Treating *Mycoplasma genitalium* Infection with a Sitafloxacin Regimen in the Context of Increased Resistance

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Background
Macrolide and fluoroquinolone resistance in *M. genitalium* is rising. In Australia, patients with macrolide-resistant *M. genitalium* who fail first-line treatment with moxifloxacin are treated second-line with either pristinamycin, minocycline or sitafloxacin-based regimens. We evaluated the efficacy of any sitafloxacin-based regimen for macrolide-resistant *M. genitalium* at Melbourne Sexual Health Centre over a 5-year period.

Methods
Patients with macrolide-resistant *M. genitalium* who received a sitafloxacin-regimen between January 2017-February 2022 were included. Prior to October 2017, patients received sequential sitafloxacin monotherapy (doxycycline followed by sitafloxacin); subsequently, patients received combination therapy (doxycycline followed by doxycycline+sitafloxacin). Microbial cure was defined as a negative test-of-cure 14-90 days after completing sitafloxacin. Logistic regression explored factors associated with sitafloxacin failure.

Results
Of 229 patients with macrolide-resistant *M. genitalium* who received a sitafloxacin-containing regimen, 80.6% (95% CI: 74.9 – 85.5) experienced microbial cure. In adjusted analyses, prior failure of moxifloxacin was the only factor associated with sitafloxacin failure (Adjusted-Odds-Ratio=7.56, 95% CI 2.38-24.04, p<0.001). Due to correlated variables, we stratified cure based on prior moxifloxacin failure to evaluate the efficacy of the two sitafloxacin regimens. We found no significant difference in microbial cure following sequential monotherapy *vs* combination therapy among patients who had not previously failed moxifloxacin (87/92 [94.6%] *vs* 11/12 [91.7%], p=0.530), or among those who had previously failed moxifloxacin (2/6 [33.3%] *vs* 87/122 [71.3%], p=0.069) however small numbers limited these comparisons.

Conclusion
Microbial cure following sitafloxacin was 81% for macrolide-resistant *M. genitalium* over the past 5 years, with past failure of moxifloxacin associated with an 8-fold increased odds of failing sitafloxacin, reflecting the likely presence of key fluoroquinolone resistance mutations. These data provide contemporary information about the efficacy of sitafloxacin for *M. genitalium* in an era of rising antimicrobial resistance, and highlight the benefit of incorporating markers of fluoroquinolone resistance into diagnostic assays to improve antibiotic selection and stewardship.