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Commentary

# Emerging Pathogenic Respiratory *Mycoplasma hominis* Infections in Lung Transplant Patients: Time to Reassesses it's Role as a Pathogen?

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The mention of mycoplasmas to a general scientific or clinical audience will most commonly invoke recollections of confounding infectious cell culture contaminants or perhaps the more astute will remember *Mycoplasma mycoides* strain JCVI-syn1.0, the first fully synthetic autonomously replicating minimal bacterial chromosome (Gibson et al., 2010). Within the veterinary community, the importance of mycoplasmas is better appreciated due to the economic detriment they cause through reduced fertility, milk and egg production and significant mortality particularly associated with respiratory infections in cattle and chickens. The importance of mycoplasmas as human pathogens has slowly been gaining visibility in the last couple of decades, as *Mycoplasma pneumoniae* has been identified as a major cause of community-acquired pneumonia: estimated to be responsible for 15–20% of adult cases and up to 40% of cases in school age children, with suspicion of extrapulmonary consequences (including encephalitis) occurring in 5–10% of some patient cohorts (Brown et al., 2016). *Mycoplasma genitalium* has emerged as the cause of 10–35% of non-specific (or non-gonococcal) urethritis in men and a significant cause of cervicitis and pelvic inflammatory disease in women, despite only being detected in 1–3% of the general population (Jensen et al., 2016).

In the *EBioMedicine* publication by Sampath et al. (Sampath et al., 2017) several lung transplant patients were identified with *Mycoplasma hominis* infections in association with pleuritic, surgical site infection and/or mediastinitis. These findings are unexpected to some degree, as historically *M. hominis* has often been dismissed as normal genital flora (Capoccia et al., 2013). However, in the current report lung infection by *M. hominis* cannot be dismissed as a common opportunistic or commensal respiratory infection, as these authors found no evidence of infection in 178 bronchoalveolar lavage samples from immunocompromised patients. Furthermore, in two of their infected transplant patients, who received a lung from a common donor, the *M. hominis* isolates had identical multi-locus sequence types (MLST). This is particularly significant as constant low level mutation for this organism means that MLST yields an almost unique fingerprint for each organism and usually is only identical when taken from the same patient (Jironkin et al., 2016). This substantiates their conclusion that the source of the infection was the organ donor.

However, the under-diagnosis of mycoplasmas is directly related to their fastidiousness. As highlighted by Sampath et al., *M. hominis* will grow on blood agar plates but the pin-prick size colonies that take 48–72 h to emerge are often overlooked. Even when grown on highly supplemented *Mycoplasma* selective agar, *M. hominis* colonies can really only be enumerated using a stereomicroscope. The underlying reason for small colonies and requirement for highly enriched media relates to their atypical physiology. *M. hominis* belongs to the bacterial class *Mollicutes*; literally smooth (mollis) skin (cutis), in recognition of the lack of a thick peptidoglycan layer or outer membrane present in Gram-stain identified bacteria. The lack of this common bacterial structural component is due to large number of genes shed to achieve their very small genome size (between 0.65 and 0.76 Mbp for *M. hominis*), along with many of the key enzymes required to make nucleotides through folic acid intermediates or generate ATP through glycolysis or pyruvate pathways. The result of this extreme evolution is that all mycoplasmas can only exist through a parasitic existence with the host, scavenging nucleotides and other key structural cell components from their host. In particular, *M. hominis* can only survive by metabolising arginine to $CO_2$ and $NH_3$ to generate ATP.

This minimalised physiology and parasitic existence also has a more significant consequence clinically: most of the targets of antibiotic therapy are also missing. All mycoplasmas are inherently resistant to beta-lactam based (e.g. penicillins), glycopeptide class (e.g. vancomycin) and lipopolysaccharide-targeting (e.g. polymyxin) antibiotics as well as anti-metabolites (e.g. trimethoprim and sulfamethoxazole). Many human mycoplasmas are facultative anaerobes or micro-aerobes and are additionally resistant to aminoglycosides (e.g. gentamicin) and seem to be resistant to RNA-polymerase targeting antibiotics such as rifampicin. Within this bacterial class, *M. hominis* is unique in its resistance to macrolides (e.g. azithromycin), as the universal sequence of the *M. hominis* single copy of 23S rRNA has a G2057A transition, or a guanidine instead of an adenine at a position known to abrogate macrolide binding to the ribosome (Pereyre et al., 2002). The only remaining effective antibiotics are tetracylcines, lincosamides (or at

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least clindamycin), and fluoroquinolones. Sampath et al., have also highlighted the importance to this as the routine perioperative bacterial prophylaxis antibiotics (vancomycin, cefepime, and trimethoprim/sulfamethoxazole) are completely ineffective against *M. hominis*.

An accumulating amount of evidence shows *M. hominis* infection is associated with adverse pregnancy outcomes and preterm respiratory pathology and this has been supported by experimental intrauterine infection of pregnant macaque primates (Novy et al., 2009). A literature search for journal reports of *M. hominis* infection shows a wide range of sporadic associations with meningitis, joint and bone infections, wound infections, endocarditis/pericarditis, brain abscesses, etc., often with the words "rare" or "uncommon" in the title. However, this report by Sampath et al. and a similar report showing disseminated *Ureaplasma* (another member of the *Mycoplasmataceae* family) infection as a cause of fatal hyperammonemia (Bharat et al., 2015) suggest that significant respiratory pathology by "genital" mycoplasmas may not be rare, just beyond identification by routine microbiological screening. The importance of increasing antimicrobial resistance prevalence and emergence of cumulative resistance to multiple classes of antibiotics is steadily becoming more important internationally and visible in the media; therefore, it is ironic that the *Mycoplasmataceae* family of bacteria have not gained notoriety previously when they have always been almost completely resistant to antimicrobials.

## Conflict of Interest

The author declares no conflict of interest.

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