models, the same is not the case for *M. hominis*. Cases of HS with temporal association with only *M. hominis* have been limited to case reports or meeting abstracts [1, 3, 15, 21–25].

Despite antibiotic treatment, mediastinitis and HS did develop in 2 cases. Antibiotic treatment was started after the results of PCR tests became available. This delay in starting antibiotic treatment might have affected treatment outcomes. Inappropriate antibiotic therapy can also predispose to infection. However, in both cases, combination therapy with levo- floxacin and doxycycline was used. Transplant recipients commonly receive peri-operative β-lactam prophylaxis, but Mollicutes lack a cell wall, which makes them intrinsically resistant to β-lactams [26]. Because of β-lactam resistance and the significant morbidity and mortality associated with infection, clinicians at our institution adopted preemptive treatment with antibiotics if colonization is detected. *M. hominis* is intrinsically resistant to azithromycin [27]. Doxycycline and levofloxacin are first-line treatment options, with other options being linezolid, clindamycin, and moxifloxacin. While azithromycin and doxycycline are considered among initial treatment options for *Ureaplasma* species, the organism has variable susceptibility to doxycycline. This has prompted some clinicians to consider dual antibiotic therapy in the absence of susceptibility results. Alternative treatment options for *Ureaplasma* species include levofloxacin, ofloxacin, and moxifloxacin, while ciprofloxacin tends to have higher MICs [26]. Whether combination therapy is needed remains to be seen. At one institution, combination antibiotic therapy with levofloxacin and azithromycin is routinely used in all transplant patients from the day of transplantation until the *Ureaplasma* screening tests return negative [14]. With this approach, HS cases decreased from 10% (3/31) to 0% (0/29). Implementation of routine prophylaxis should include discussion about the lack of coverage of resistant Mollicutes, associated microbiome disturbances, and selection of resistance in commensal bacteria. Additionally, duration of antibiotic therapy and utility of test of cure are unknown. In our cohort, durations of antibiotic therapy ranged from 1 to 12 weeks, in contrast to 2 weeks of therapy used by Roberts et al. Larger studies and local/institutional prevalence data will be helpful to make these decisions.

In all cases, post-transplant infection developed within the first few months after transplantation; however, in cases where antibiotic treatment was given for a positive screening, a direct correlation between the isolate detected by screening and post-transplant complication could not be made in the absence of sequencing. Lack of urine and bronchial testing in all cases also limits the conclusions of this study. A prospective study with urine and bronchial testing in all patients would be better able to evaluate the utility of screening. Another limitation is our inability to determine the effectiveness and appropriate duration of antibiotic treatment because of small sample sizes and varying antibiotic regimens. In addition, in a majority of cases, susceptibility testing was not performed.

Apart from the lack of benefit from screening, widespread adoption of donor screening may be challenging. In this study, a laboratory-developed test was utilized for screening transplant donors and recipients for *M. hominis* and
that test negative. More research is needed to determine the definition of HS. It is possible that some of these patients developed HS in the absence of Mollicute infection, 15 tested negative for Mollicutes at the time they had elevated ammonia levels. Nonetheless, antibiotic treatment was administered in 16 cases.

In conclusion, donor-derived Mollicute positivity is more common than recipient positivity for Mollicutes in lung transplant patients. Screening of transplant candidates is not worthwhile, as urinary colonization does not translate to infection in lung transplant recipients. Transplant recipients of lungs positive for Mollicutes at the time of organ transplant appear to be at increased risk of subsequent Mollicute infection or HS, despite treatment, than those who receive lungs that test negative. More research is needed to determine whether prophylaxis, preemptive therapy, or neither is beneficial and to address the choice and duration of antibiotics if there is benefit.

Acknowledgments

Financial support. The authors received no financial support for the research, authorship, and/or publication of this article. Dr. Patel is supported by R21 AI150649 from the National Institute of Allergy and Infectious Diseases.

Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. P.V., Z.E.G., and E.B. conceived the study and prepared the manuscript. F.V. and Z.E.G. collected and verified the data. C.C.K., R.C.D., M.E.W., and R.P. contributed to reviewing and editing the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Patient consent. The study was exempt from patient consent. The study was approved by the Mayo Clinic Institutional Review Board (ID: 19-011956).

References

1. Buze 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 2020; 21: 2123–31.
2. Bharat A, Cunningham SA, Scott Budinger GR, et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med 2015; 7:284re3.
3. Smibert OC, Wilson HL, Sohal A, et al. Donor-derived Mycoplasma hominis and an apparent cluster of M. hominis cases in solid organ transplant recipients. Clin Infect Dis 2017; 65:1504–8.
4. Krutsinger D, Pezzulo A, Blevins AE, Reed RM, Voigt MD, Eberlein M. Idiopathic hyperammonemia after solid organ transplantation: primarily a lung problem? A single-center experience and systematic review. Clin Transplant 2017; 31.
5. Bharat A, Scott Budinger GR, Ison MG. Donor-derived Ureaplasma is a potentially lethal infection in lung allograft recipients. J Heart Lung Transplant 2017; 36: 917–8.
6. Mitsani D, Nguyen MH, Sáveira FP, et al. Mycoplasma hominis pericarditis in a lung transplant recipient: review of the literature about an uncommon but important cardiothoracic pathogen. Transpl Infect Dis 2010; 12:146–50.
7. Chang SY, Price TK, Beard OE, et al. Mycoplasma hominis infections in solid organ transplant recipients: clinical characteristics, treatment outcomes, and comparison of phenotypic and genotypic susceptibility profiles. Transpl Infect Dis 2022; 24:e13822.
8. Lichtenstein GR, Kaiser LR, Tuchman M, et al. Fatal hyperammonemia following orthotopic lung transplantation. Gastroenterology 1997; 112:236–40.
9. Roberts SC, Malik W, Ison MG. Hyperammonemia syndrome in immunosuppressed individuals. Curr Opin Infect Dis 2022; 35:262–8.
10. 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.
11. Cunningham SA, Mandrekar IN, Rosenblatt JE, Patel R. Rapid PCR detection of Mycoplasma hominis, Ureaplasma urealyticum, and Ureaplasma parvum. Int J Bacteriol 2013; 2013:168742.
12. Taylor-Robinson D. Mollicutes in vaginal microbiology: mycoplasma hominis, Ureaplasma urealyticum, Ureaplasma parvum and Mycoplasma genitalium. Res Microbiol 2017; 168:875–81.
13. Hornor P, Donders G, Cusini M, Gomborg M, Jensen JS, Unemo M. Should we be testing for urogenital Mycoplasma hominis, Ureaplasma parvum and Ureaplasma

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.
urealyticum in men and women?—A position statement from the European STI Guidelines Editorial Board. J Eur Acad Dermatol Venereol 2018; 32:1845–51.

14. Roberts SC, Bharat A, Kurihara C, Tomic R, Ison MG. Impact of screening and treatment of Ureaplasma spp on hyperammonemia syndrome in lung transplant recipients: a single center experience. Clin Infect Dis 2021; 73: e2531–7.

15. Gerber L, Gaspert A, Braghetti A, et al. Ureaplasma and Mycoplasma in kidney allograft recipients—a case series and review of the literature. Transpl Infect Dis 2018; 20:e12937.

16. Mufson MA. Mycoplasma hominis: a review of its role as a respiratory tract pathogen of humans. Sex Transm Dis 1983; 10:335–40.

17. Hendley JO, Jordan WS Jr. Mycoplasma pharyngeal flora in civilians. Am Rev Respir Dis 1968; 97:524–32.

18. Cultrera R, Seraceni S, Germani R, Contini C. Molecular evidence of Ureaplasma urealyticum and Ureaplasma parvum colonization in preterm infants during respiratory distress syndrome. BMC Infect Dis 2006; 6:166.

19. Lyon GM, Alspaugh JA, Meredith FT, et al. Mycoplasma hominis pneumonia complicating bilateral lung transplantation: case report and review of the literature. Chest 1997; 112:1428–32.

20. McCormack WM, Rosner B, Alpert S, Evrard JR, Crockett VA, Zinner SH. Vaginal colonization with Mycoplasma hominis and Ureaplasma urealyticum. Sex Transm Dis 1986; 13:67–70.

21. Wylam ME, Kennedy CC, Hernandez NM, et al. Fatal hyperammonaemia caused by Mycoplasma hominis. Lancet 2013; 382:1956.

22. Aguilar C, Gohir W, Tikkonen J, et al. Ureaplasma spp. and Mycoplasma hominis PCR in respiratory samples from lung transplant recipients with hyperammonemia syndrome and cerebral edema. J Heart Lung Transpl 2018; 37:S360.

23. Somerville L, Shigl W, Zelyas N, Lien D, Preiksaitis J. Surveillance for Mycoplasma/ Ureaplasma infection in lung transplant recipients (LTRs). Am J Transpl 2018; 18:858–9.

24. Baker AW, Messina JA, Maziarz EK, et al. 1758. Epidemiology of invasive Mycoplasma and Ureaplasma infections early after lung transplantation. Open Forum Infect Dis 2019; 6:5646.

25. Nowbakh 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:ofz033. doi: 10.1093/ofid/ofz033.

26. Martin DH. Genital mycoplasmas: Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma species. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases. Elsevier; 2015:2190–3.

27. Pereyre S, Gonzalez P, De Barbeyrac B, et al. Mutations in 23S rRNA account for intrinsic resistance to macrolides in Mycoplasma hominis and Mycoplasma fermentans and for acquired resistance to macrolides in M. hominis. Antimicrob Agents Chemother 2002; 46:3142–50.