

CASE ANECDOTES, COMMENTS AND OPINIONS

Donor-derived ureaplasma is a potentially lethal infection in lung allograft recipients



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Ureaplasma species are Mollicutes that are commensals of the urogenital tract. These organisms are dependent on urea hydrolysis for energy production, which generates ammonia and carbon dioxide. We recently hypothesized that systemic infection with *Ureaplasma* species may pose a unique challenge to human ammonia metabolism by simultaneously disrupting hepatic clearance of ammonia through urea production and liberating free ammonia, resulting in the lethal hyperammonemia syndrome which affects lung transplant recipients.^{1,2} When we assessed residual specimens of lung transplant recipients from multiple centers who succumbed to the hyperammonemia syndrome, we found that all patients had evidence of disseminated *Ureaplasma* infection and none without the syndrome had detectable *Ureaplasma*.¹ The series also included samples from a previously published case report from *The Lancet* in which *Mycoplasma hominis* was proposed to be the cause of hyperammonemia.³ All samples that we retrospectively tested on this patient were positive for both *Ureaplasma* and *Mycoplasma*. In a separate study, we inoculated *Ureaplasma*, isolated from lung recipients who developed hyperammonemia syndrome, into immunocompetent mice and found that it led to hyperammonemia in the infected animals.⁴ Other groups have independently reported that *Ureaplasma* can induce hyperammonemia in immunosuppressed mice.⁵ Together, these studies fulfill Koch's postulates establishing causality between *Ureaplasma* and fatal hyperammonemia.

Ureaplasma species are not detected on Gram stain and do not grow on the standard microbial cultures. In our recent study we found that unexplained altered mental status and ammonia elevation may be early signs suggestive of *Ureaplasma* infection.⁴ Hence, *Ureaplasma* testing should be performed if either of these occur after lung transplantation. Fortunately, both polymerase chain

reaction (PCR) and specialized cultures are available for accurate detection of *Ureaplasma* species. Although *Ureaplasma* can be found colonizing the urinary tract of recipients, our ongoing work further suggests donor lung as the source of disseminated *Ureaplasma* infection leading to hyperammonemia.⁴ In a prospective study, *Ureaplasma* was detected in ~14% of lungs, typically obtained from young, sexually active male donors with an aspiration event, and was associated with comorbidities such as primary graft dysfunction, acute renal failure, bronchial dehiscence and acute rejection, in addition to hyperammonemia.⁴

The lack of cell wall in the Mollicutes renders them resistant to commonly used antibiotic prophylaxis regimens used during lung transplantation. Therefore, a strategy of *Ureaplasma* prophylaxis or treatment requires inclusion of fluoroquinolones, macrolides or tetracyclines. We observed the emergence of anti-microbial resistance to macrolides during treatment with macrolide monotherapy, which was associated with fatal recurrence of hyperammonemia.¹ Therefore, an optimal therapeutic strategy should be guided by susceptibility patterns of *Ureaplasma* in the community, and likely require combination therapy to prevent the emergence of resistance. Given the clinical implications, available treatment and ability to test donors, we believe that epidemiologic studies should be conducted to evaluate for routine screening of *Ureaplasma* in donor lungs before or at the time of transplantation. Present investigation has not found the other common Mollicute, *Mycoplasma* species, with the same frequency in the donor lungs, but further studies are necessary to determine the pathogenicity of this organism in transplant recipients.

At our center, we test bronchoalveolar lavage fluid from the donor lung at the time of transplantation for *Ureaplasma* using a rapid polymerase chain reaction test and obtain cultures of the bronchoalveolar lavage fluid for *Ureaplasma*. If either test is positive, we initiate anti-microbials in 2 classes (typically a macrolide and a fluoroquinolone), as previously described.¹ Therapy is continued for at least 2 weeks and eradication of the organism is confirmed by repeat culture of bronchoalveolar fluid.

We recognize the urgent need for additional data to inform clinical practice with respect to screening, choice of therapy, duration of therapy and risk of recurrence. However, we believe the available data are sufficient to suggest that early detection and treatment of donor-derived *Ureaplasma* can prevent the high morbidity and mortality associated with this pathogen in lung transplant recipients.

Disclosure statement

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References

1. Bharat A, Cunningham SA, Scott Budinger GR, et al. Disseminated *Ureaplasma* infection as a cause of fatal hyperammonemia in humans. *Sci Transl Med* 2015;7:284re283.
2. Fernandez R, Ratliff A, Crabb D, et al. *Ureaplasma* transmitted from donor lungs is pathogenic after lung transplantation. *Ann Thorac Surg* 2017;103:670-1.
3. Wylam ME, Kennedy CC, Hernandez NM, et al. Fatal hyperammonaemia caused by *Mycoplasma hominis*. *Lancet* 2013;382:1956.
4. Fernandez R, Chi M, Ison MG, et al. Sequelae of donor-derived Mollicutes transmission in lung recipients. *Am J Respir Crit Care Med* 2017;195:687-9.
5. Wang X, Greenwood-Quaintance KE, Karau MJ, et al. *Ureaplasma parvum* causes hyperammonemia in a pharmacologically immunocompromised murine model. *Eur J Clin Microbiol Infect Dis* 2017 517-22.