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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Mycoplasma hominis infections in solid organ transplant recipients: Clinical characteristics, treatment outcomes, and comparison of phenotypic and genotypic susceptibility profiles

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Abstract

Background: *Mycoplasma hominis* can cause significant infections after solid organ transplantation (SOT). Treatment should be guided by susceptibility testing, but conventional lab methods are laborious with prolonged turnaround time (TAT). This case series compares the phenotypic and genotypic susceptibility profiles of *M. hominis* isolates identified from SOT patients.

Methods: This is a single-center retrospective study evaluating SOT recipients with confirmed *M. hominis* infections. Patients' demographic, clinical, microbiological, and radiographic data were collected. Culture of *M. hominis* isolates was performed according to current Clinical and Laboratory Standards Institute guidelines. Phenotypic susceptibility testing was performed by University of Alabama Diagnostic Mycoplasma Laboratory. Whole genome sequencing (WGS) was performed followed by bioinformatic analysis of known genetic determinants of resistance.

Results: Seven SOT recipients with *M. hominis* infections were identified. Two out of seven (28.5%) patients had resistance detected by phenotypic susceptibility testing (Case 5 to levofloxacin and Case 7 to tetracycline). Genomic analyses confirmed the presence of mutations in the *parC* and *parE* topoisomerase genes at positions conferring to fluoroquinolone resistance in the isolate from Case 5, while the tetracycline-resistant isolate from Case 7 harbored the *tetM* gene. The median TAT from the date of specimen collection was 24 days for phenotypic susceptibility testing and 14 days for genotypic susceptibility testing. All seven patients received antimicrobials directed toward *M. hominis* and recovered with complete resolution of infection.

Conclusions: WGS may offer a novel and more rapid methodology for *M. hominis* susceptibility testing to help optimize antimicrobial usage, but more data are needed.

Abbreviations: ATG, anti-thymocyte globulin; BLT, bilateral lung transplantation; CLSI, Clinical and Laboratory Standards Institute; ECMO, extracorporeal mechanical oxygenation; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; *M. hominis*, *Mycoplasma hominis*; MIC, minimum inhibitory concentration; MLST, multilocus sequence typing; NCBI, National Center for Biotechnology Information; OHT, orthotopic heart transplantation; OLT, orthotopic liver transplantation; PAH, pulmonary arterial hypertension; SLT, single lung transplantation; SOT, solid organ transplantation; TAT, turnaround time; UCLA, University of California, Los Angeles; WGS, whole genome sequencing; WT, wild type

KEYWORDS
antimicrobial susceptibility, *Mycoplasma hominis*, solid organ transplant, whole genome sequencing

1 | INTRODUCTION

Mycoplasma hominis is an established but under-recognized pathogen complicating solid organ transplantation (SOT). In SOT recipients, *M. hominis* has been associated with surgical site infections, sternal osteomyelitis, mediastinitis, pleural space infections, peritonitis, pyelonephritis, intra-abdominal abscesses, infected hematoma, bursitis, as well as disseminated infection which may be associated with hyperammonemia and encephalopathy.[1–11]

Despite its potential to cause significant morbidity and mortality in SOT recipients, the ideal empirical antimicrobial regimen and duration of therapy for *M. hominis* has not been established. *M. hominis* is intrinsically resistant to macrolides and has variable susceptibility to other antimicrobial classes. Effective antimicrobial options include tetracyclines, lincosamides, and fluoroquinolones, but there have been increasing reports of resistance to tetracyclines and fluoroquinolones.[12] Thus, empirical combination therapy is recommended until susceptibility results become available.[13] Due to the labor-intensive, time-consuming, and specialized culture techniques required,[14,15] in vitro susceptibility testing is not readily performed by most clinical and commercial microbiology laboratories. The turnaround time (TAT) can take weeks, meaning patients are treated by default with prolonged dual antimicrobial therapy, leading to increased risk of antimicrobial-associated toxicities. Obtaining susceptibility profiles more quickly could decrease polypharmacy and prevent drug-drug interactions, reduced adherence, and adverse drug events.

Compared to conventional phenotypic in vitro susceptibility testing, whole genome sequencing (WGS) has been shown to be a faster and equally reliable method of detecting antimicrobial resistance in slow-growing pathogens such as *Mycobacterium tuberculosis*.[16] Here, we report seven cases of *M. hominis* infections in SOT recipients. Phenotypic susceptibility testing and genotypic antimicrobial resistance prediction were performed on each isolate as a proof-of-concept exercise to determine the potential clinical utility of WGS for guiding antimicrobial therapy.

2 | MATERIALS AND METHODS

This is a single-center retrospective study evaluating SOT recipients with confirmed *M. hominis* infections at the University of California, Los Angeles (UCLA) Medical Center between January 1, 2020 and February 28, 2021 (Table 1). Patients' demographic, clinical, microbiological, and radiographic data were collected and recorded in a secure electronic database. This study has been exempted from review per the UCLA Institutional Review Board because it did not constitute human subjects research.

2.1 | Clinical information

All patients received induction immunosuppression with either basiliximab or anti-thymocyte globulin (ATG), and maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and glucocorticoid taper. Standard peri-transplant antibacterial prophylaxis consisted of piperacillin-tazobactam and vancomycin, which was subsequently tailored based on pertinent donor and recipient cultures and susceptibilities.

Clinical decision-making regarding empirical and definitive antimicrobial therapy for *M. hominis* was at the discretion of the treating clinicians based on the patient's clinical condition and phenotypic susceptibility testing. WGS was not used to guide antimicrobial therapy for these patients because it had not yet been validated for clinical use.

2.2 | Isolation and identification of *M. hominis*

Clinical specimens were inoculated in M5 transport media. 10B arginine broth and A8 selective agar plates (Thermo Scientific™ Remel) were then inoculated and incubated aerobically at 37°C and observed daily for growth and color change of the media. Positive (i.e., pink and turbid) 10B broth cultures were subcultured to A8 agar and incubated accordingly. Growth on the A8 agar plates was examined under 100x magnification. Colonies were identified using the VITEK MS matrix-assisted laser desorption ionization time-of-flight system (bioMérieux Inc, Hazelwood, MO). Cultures were finalized as negative after 7 days of incubation. Some isolates were sequenced retrospectively from frozen (-80°C) stocks. These are indicated in Table 2.

2.3 | Whole genome sequencing and bioinformatics

The Qiagen EZ1 Blood and Tissue Kit and the EZ1 Advanced XL instrument were used to extract genomic DNA from pure isolates of *M. hominis*. Library preparation was performed using the Nextera DNA Flex Library Prep Kit (Illumina) according to manufacturer's instructions. Sequencing was performed using the Illumina MiSeq v2 or v3 reagent kit to generate 250 bp paired-end reads.

Seven *M. hominis* isolates (one from each patient) were sequenced. Sequences were uploaded to National Center for Biotechnology Information (NCBI) under the BioProject PRJNA721191. Sequencing data, specimen source, and corresponding patient's case number for each isolate are listed in Table 2.

TABLE 1 Clinical information of solid organ transplantation recipients with *Mycoplasma hominis* infections at University of California, Los Angeles (UCLA) Medical Center between January 1, 2020 and February 28, 2021

Case	Age/sex	Transplantation indication	Transplantation type	Immunosuppression		Time of positive culture(s) (days post-transplant)	Clinical manifestations	Antimicrobial therapy	Infection outcome
				Induction	Maintenance				
1	34y/M	CHD, cardiac cirrhosis	OHT, OLT	BSX	Tacrolimus (goal 6–8 ng/ml) Prednisone 20 mg/d	14	PNA, PSI, septic shock	Doxycycline 100 mg BID for 42d and Levofloxacin 500 mg QD for 42d	Resolved
2	24y/M	ILD, PAH	BLT	BSX	Tacrolimus (goal 8–12 ng/ml) MMF 2 g/d Prednisone 25 mg/d	11	PSI	Doxycycline 100 mg BID for 53d	Resolved
3	64y/M	COPD	BLT	BSX	Tacrolimus (goal 8–10 ng/ml) MMF 2 g/d Prednisone 25 mg/d	10	AMS, hyperammonemia, PNA, septic shock, SSTI	Doxycycline 100 mg BID for 42d and Levofloxacin 750 mg QD for 42d	Resolved
4	63y/M	HP	SLT	BSX	Tacrolimus (goal 8–10 ng/ml) MMF 2 g/d Prednisone 20 mg/d	37	SSTI	Doxycycline 100 mg BID for 42d and Moxifloxacin 400 mg QD for 31d	Resolved
5	68y/M	IPF, PAH	SLT	BSX	Tacrolimus (goal 7–10 ng/ml) MMF 2 g/d Prednisone 25 mg/d	29	PSI	Doxycycline 100 mg BID for 42d and Levofloxacin 750 mg QD for 21d	Resolved
6	31y/M	IPF, CLAD	BLT	BSX	Tacrolimus (goal 8–12 ng/ml) MMF 2 g/d Prednisone 25 mg/d	11	PSI	Levofloxacin 750 mg QD for 10d, then Doxycycline 100 mg BID for 32d	Resolved
7	43y/M	HP	BLT	ATG	Tacrolimus (goal 8–12 ng/ml) MMF 2 g/d Prednisone 50 mg/d	9	PNA, septic shock	Doxycycline 100 mg BID for 17d and Levofloxacin 750 mg QD for 14d	Resolved

Abbreviations: AMS, altered mental status; ATG, anti-thymocyte globulin; BID, twice daily; BLT, bilateral lung transplantation; BSX, basiliximab; CHD, congenital heart disease; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; d, days; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; M, male; MMF, mycophenolate mofetil; OHT, orthotopic heart transplantation; OLT, orthotopic liver transplantation; PAH, pulmonary arterial hypertension; PNA, pneumonia; PSI, pleural space infection; QD, once daily; SLT, single lung transplantation; SSTI, skin and soft tissue infection; y, years.

TABLE 2 Phenotypic and genotypic susceptibility profiles of *Mycoplasma hominis* isolates from solid organ transplantation recipients at University of California, Los Angeles (UCLA) Medical Center between January 1, 2020 and February 28, 2021

			Phenotypic susceptibility results (MIC)				Genotypic resistance prediction				
Case	Specimen source	NCBI SRA files[a]	CLN	LVF	TCN	TAT (days)	GyrA	ParC	ParE	Res Finder 4.1	TAT (days)
1	Chest tube site	SRR14208165	0.016 (S)	0.125 (S)	0.25 (S)	20	WT	K144R	WT	ND	12
2	Pleural fluid	SRR14208166	0.031 (S)	0.25 (S)	0.25 (S)	35	WT	WT	WT	ND	14[b]
3	Surgical incision site and lower respiratory tract	SRR14208167	0.016 (S)	0.125 (S)	0.063 (S)	24	WT	WT	WT	ND	14[b]
4	Surgical incision site	SRR14208168	0.031 (S)	0.25 (S)	0.125 (S)	35	WT	K144R	WT	ND	21
5	Pleural fluid	SRR14208169	0.016 (S)	4 (R)	0.063 (S)	33	WT	K144R	D426N	ND	14[b]
6	Pleural fluid	SRR14208170	0.063 (S)	0.5 (S)	0.25 (S)	24[b]	WT	K144R	WT	ND	14[b]
7	BALF	SRR14208171	0.031 (S)	0.125 (S)	64 (R)	23	WT	WT	WT	*tetM*	13

Abbreviations: BALF, bronchoalveolar lavage fluid; CLN, clindamycin; LVF, levofloxacin; MIC, minimum inhibitory concentration; NCBI SRA, National Center for Biotechnology Information Sequence Read Archive; ND, not detected; R, resistant; S, susceptible; TAT, turnaround time; TCN, tetracycline; WT, wild type; y, years.

[a]Sequences were uploaded to NCBI under the BioProject PRJNA721191.

[b]These data were obtained retrospectively starting from frozen stocks of the pure isolates.

CLC Genomics Workbench version 12.0.3 (Qiagen, Valencia, CA, USA) was used to pair, trim, and map the sequence reads. Reads were mapped to a reference *M. hominis* complete genome (ATCC23114, NC_013511). The number of sequence reads ranged from 693,832-2,512,373. The percentage of reads mapped to the reference genome ranged from 82.08% to 94.60%. The percentage of the reference genome with at least 10x coverage of mapped reads ranged from 94.62% to 97.32%.

Sequences were uploaded to the website of Center for Genomic Epidemiology (https://www.genomicepidemiology.org/). The presence of acquired antimicrobial-resistance genes was assessed using ResFinder 4.1.[17,18] The presence of chromosomal point mutations associated with antimicrobial resistance was assessed using CLC Genomics Workbench. Sequence reads were mapped to the *gyrA*, *parC*, and *parE* genes of the *M. hominis* reference genome to generate consensus sequences, which was further analyzed by Geneious Prime version 2020.0.3 (Biomatters, New Zealand). The following amino acid positions were assessed for the presence of specific variants: GyrA: S153L/W, S154W, E157K, A189V/E, ParC: S91I, S92P, E95Q, K144R, A154T, ParE: D426N, L446F, A463S, E466K, A468V.[19–21] Antimicrobial resistance genes and amino acid variants found in each isolate are listed in Table 2.

2.4 | Phenotypic susceptibility testing

Antimicrobial susceptibility testing by broth microdilution was performed by the Diagnostic Mycoplasma Laboratory at the University of Alabama at Birmingham in accordance with Clinical and Laboratory Standards Institute (CLSI). The CLSI minimum inhibitory concentration (MIC) breakpoints were used for interpretation of the following drugs: Levofloxacin (≥2 μg/ml), tetracycline (≥8 μg/ml), and clindamycin (≥0.5 μg/ml) (M43-A, 2011). The results and TAT are listed in Table 2.

Statistical analysis was performed using VassarStats (online software). The Mann-Whitney *U* test was used to compare TAT and level of significance was set at $\alpha = 0.05$.

3 | RESULTS

3.1 | Case series

3.1.1 | Case 1

A 34-year-old man with congenital heart disease (levo-transposition of the great arteries, left atrioventricular valve atresia, and hypoplastic right ventricle) and cardiac cirrhosis underwent orthotopic heart transplantation (OHT) and orthotopic liver transplantation (OLT). His intraoperative course was complicated by disseminated intravascular coagulation with airway bleeding and alveolar hemorrhage, requiring veno-venous extracorporeal mechanical oxygenation (ECMO). He had persistent septic shock post-transplantation despite broad-spectrum antimicrobials. On post-transplantation day 14 (D14), he returned to the operating room for biliary reconstruction, and fluid was noted to be draining from a chest tube insertion site. *Mycoplasma/Ureaplasma* cultures of pleural fluid and lower respiratory tract grew *M. hominis*. Phenotypic susceptibility testing resulted 20 days later, demonstrating susceptibility to clindamycin, levofloxacin, and tetracycline. He received doxycycline 100 mg twice daily and levofloxacin 750 mg once daily for 42 days of therapy with infection resolution.

3.1.2 | Case 2

A 24-year-old man with systemic sclerosis-associated interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) underwent bilateral lung transplantation (BLT). On post-transplantation D11, he was noted to have increasing chest tube output. Imaging demonstrated a pleural effusion for which he underwent thoracentesis. Pleural fluid studies were exudative by Light's criteria and *Mycoplasma/Ureaplasma* culture of the pleural fluid grew *M. hominis*. Phenotypic susceptibility testing resulted 35 days later, demonstrating susceptibility to clindamycin, levofloxacin, and tetracycline. He received doxycycline 100 mg twice daily for 53 days of therapy with infection resolution.

3.1.3 | Case 3

A 64-year-old man with chronic obstructive pulmonary disease underwent BLT. On post-transplantation D10, he developed altered mental status, septic shock, and hypoxemic respiratory failure requiring endotracheal intubation and mechanical ventilation. The serum ammonia level was elevated at 126 μg/dL (reference range, 30–90 μg/dL). Serous fluid was noted to be draining from the clamshell thoracotomy incision site. *Mycoplasma/Ureaplasma* cultures of both surgical site serous fluid drainage and respiratory tract specimens grew *M. hominis*. Phenotypic susceptibility testing resulted 24 days later, demonstrating susceptibility to clindamycin, levofloxacin, and tetracycline. He received doxycycline 100 mg twice daily and levofloxacin 750 mg once daily for 42 days of therapy with infection resolution.

3.1.4 | Case 4

A 63-year-old man with hypersensitivity pneumonitis (HP) underwent single lung transplantation (SLT). His post-transplantation course was complicated by persistent hypoxemia that required mechanical ventilation. On post-transplantation D36, purulent fluid was draining from his surgical incision site. *Mycoplasma/Ureaplasma* culture of this fluid grew *M. hominis*. He underwent surgical debridement and was noted to have thin purulent fluid along the surgical incision. Multiple intraoperative cultures also grew *M. hominis*. Phenotypic susceptibility testing resulted 35 days later, demonstrating susceptibility to clindamycin, levofloxacin, and tetracycline. He initially received empirical therapy with doxycycline 100 mg twice daily and moxifloxacin 400 mg once daily. Once susceptibility testing results were available, moxifloxacin was discontinued after 31 days and doxycycline was continued to complete 42 days of therapy with infection resolution.

3.1.5 | Case 5

A 68-year-old man with idiopathic pulmonary fibrosis (IPF) and PAH underwent SLT. His intraoperative course was complicated by extensive hemorrhage, and due to incompletely revascularized coronary artery disease, he was placed on venoarterial ECMO. He recovered and eventually was weaned off of supplemental oxygen. However, on post-transplantation D25, he again became hypoxemic and was also noted to have a unilateral pleural effusion adjacent to the allograft. Thoracentesis was performed and pleural fluid studies were exudative by Light's criteria. *Mycoplasma/Ureaplasma* culture of the pleural fluid grew *M. hominis*. Phenotypic susceptibility testing resulted 33 days later, demonstrating susceptibility to clindamycin and tetracycline but resistance to levofloxacin. He initially received empirical therapy with doxycycline 100 mg twice daily. Empirical levofloxacin 750 mg once daily was added 1 week later for respiratory decompensation. Once susceptibility testing results were available, levofloxacin was discontinued after 21 days and doxycycline was continued to complete 42 days of therapy with infection resolution.

3.1.6 | Case 6

A 31-year-old man with IPF underwent BLT that was complicated by chronic lung allograft dysfunction for which he underwent re-do BLT. He had persistent fevers and a unilateral pleural effusion during the first week post-transplantation. Thoracentesis was performed and pleural fluid was exudative by Light's criteria. *Mycoplasma/Ureaplasma* culture of pleural fluid grew *M. hominis*. Phenotypic susceptibility testing resulted 24 days later, demonstrating susceptibility to clindamycin, levofloxacin, and tetracycline. He initially received levofloxacin 750 mg once daily but subsequently developed abdominal pain secondary to gastritis and gastroparesis, prompting its discontinuation after 10 days. He then received doxycycline 100 mg twice daily for 32 days to complete 42 days of therapy with infection resolution.

3.1.7 | Case 7

A 43-year-old man with HP underwent BLT. On post-transplantation D7, he developed septic shock and hypoxemic respiratory failure that required mechanical ventilation. Bronchoscopic examination revealed purulent secretions. *Mycoplasma/Ureaplasma* culture of bronchoalveolar lavage fluid grew *M. hominis*. Phenotypic susceptibility testing resulted 23 days later, demonstrating susceptibility to clindamycin and levofloxacin but resistance to tetracycline. He received doxycycline 100 mg twice daily for 17 days and levofloxacin 750 mg once daily for 14 days of therapy with infection resolution.

3.2 | Antimicrobial susceptibility results

Two of the seven cases (28.5%) had *M. hominis* isolates that tested resistant to one of the three drugs (i.e., levofloxacin, tetracycline, clindamycin) assessed by phenotypic susceptibility testing. The isolate from Case 5 was resistant to levofloxacin (MIC 4 μg/ml), while the isolate from Case 7 was resistant to tetracycline (MIC 64 μg/ml) (Table 2).

Genomic resistance prediction showed 100% concordance to the phenotypic susceptibility results. Using ResFinder 4.1, all isolates had no detectable acquired antimicrobial resistance genes, except the isolate from Case 7. This isolate was found to harbor the *tetM* ribosomal protection protein gene that confers resistance to tetracyclines; this was the only isolate to show resistance to tetracycline in vitro, thus demonstrating concordance (Table 2). Analysis of the topoisomerase genes showed wild type (WT) amino acids present at all positions assessed in *gyrA* (i.e., S153, S154, E157, A189) and most positions in *parC* (i.e., S91, S92, E95, A154) and *parE* (i.e., L446, A463, E466, A468). Isolates from Cases 1, 4, 5, and 6 had the K144R variant in *parC*, while only the isolate from Case 5, which showed resistance to fluoroquinolones (i.e., levofloxacin) in vitro, had an additional D426N mutation in *parE*. Therefore, the K144R mutation in *parC* alone does not contribute to fluoroquinolone resistance. Our results showed resistance to fluoroquinolones requires the D426N mutation in *parE*, but the role of the K144R mutation in *parC* is unclear (Table 2).

Phenotypic susceptibility testing had a median TAT of 24 days (IQR 23–35) and genotypic resistance prediction had a median TAT of 14 days (IQR 13–14), $p = .003$. For a single isolate, the cost of WGS analysis is approximately $200-$300 and the cost of send-out phenotypic antimicrobial susceptibility testing is $400.

4 | DISCUSSION

M. hominis is part of the commensal flora of the urogenital tract in 20%–50% of adults.[22–24] It has been estimated that 1%–3% of adults are colonized with *M. hominis* in the respiratory tract; however, the frequency of extragenital colonization is likely underestimated as this organism requires specialized culturing conditions that are not routinely performed on non-urogenital specimens. Because of the potentially severe manifestations associated with *M. hominis* infection, clinical suspicion and early recognition are paramount to institute appropriate antimicrobial therapy in an expeditious manner to optimize outcomes.

A molecular-based approach for diagnosing *M. hominis* infections can be useful when standard microbiology methods are unrevealing. Modalities such as real-time polymerase chain reaction and next-generation sequencing[25–28] have become increasingly popular in recent years. WGS has been used to determine antimicrobial resistance for other bacteria and can potentially replace or augment currently used methods,[29] but data on clinical utility remain scarce. To our knowledge, this is the first report comparing the phenotypic and genotypic susceptibility profiles for *M. hominis* in SOT recipients. Immunocompromised patients with prior exposure to fluoroquinolones have increased risk of developing resistant *Mycoplasma* spp.[21] Thus, susceptibility testing is recommended, but conventional laboratory techniques are labor-intensive, time-consuming, and not readily available. WGS allows for a faster, equally reliable, and more standardized diagnostic modality.

WGS of *M. hominis* has been previously used in the investigation of potential donor-derived infections.[2,13,30] Hinić et al. described donor-derived *M. hominis* infections affecting two kidney transplant recipients who shared a common donor. Although Hinić et al were unable to test the donor, they hypothesized that the infections were donor-derived based on multilocus sequence typing (MLST) analysis showing that the two isolates were identical to each other.[30] Sampath et al. reported seven cases of *M. hominis* infections following cardiothoracic organ transplantation at a single center. Of the seven cases, two were paired lung transplant recipients. MLST analysis of the isolates from the two paired lung transplant recipients revealed identical isolates, which is suggestive of donor-derived infection.[13] Similarly, Smibert et al. identified three cases of *M. hominis* infections in lung transplant recipients, and were able to perform genomic sequencing on the isolate from both the donor and the recipient in one of the cases. Their WGS analysis proved that the *M. hominis* infection was indeed donor-derived.[2] Novosad et al. described four patients with *M. hominis* spinal surgical site infections after receiving amniotic tissue product recovered from the same donor. WGS analysis between the donor tissue and one of the patient isolates showed that the isolates were identical.[31]

While WGS has proven to be a useful tool in cluster-outbreak and donor-transmission investigations, it can also be used to predict antimicrobial susceptibilities by detection of resistance genes.[29] The presence of the *tetM* gene confers tetracycline resistance in *M. hominis*, and prior studies have shown concordance between the biochemical susceptibility testing and detection of the specific gene.[32–36] The relationship between phenotypic and genotypic resistance for fluoroquinolones in *M. hominis* is less clear. Fluoroquinolone resistance has been associated with the presence of mutations in *gyrA*, *parC*, and *parE*, such as the K144R mutation in *parC* and the D426N mutation in *parE*. Interestingly, our isolates that possessed the K144R mutation remained fluoroquinolone-susceptible, with the exception of isolate 5 which had both the K144R and D426N mutations. The discordance has been seen in other studies. In a study by Zhang et al., all *M. hominis* isolates possessing the K144R mutation were fluoroquinolone-resistant,[37] whereas Yang et al. showed that isolates possessing the K144R mutation remained fluoroquinolon-susceptible.[38] This would suggest that the mutation database for genotypic prediction of fluoroquinolone resistance is still incomplete for *M. hominis*; however, the absence of mutations may still provide some insight clinically, as demonstrated in a case of *M. hominis* ventriculitis in a preterm infant that was successfully treated after WGS did not identify any known fluoroquinolone resistance markers.[39]

Delays in the institution of appropriate antimicrobial therapy for serious *M. hominis* infections in SOT recipients can lead to significant morbidity and mortality.[40] This may be due to a lack of clinical suspicion, not performing the requisite culture techniques, and/or the time required to obtain the results of phenotypic susceptibility testing. Most clinical and commercial microbiology laboratories, including our facility, are not equipped to perform susceptibility testing of *M. hominis* and are therefore required to send the isolate to a reference laboratory. Because of variable antimicrobial susceptibility among *M. hominis* isolates, combination antimicrobial therapy with two potentially active agents is often employed empirically. This strategy

carries increased risks for drug-related adverse events (including fluoroquinolone-associated toxicities), polypharmacy, and costs. Compared to phenotypic susceptibility testing, WGS has the potential to decrease the TAT by almost half. A more rapid access to resistance profiles is likely to improve patient outcomes.

In summary, this was a single-center retrospective study evaluating seven SOT recipients with confirmed *M. hominis* infections. The phenotypic and genotypic susceptibility profiles of *M. hominis* isolates from each patient were compared and were found to be concordant. This study demonstrates a proof-of-concept that WGS may be an effective tool in the armamentarium for obtaining faster and useful antimicrobial susceptibility testing results for *M. hominis* infections. The clinical utility of WGS for treatment decision-making remains to be established but the available data, including that from our study, show its promise.

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CONFLICT OF INTEREST

The authors do not have any potential sources of conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Authors Sandy Y. Chang, Travis K. Price, Shangxin Yang, and Ashrit Multani contributed equally to this manuscript. Sandy Y. Chang, Travis K. Price, Shangxin Yang, and Ashrit Multani conceived and designed the work; Sandy Y. Chang, Travis K. Price, Shangxin Yang, and Ashrit Multani collected and analyzed the data; Sandy Y. Chang and Travis K. Price drafted the manuscript; all authors have critically reviewed and revised the manuscript; all authors have approved the final version of the manuscript to be published.

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