BACKGROUND

The development of idiopathic hyperammonemia following lung transplant has been reported to have a 30 day post-transplant mortality rate of 67%. Death typically occurs as a consequence of cerebral edema and severe neurological symptoms. In 2015, disseminated Ureaplasma species infection was first reported to be a cause of this syndrome. Four patients that died of hyperammonemia syndrome were found to have evidence of disseminated Ureaplasma urealyticum or parvum infection post-mortem. Of these cases, one had initially responded to empiric azithromycin therapy, but later relapsed and died with rising ammonia levels. Disseminated U. urealyticum infection with macrolide resistance was subsequently identified. Twenty control lung transplant patients without hyperammonemia syndrome did not have evidence of Ureaplasma species infection. Additionally, two prospective patients identified with hyperammonemia syndrome and U. parvum infection responded to antimicrobial treatment. Subsequently, a murine model was used to confirm that U. urealyticum and U. parvum infection could cause elevated plasma ammonia concentrations in pharmacologically immunocompromised mice.

Here we report a case of a lung transplant recipient with hyperammonemia syndrome, who was empirically treated with doxycycline in addition to other measures to lower ammonia levels. He clinically responded to these treatments. A bacterial identification assay using 16S ribosomal RNA gene PCR/sequencing of pleural fluid and by culture of bronchoalveolar (BAL) fluid. This case provides further support for empiric treatment of Ureaplasma species upon recognition of hyperammonemia syndrome post-lung transplant.

KEYWORDS
Hyperammonemia, lung transplantation, Ureaplasma
A 62 year old male with end stage chronic obstructive pulmonary disease underwent bilateral lung transplant, which was complicated by coagulopathy requiring temporary chest closure. He returned to the operating room on postoperative day 1 for hemothorax evacuation, and on postoperative day 2 for delayed closure of the thoracosternotomy. Induction immunosuppression included basiliximab (20 mg on day 0 and 4) and methylprednisolone (initial dose 125 mg every 8 hours x 2 doses, then tapered), after which he was maintained on tacrolimus (goal troughs 10-15 ng/mL), mycophenolate mofetil (1000 mg twice daily) and prednisone. Due to persistent delirium following transplantation, the tacrolimus was discontinued and cyclosporine started (goal concentration 225-260 ng/mL) on postoperative day 11.

The patient had been initiated on empiric piperacillin-tazobactam (3.375 grams every 8 hours) and IV vancomycin (1.5 grams every 12 hours) following transplantation. A sputum culture obtained via an endotracheal tube on postoperative day 2 identified methicillin-resistant Staphylococcus aureus. A BAL obtained later that same day identified no bacteria at 10^{3} CFU/mL.

The patient's postoperative clinical course was complicated by recurrent aspiration events. He had been extubated on postoperative day 4 but reintubated the same day. He was again extubated on postoperative day 6, but required reintubation on postoperative day 11. Bronchoscopy at that time removed a mucus plug from the right bronchial tree. BAL again revealed no growth at 10^{3} CFU/mL. A percutaneous tracheostomy was placed.

The patient subsequently improved with decreasing oxygen requirements and resolution of delirium until postoperative day 28, when he became increasingly lethargic and difficult to arouse. Labs revealed a WBC of 20 k/μL, normal liver functions tests other than a total bilirubin of 2.1 mg/dL, and an ammonia level of 196 μmol/L. Serial brain imaging revealed a chronic, stable 4 mm left frontoparietal chronic subdural hematoma, which was not thought to be responsible for his mental status changes. The patient had been diagnosed with factor VII deficiency post-operatively, and abnormalities in coagulation precluded immediate lumbar puncture. He was initiated on empiric antimicrobial therapy with IV vancomycin (goal trough 15-20), ceftriaxone (2 grams twice daily), and voriconazole (200 mg twice daily). Doxycycline (100 mg twice daily) was also initiated for hyperammonemia syndrome based on prior case reports which implicated Ureaplasma species as a possible cause. The patient was also initiated on rifaximin (550 mg twice daily), lactulose (10 grams three times per day), and metronidazole (500 mg every 8 hours), in an attempt to lower the blood ammonia level via bowel decontamination, along with a low protein diet.

On postoperative day 29, the blood ammonia level had risen to 246 μmol/L. The patient was comatose and did not arouse to noxious stimuli. He had no spontaneous eye opening or movement. Electroencephalogram (EEG) was severely abnormal due to the presence of unreactive low-frequency, low-voltage, delta band activity throughout, suggesting severe cerebral dysfunction. CT chest revealed small right and tiny left pleural effusion, with collapse of the right lower lobe with large amount of debris in the right lower lobe bronchus. Routine aerobic/anaerobic bacterial culture of pleural fluid obtained from an indwellling chest tube revealed Candida dubliensis. A 16S ribosomal RNA gene PCR/sequencing assay performed on this pleural fluid identified Ureaplasma species, although this result was not available until postoperative day 34.

The patient did receive prothrombin complex PCC (Kcentra) on postoperative days 28-30, after which his factor VII activity improved from 14% to 33%, and INR decreased from 3.6 to 1.4. He then underwent lumbar puncture on postoperative day 30, with cerebrospinal fluid (CSF) showing <1/μL nucleated cell, 625/μL red blood cells, glucose 91 mg/dL, and protein 20 mg/dL. CSF bacterial culture and 16S ribosomal RNA gene PCR/sequencing were negative.

The patient additionally underwent bronchoscopy with BAL on postoperative day 30, with negative results for routine bacteria, Legionella, M. hominis, fungal and mycobacterial cultures. Mycoplasma pneumonia and Cytomegalovirus were not detected by PCR. BAL cultures were positive for Ureaplasma species, although this was a sendout test to ARUP laboratories, and the result did not return until postoperative day 39. A nitrogen scavenger, sodium phenylbutyrate (5 grams four times per day), was added as an additional measure to lower the blood ammonia level.

By postoperative day 33, the blood ammonia level had normalized to 40. The patient was alert and following simple commands. Doxycycline was continued but additional therapies to lower ammonia levels were discontinued. The patient continued to improve without relapse of hyperammonemia.

### 3 | DISCUSSION

Idiopathic hyperammonemia has been reported to occur in 0.5%-4.1% of lung transplant recipients. It has been defined as elevated plasma ammonia concentrations, >200 μmol/L, in the absence of significant liver dysfunction. Patients typically present with mental status changes. Among solid organ transplants, this syndrome most commonly affects lung transplant recipients, although has been reported in heart, combined heart-lung, and renal transplant recipients. Total parenteral nutrition, gastrointestinal complications and lung transplantation for primary pulmonary hypertension have been associated with increased risk for this syndrome in lung transplant patients. Idiopathic hyperammonemia has also been reported following bone marrow transplantation, and in individuals receiving chemotherapy.

Disseminated Ureaplasma species infection was first reported as a cause of idiopathic hyperammonemia among lung transplant recipients in 2015. The genera Ureaplasma consists of 2 human species, urealyticum and parvum, and belongs to the class Mollicutes. Ureaplasma produce the enzyme urease, which hydrolyzes urea into the products ammonia (NH₃) and carbon dioxide (CO₂). While a number of bacteria produce urease, Ureaplasma is unique in requiring hydrolysis of urea for nearly all ATP generation. This ATP synthesis is thought to be dependent on an ammonia chemical potential.
generated through urea hydrolysis. In addition, the U. urealyticum urease has also been shown to be a much more potent energy producer than other bacterial ureases.7

Bharat et al performed molecular studies on 4 lung transplant recipients who had died of hyperammonemia syndrome. All were found to have evidence for a Ureaplasma species infection in the lung. BAL and/or plasma, three with U. urealyticum and one with U. parvum. BAL and serum from 20 lung transplant recipients without hyperammonemia were also tested for Ureaplasma species and were found to be PCR negative. Subsequently, two prospective patients with hyperammonemia syndrome tested positive for U. parvum in blood and BAL fluid and responded to Ureaplasma-directed antimicrobials.2

The ability of U. urealyticum to cause hyperammonemia has also been confirmed in a murine model. Pharmacologically immunosuppressed mice challenged intratracheally (IT) or intraperitoneally (IP) with U. urealyticum were found to have significantly higher plasma ammonia concentrations than those challenged with a negative vehicle-control. Interestingly, U. urealyticum IT/IP challenged immunocompetent mice did not develop hyperammonemia.3 A follow up study using U. parvum found similar results, with hyperammonemia only seen in immunosuppressed mice, not immunocompetent mice, challenged with U. parvum IT/IP.4 As seen in human case reports, the immunocompromised state appears to be important for the development of Ureaplasma-induced hyperammonemia.

Ureaplasma species are common inhabitants of the genitourinary tract. It is possible that immunosuppression allows for dissemination from the genitourinary tract in transplant recipients. However donor-derived transmission of Ureaplasma species has been reported. In 2015, hyperammonemia syndrome in a lung transplant recipient was described in which the native lung tissue was negative for Ureaplasma species, but donor BAL was positive for U. urealyticum.5 Subsequently, a prospective study tested pretransplant urine and BAL fluid from Mollicutes in 29 lung transplant recipients, and BAL fluid from donors. One recipient tested positive for U. urealyticum in the pretransplant urine, and received 2 weeks of directed therapy. Pretransplant BAL fluid was negative for Ureaplasma species in all recipients. BAL fluid from four donors was positive for Ureaplasma species, and all recipients of these lungs developed lung infiltrates and systemic inflammatory response syndrome post-transplant, in association with elevated ammonia levels, which responded to Ureaplasma-directed therapy. Donors with Ureaplasma species were found to be of a significantly younger age, were all reported to be sexually active with multiple sexual partners, and all had documented aspiration events. The authors hypothesized that sexual activity may increase the risk for oral cavity colonization of Ureaplasma species, which may then be introduced into the lungs during aspiration.9 At our hospital, testing for Ureaplasma species from donor BAL is not routinely done, and was not performed in our case.

Ureaplasma species may cause hyperammonemia syndrome in individuals immunocompromised due to etiologies other than lung transplantation. Recently, U. parvum was identified by tracheal aspirate PCR in a bone marrow transplant recipient with hyperammonemia syndrome. The patient’s ammonia levels and mental status improved after starting Ureaplasma-directed antimicrobials.9

Mycoplasma species, like Ureaplasma species, also belong to the class Mollicutes. In 2013, disseminated M. hominis infection was reported to be the cause of a fatal case of hyperammonemia in a lung transplant recipient.10 This patient was subsequently found to have had a co-infection with both M. hominis and U. parvum after retrospective PCR testing for Ureaplasma species identified U. parvum in BAL fluid and blood.2 Another retrospective study identified eight lung transplant recipients with hyperammonemia syndrome, and another two lung transplant recipients with normal serum ammonia levels who developed cerebral edema while receiving hemodialysis. PCR was performed to identify Mollicutes on donor bronchial wash and recipient BAL specimens from these individuals. Six donor bronchial wash specimens were positive for Ureaplasma species by PCR, including two with M. hominis co-infection, and 5 recipient BAL specimens were positive for U. urealyticum, including 1 with a M. hominis co-infection. None had a M. hominis infection alone.11 Further, a recent review of M. hominis surgical site infections following cardiothoracic transplant did not identify any cases of hyperammonemia syndrome associated with this infection alone.12 Therefore, the role of M. hominis, if any, in hyperammonemia syndrome has not been proven.

It is important to be aware of Ureaplasma species as a cause of hyperammonemia syndrome. Ureaplasma species cannot be seen on gram stain as they lack cell walls, and routine bacterial cultures will not identify this organism. At our institution, culture for Ureaplasma species is performed at an outside lab, and results in this case were not available for 10 days. Molecular identification may be needed, and in this case provided earlier confirmation. In our hospital laboratory, 16S ribosomal RNA gene PCR/sequencing is performed twice weekly. A limitation of this assay is that it could not distinguish between U. parvum and U. urealyticum. A Ureaplasma species specific PCR can provide rapid results and would have been helpful to determine the species, but is a sendout test at our hospital and was not performed.

Treatment options may include tetracycline, macrolide and fluoroquinolone antibiotics, although resistance has been reported to all of these classes.13 In this case report, the patient had already improved on empiric doxycycline before the positive BAL culture was available, and antimicrobial susceptibilities were not obtained.

Potential strategies for prevention in lung transplant recipients that have been proposed, and warrant further study, include universal screening of donors and recipients for Ureaplasma species, treatment of proven infections vs universal prophylaxis pending results, and systemic post-transplant monitoring of ammonia levels in lung transplant recipients.8 Given the potential for antimicrobial resistance, prolonged time to culture confirmation, and high mortality with this syndrome, empiric therapy with two Ureaplasma directed antimicrobials may be warranted.

In summary, this case adds to the growing literature that Ureaplasma species are an important cause of hyperammonemia syndrome post-lung transplant, and that early directed treatment can be associated with good outcomes.
AUTHORS' CONTRIBUTIONS

KMM wrote the manuscript. DAS reviewed the manuscript for accuracy. Both authors approved the final version.

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REFERENCES


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