Impact of Screening and Treatment of *Ureaplasma* species on Hyperammonemia Syndrome in Lung Transplant Recipients: A Single Center Experience

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Background. Infection with *Ureaplasma* species (spp) has been linked to fatal hyperammonemia syndrome (HS) in lung transplant recipients. We sought to characterize the epidemiology of *Ureaplasma* spp in candidates and donors and describe outcomes of antimicrobial therapy in preventing and treating HS.

Methods. Candidate testing for *Ureaplasma* spp was performed with urine culture and polymerase chain reaction (PCR) pretransplant. Positive candidates were treated with levofloxacin. Donor testing was performed with bronchoalveolar lavage (BAL) culture and PCR intraoperatively. From 7/2014 to 2/2017 patients were treated according to results; from 2/2017 to 10/2018 recipients received empiric levofloxacin and azithromycin at transplant until testing returned negative. HS was defined as new onset altered mental status after transplant with ammonia > 200 µmol/L.

Results. In total, 60 patients who underwent lung transplant were included. And 80% (n = 48) of patients had negative screening tests in donor and candidate pre-lung transplant, 8.3% (n = 5) of recipients had positive *Ureaplasma* spp testing in urine pretransplant, and 13.3% (n = 8) had positive donor BAL testing at the time of lung transplant. Three patients developed HS a median of 7 days posttransplant; 2 died of HS. Recipients of organs with *Ureaplasma* spp who received empiric therapy did not develop HS. Donors with *Ureaplasma* spp were younger and more sexually active.

Conclusions. Donor-derived *Ureaplasma* spp in lung transplant was associated with HS. Screening lung donors for *Ureaplasma* spp might allow for targeted therapy to reduce risk for development of HS, but future confirmatory studies are needed.

Keywords. *Ureaplasma* spp; hyperammonemia syndrome; donor-derived infection; lung transplant.

Lung transplantation (LTx) is a therapeutic option for end-stage pulmonary diseases. Mortality rates continue to be high in comparison to other solid organ transplantations with a median survival time of 6.0 years [1]. A rare yet frequently fatal complication of LTx is hyperammonemia syndrome (HS). HS is an early posttransplant condition where high serum ammonia levels generally leads to increased cerebral pressure, coma, and death. Incidence rates in LTx recipients (LTxR) are between 1 and 6% [2–4]. Historically, mortality rates approach 70% in spite of aggressive measures to decrease serum ammonia levels such as renal replacement therapy (RRT), bowel decontamination, and nitrogen scavengers [5].

Recently, studies have linked infection with *Ureaplasma* species (spp), a urease-producing Mollicute and common commensal of the genitourinary tract able to produce ammonia

and carbon dioxide from hydrolyzing urea, to HS [6–10]. Extragenital infections, such as pneumonia and disseminated disease, are uncommon and almost universally occur in immunocompromised settings. The prevalence and clinical significance of pulmonary colonization is unknown; however, the discovery of disseminated infection with *Ureaplasma* spp in LTxR has raised concern that donor-derived transmission is possible. Current experience is limited to case reports and the impact of screening and treatment is unknown. In this retrospective cohort, we sought to characterize the prevalence of *Ureaplasma* spp in both candidates and donors and describe outcomes of antimicrobial therapy in preventing and treating HS.

METHODS

Patients

All patients ≥18 years old who received a single or bilateral LTx at Northwestern Memorial Hospital from July 2014 to October 2018 were identified. All dual-organ or repeat LTxR were excluded. This study was approved by the Northwestern Memorial Hospital Institutional Review Board (STU00208882).

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Procedures

Institutional antibiotic prophylaxis and immunosuppression protocols are listed in the Online Supplement. Cultures and polymerase chain reaction (PCR) of *Ureaplasma* spp (inclusive of both *Ureaplasma urealyticum* and *Ureaplasma parvum*) were performed through procedures previously outlined by our group [6]. Following our index patient with *Ureaplasma*-associated hyperammonemia, all candidates had urine tested for *Ureaplasma* spp prior to transplant but after listing. After July 2018, all candidates also had saliva collected in addition to urine *Ureaplasma* spp testing. Positive candidates were treated with levofloxacin 500 mg daily for 14 days prior to undergoing transplant. After the index patient, all donor lungs were tested by bronchoalveolar lavage (BAL) intraoperatively after organ implantation. From July 2014 to February 2017 recipients were treated only if positive donor testing resulted; after February 2017 all recipients were routinely started on levofloxacin 500 mg daily and azithromycin 500 mg daily starting at postoperative day 0 until testing returned negative. If BAL results were positive, treatment was continued for 14 days. Repeat BAL was performed after treatment to ensure clearance.

Outcomes

Primary outcome was the development of HS. For the purposes of this study, HS was defined as new onset altered mental status (AMS) without any other identifiable cause after lung

transplant and a concurrent ammonia value of >200 $\mu\text{mol/L}$ on at least 1 occasion. Ammonia, when tested, was at minimum obtained daily. If no ammonia was tested, the recipient was classified as not developing HS. Secondary outcomes were initial ammonia levels on day 1 of diagnosis, peak ammonia levels, hospital length of stay (LOS), AMS, requirement of RRT, 30-day mortality, and 1-year mortality. Statistical methods are in the [Supplementary Data](#).

RESULTS

Overall Demographics

A total of 60 of the 67 patients who underwent LTx during the study period with donor screening were included ([Figure 1](#)). One dual lung-liver transplant recipient and 6 LTxR without donor BAL testing were excluded. Mean age was 54.5 years; 53.3% ($n = 32$) were male. Most (45%, $n = 27$) were transplanted for interstitial lung disease (ILD), and 73.3% ($n = 44$) received bilateral LTx. Twelve recipients (20%) received organs from Public Health Service (PHS) increased risk donors. *Ureaplasma* testing was D-/R- in 48, D+/R- in 7, and D-/R+ in 4. One patient was positive on both candidate and donor testing (D+/R+) and was included in both categories for analysis ([Figure 1](#)). Twenty-nine recipients received empiric therapy at transplant, whereas 31 did not. Of the 29 recipients, 21 received azithromycin and levofloxacin, whereas 8 received azithromycin and doxycycline. No medication side effects were observed.

Figure 1. Study design. Flow chart of study design, empiric treatment according to subgroup, and subsequent patients in each group who went on to develop HS. Abbreviation: HS, hyperammonemia syndrome.

Candidate Demographics

Demographics of candidates with positive testing were similar to those with negative testing with few exceptions (Supplementary Table 1). Candidates who tested positive were more likely to be younger (42.0 vs 55.7 years, $P = .01$) and of female sex (100% vs 41.8%, $P = .01$). Five candidates had positive urine testing before transplantation and were treated with 2 weeks of therapy (Supplementary Table 2). Of the positive tests, 4 were both culture and PCR positive, and 1 was PCR positive only. One was identified as *Ureaplasma urealyticum*, although the other 4 were *Ureaplasma parvum*. Four of these 5 had follow-up testing to confirm clearance with negative cultures that resulted before transplant; 1 did not have follow-up testing as transplant was done shortly after treatment in the same hospitalization. This patient was found to be urine culture negative and PCR positive prompting treatment and completed 2 weeks of therapy before LTx. Donor characteristics, including age, sex, and sexual activity, were not different between the 2 groups.

Candidate Outcomes

There was no difference in any of the tested primary or secondary outcomes between positive tested candidates who received treatment for *Ureaplasma* spp before transplant compared to those with negative candidate screening (Supplementary Table 3). No patient in either group developed HS. Candidates with positive and negative testing had mean initial (45.3 and 86.3 $\mu\text{mol/L}$, respectively) and peak posttransplant ammonia values (59.0 and 122.0 $\mu\text{mol/L}$, respectively). Our laboratory normal range was (0–53 $\mu\text{mol/L}$). No differences in mortality, AMS, RRT, or hospital LOS were observed.

Donor Demographics

There were no significant difference among lung transplant recipients with positive or negative donor *Ureaplasma* testing (Table 1). In contrast, donor characteristics were different between the 2 groups. Donors who tested positive were younger (26.6 vs 39.7 years, $P = .01$) and more likely to be sexually active (100% vs 65.4%, $P = .05$) as defined by any reported sexual activity within the 5 years preceding donor death per the next of kin. There were no data on recent sexual activity or oropharyngeal activity specifically. Donors were more likely to be male (87.5% vs 59.6%, $P = .13$) and of Black race (62.5% vs 30.8%, $P = .31$); however, neither reached statistical significance.

Transplant Outcomes

Recipients with positive donor testing were more likely to develop HS when compared with those with negative donor testing (37.5% vs 0%, $P = .00$); these cases all developed prior to initiation of *Ureaplasma*-active therapy for all patients posttransplant. Mean initial and peak ammonia values in those who were transplanted with positive donors were higher (169.5 and 225.9 $\mu\text{mol/L}$, respectively) compared to those with

Table 1. Lung Transplant Recipient Demographics

	Donor BAL Negative (n = 52)	Donor BAL Positive (n = 8)	P value
Age (LTxR)	54.3	55.6	.78
Sex			.84
Female	24 (46.2%)	4 (50.0%)	
Race			.37
White	31 (59.6%)	3 (37.5%)	
Hispanic	9 (17.3%)	1 (12.5%)	
Black	6 (11.5%)	3 (37.5%)	
Asian	2 (3.8%)	0 (0%)	
Other	4 (7.7%)	1 (12.5%)	
Indication			.40
ILD	22 (42.3%)	6 (75.0%)	
COPD	11 (21.2%)	1 (12.5%)	
CF	6 (11.5%)	0 (0%)	
PH	5 (9.6%)	1 (12.5%)	
Other	8 (15.4%)	0 (0%)	
Lung site			.85
Bilateral	38 (73.1%)	6 (75.0%)	
Right	2 (3.8%)	0 (0%)	
Left	12 (23.1%)	2 (25.0%)	
Donor			
Age	39.7	26.6	.01
Sex			.13
Female	21 (40.4%)	1 (12.5%)	
Race			.31
White	28 (53.8%)	3 (37.5%)	
Hispanic	6 (11.5%)	0 (0%)	
Black	16 (30.8%)	5 (62.5%)	
Asian	2 (3.8%)	0 (0%)	
Sexually active	34 (65.4%)	8 (100%)	.05
PHS increased risk	10 (19.2%)	2 (25.0%)	.70

Abbreviations: BAL, bronchoalveolar lavage; LTxR, lung transplantation recipient; PH, hyperammonemia syndrome; PHS, Public Health Service.

negative donors (48.3 and 73.4 $\mu\text{mol/L}$, respectively), although differences were statistical significance for peak values only (see Supplementary Data for detailed descriptions of HS patients). Recipients from positive donors had longer hospital LOS (87.5 vs 31.4 days, $P = .00$). There was a trend to those with positive donors as being more likely to have a higher 1-year mortality (50% vs 11.5%, $P = .07$), AMS (62.5% vs 28.8%, $P = .06$), and require RRT (37.5% vs 13.5%, $P = .09$) (Table 2).

When comparing recipients of positive donors who developed HS (n = 3) with those who did not develop HS (n = 5), peak ammonia values were significantly higher (499.7 vs 61.6 $\mu\text{mol/L}$, $P = .04$). Initial ammonia values were also higher (378.0 vs 44.4 $\mu\text{mol/L}$, $P = .17$) but was not statistically significant (Table 3). When comparing those who developed HS (n = 3) to all other recipients in the study time period who did not develop HS (n = 57), aside from positive *Ureaplasma* spp, elevated NH₃ values, and receipt of RRT to clear NH₃, the only predictive variables associated with HS were use of cyclosporine (33.3% vs 0%, $P = .00$), piperacillin-tazobactam (100% vs 19.3%, $P = .01$), linezolid (66.6% vs 10.5%, $P = .01$), and amikacin

Table 2. Lung Transplant Outcomes

	Donor BAL Negative (n = 52)	Donor BAL Positive (n = 8)	P value
HS	0 (0%)	3 (37.5%)	.00
Mortality (30-day)	3 (5.8%)	0 (0%)	.49
Mortality (1-year)	6 (11.5%)	4 (50.0%)	.07
AMS	15 (28.8%)	5 (62.5%)	.06
RRT	7 (13.5%)	3 (37.5%)	.09
Hospital LOS (days)	31.4	87.5	.00
Initial NH3	48.3 (n = 21)	169.5 (n = 8)	.09
Peak NH3	73.4 (n = 21)	225.9 (n = 8)	.04

Abbreviations: AMS, altered mental status; BAL, bronchoalveolar lavage; HS, hyperammonemia syndrome; LOS, length of stay; RRT, renal replacement therapy.

(66.6% vs 3.5%, $P = .00$). Full case descriptions of the 3 patients who developed HS are outlined in the Supplementary Data.

The characteristics of diagnosis and follow-up testing of LTxR with donor positive organs are outlined in [Supplementary Table 4](#). Starting February 2017, donors began receiving empiric azithromycin and levofloxacin (or doxycycline) prior to organ procurement at the request of the recipient surgical team in addition to institutional empiric therapy after transplant. Four recipients were given therapy at the time of transplantation, and all were PCR positive; only 1 had a positive *Ureaplasma* culture. None went on to develop HS. One recipient who did not receive perioperative treatment previously classified as HS by our group did not meet inclusion in this study ([Supplementary Data](#)) [7]. Of all positive *Ureaplasma* spp cultures in this study ($n = 8$), isolated resistance was noted separately to erythromycin, levofloxacin, and doxycycline once each (12.5%). With combination therapy all recipients received antimicrobial therapy with at least 1 sensitive agent per MIC data ([Supplementary Tables 2 and 4](#)).

DISCUSSION

In this retrospective cohort study, we sought to evaluate the incidence of *Ureaplasma* spp in LTxR, the effect of candidate and donor screening, and treatment on the development of HS and its outcomes at our center. Screening and treating candidates based on detection of *Ureaplasma* spp in the urine does

not appear to correlate with development of HS. On the other hand, donors with *Ureaplasma* spp in the lung are associated with development of HS. Universal treatment of all candidates until negative *Ureaplasma* testing resulted in no further cases of HS at our center.

Presentation of HS occurred early (median of 7 days) after transplantation, and patients had high peak ammonia levels (median peak value of 291 $\mu\text{mol/L}$), although levels at our center were lower than those previously described in the literature. As 2 of our patients were initiated on RRT prior to the initial ammonia value, we suspect this confounding accounts for this discrepancy and represents the difficulty in standardizing a diagnostic criterion in this complex population. At least 1 group has noted patients with *Ureaplasma* spp in donor BALs with cerebral edema and normal ammonia levels, although patients were on hemodialysis at the time [11]. Other challenges in standardization include delayed recognition limiting accurate ammonium trends and broad-spectrum antibiotic use given to this population. We elected to define HS as a compatible clinical syndrome occurring after LTx with a concurrent ammonia value of $>200 \mu\text{mol/L}$ on at least 1 occasion. One patient our group had previously described as having HS who tested positive for *Ureaplasma parvum* did not fulfill this criterion and was excluded as an HS case in our analysis [7]. This patient had ammonia levels well within the normal range, except for a single measurement of 80 $\mu\text{mol/L}$, which was not confirmed with repeat testing within an hour of the earlier draw, making HS unlikely. Based on the existing literature, we would propose that our definition is consistent with the published cases of HS and is a useful definition for future studies of this important condition.

Treatment for *Ureaplasma* spp resulted in drastic decreases in serum ammonia levels within days. And 2 of the 3 patients who developed HS never regained appropriate mentation and ultimately died secondary to complications from HS. One patient presented late posttransplant, and initial perioperative donor testing was negative, later becoming positive and represents an outlier from our other HS cases. Because the patient did not receive empiric treatment, it is unclear if universal treatment would have prevented this case. None of these 3 HS patients received empiric therapy at the time of transplantation or at procurement, and treatment was begun only after establishing a microbiologic diagnosis. Interestingly, none of the 3 received 3 times/weekly low dose azithromycin prophylaxis after transplant either, as this strategy was not implemented at our institution until mid-2016, and it remains unclear if this low dose would have mitigated subsequent HS. The index patient died when the *Ureaplasma* spp infection relapsed likely due to development of resistance that developed in the setting of monotherapy used to treat the initial infection. Furthermore, 2 of the patients had negative candidate testing supporting donor origin of the infection. All were both PCR and culture positive

Table 3. HS Outcomes in Donor Positive Lung Transplant Recipients

	No HS (n = 5)	HS (n = 3)	P value
30-day mortality	0 (0%)	0 (0%)	n/a
1-year mortality	2 (40%)	2 (66.7%)	.47
AMS	2 (40%)	3 (100%)	.09
RRT	1 (20%)	2 (66.7%)	.19
Hospital LOS	86.0	90.0	.94
Initial NH3	44.4	378.0	.17
Peak NH3	61.6	499.7	.04

Abbreviations: AMS, altered mental status; HS, hyperammonemia syndrome; LOS, length of stay; RRT, renal replacement therapy.

suggesting viable *Ureaplasma* spp persisted in the donor lungs. Taken together, along with work in animals that inoculation of *Ureaplasma* spp in immunocompromised mice induces hyperammonemia, the available data strongly suggest that HS is associated with acquisition of *Ureaplasma* spp from the donor and supports screening of all lung donors for infection with *Ureaplasma* spp [12, 13]. Broad screening may help to understand risk factors associated with donors harboring transmissible *Ureaplasma* spp.

All donors who tested positive for *Ureaplasma* spp in this cohort were younger and more sexually active than those who tested negative. Respiratory tract colonization is common in infants; however, rates in adults are unknown. The pathogenesis of transmission to the lungs is unclear; routine colonization and aspiration are postulated mechanisms. Unique features (in the lung transplant setting) that lead to *Ureaplasma* spp overgrowth and development of HS need further studies. We found rates of *Ureaplasma* spp in donor lungs to be high at 13.3%. We also had a high rate of HS prior to initiation of universal empiric treatment (3/33, 9%). It is possible this is secondary to donors with oropharyngeal colonization who aspirated leading to pulmonary colonization: one study noted oropharyngeal colonization rates of *Ureaplasma* spp to be as high as 14.8% [14]. This is especially notable as individuals who engage in orogenital sexual activity may be missed as this is not specifically noted on routine sexual activity donor evaluations.

Interestingly, none of the remaining 5 patients with donor-derived transmission developed HS, and all but one received empiric therapy at the time of lung implantation. It is unclear if this represents perioperative empiric treatment success or is a reflection of changes to our organ procurement structure where the recipient transplant team requested levofloxacin administration to donors prior to procurement and occurred in these 4 patients as well. The fact that 3 of these 4 patients receiving treatment were PCR positive and culture negative may reflect this change as these may have been killed organisms detected by high sensitivity PCR testing. This highlights a number of potential approaches to prevention of HS in lung transplantation. Providing empiric antimicrobials to the donor preimplantation may reduce the risk of transmission, but this cannot be assessed in this study as most also got active postimplantation antibiotics against *Ureaplasma* spp. Alternatively, and likely more consistent with general stewardship principals, the focus should be on early treatment of recipients. Although we found no cases of HS with universal prophylaxis, patients at our center received on average 1 week of exposure to levofloxacin and azithromycin because of long delays in getting donor testing results. Testing with more rapid turnaround, which is available, likely could identify recipients of *Ureaplasma* spp positive donors who could get treatment initiated early after transplant and avoid exposure to the majority of patients who may not derive benefit but are at risk of antibiotic complications.

Treatment of urine-colonized candidates prior to transplant had no effect on outcome, supporting the theory of *Ureaplasma* spp is donor-derived. Further, these data suggest that there is little role for screening or treating candidates for colonization with *Ureaplasma* spp in the urinary tract. Interestingly, the majority of colonized candidates tested positive for *Ureaplasma parvum*, whereas donors, in contrast, were mostly *Ureaplasma urealyticum*. The implications of this are unclear, and perhaps ongoing study of these 2 species may reveal differing mechanisms of pathogenicity.

HS has now been described in recipients of heart, lung, kidney, liver, bone marrow, and pancreas transplants, and neutropenic patients, although it is most common in LTxR [15–50] (Supplementary Table 5). Pooled mortality rates in LTxR were high (62.7%), highlighting the need to identify approaches to mitigate risk of HS development. Notably, every patient with HS who was tested for *Ureaplasma* spp was found to be positive except 1, highlighting this likely causal relationship. The relationship between *Mycoplasma hominis* and HS in lung transplantation is less clear, although this has been implicated as an infectious etiology as well [10, 21]. One recipient who developed HS tested positive for both *Ureaplasma urealyticum* and *Mycoplasma hominis*; thus, it is unclear if *Mycoplasma* played any role in the pathogenesis of HS, and we did not find isolated *Mycoplasma* spp in any study participant. Donor transmission has also been shown, yet HS is rare; on several occasions, diagnostic testing later returned with *Ureaplasma* spp coinfection [8, 51, 52].

This study has a number of limitations. With only 8 positive donors with 3 patients developing HS, causality must be interpreted with caution. Nonetheless, it is the largest series of candidate and donor screening for *Ureaplasma* spp in the literature. Institutional perioperative treatment protocols changed halfway through the study period which may have impacted incidence rates of HS but also provides potential insight into the role of early treatment. The retrospective and single-center nature of this study warrants further validation prospectively with a more standardized screening program at multiple centers to enhance generalizability. Finally, because candidate testing was limited to urine, it is possible colonization in other areas is associated with posttransplant HS. Three patients had buccal testing in addition to urine testing, no additional cases were detected with buccal testing, and all were found to be negative in both sites.

Donor screening and early therapy for *Ureaplasma* spp appears to reduce the risk of developing HS in lung transplant recipients, and this study supports routine screening of all donors. Candidate screening of urine is not associated with HS and is likely unnecessary to prevent HS development. Future studies are needed on a larger pool of donors to identify risk factors for infection that may be transmitted and result in development of HS, and to determine if targeted treatment is equally effective as empiric treatment of all recipients in preventing HS.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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