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Minocycline use in the treatment of multi-drug resistant *Mycoplasma genitalium*: a narrative review of the evidence

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Background *Mycoplasma genitalium* is an emerging sexually transmitted pathogen that is rapidly becoming multi-drug resistant. Current treatment guidelines recommend a resistance-guided approach with the use of macrolides and fluroquinolones as initial treatment agents, with alternative agents in the event of treatment failure. One agent, minocycline, has demonstrated efficacy in a small number of patients with multi-drug resistant *Mycoplasma genitalium*.
Methods A narrative review of studies describing the use of minocycline in the treatment of *Mycoplasma genitalium* was undertaken. A detailed literature search was conducted in Cochrane Central Register of Controlled Trials (CENTRAL); PubMed, Medline, Embase, and CINAHL, on 4 February 2021. Search terms and descriptors included: Minocycline and Mycoplasma genitalium.
Results The search generated 1,194 records. Titles and abstracts were searched for relevant papers; once duplicates were removed; six papers were reviewed and critiqued. Three case reports of five men and three cohort studies were included in this narrative review.
Conclusion There is a paucity of evidence for the effectiveness of minocycline in the treatment of multi-drug resistant *Mycoplasma genitalium*. Small patient numbers and differing dosages and durations of treatment demonstrate an efficacy rate of between 43-100%.

INTRODUCTION and OBJECTIVES: *Mycoplasma genitalium* (*M. genitalium*) is a sexually transmitted pathogen that is a proven cause of non-gonococcal urethritis (NGU), proctitis, cervicitis, pelvic inflammatory disease (PID), epididymitis, and adverse pregnancy outcomes [1-6]. It was first discovered in 1981 when detected in the urethral samples of two men with NGU [7]. Epidemiological data from Australia reports a prevalence rate of between 1.3 to 4% in the community [5, 8, 9]. M. genitalium is an increasingly difficult pathogen to treat as it lacks a cell wall, thus antimicrobial agents that target the cell wall are ineffective, and its fastidious growth impairs routine antimicrobial susceptibility testing [2-4, 10, 11]. *M. genitalium* is difficult to treat due to its ability to rapidly evolve resistance to current antimicrobials. There have been several studies on regional differences in antimicrobial resistance and *M. genitalium*; with macrolide resistance surpassing 50% in urban centres and 40% in rural and remote centres, and quinolone resistance as high as 18% in South-East Queensland (SEQ) and 3.4% in Northern Queensland (NQ) [9,12-16]. Dual-class resistance to macrolide and fluroquinolones is reported at up to 13.4% in Queensland [12]. International and national guidelines for *M. genitalium* utilise several antimicrobial classes, however they differ in recommendations for dosage and duration of treatment [13, 17-22]. Currently in Australia, *M. genitalium* is primarily treated with doxycycline followed by either a macrolide (azithromycin) or fourth-generation fluroquinolone (moxifloxacin) [19, 21, 23]. Minocycline is listed as a second-line or alternative regimen in Australian and British treatment guidelines for *M. genitalium* [17, 21]. The aim of this narrative review was to consolidate available evidence for the use of minocycline in the treatment of *M. genitalium*.

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MATERIALS and METHODS: A narrative review was undertaken using the criteria established by Green et al [24]. Due to variation in study design, critical appraisal was conducted using the Mixed Methods Appraisal tool (MMAT) developed by Hong et al [25]. A detailed literature search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed, Medline, Embase, and CINAHL, on 4 February 2021, to identify the use of minocycline in the treatment of *M. genitalium*. Search terms and descriptors included: Minocycline and Mycoplasma genitalium.

Data collection and analyses: Two review authors (AS, NM) independently screened, extracted data and performed quality assessment for the included studies.

RESULTS: Deguchi et al [26] report on two cases of multi-resistant M. genitalium in Japan, cured with 100 mg minocycline orally twice daily for 14 days. Yang and Ke [27] report on a single case of a 48-year-old man with multi-drug resistant *M. genitalium* who was treated but not cured with minocycline, eventually cured with doxycycline. Dupin et al [28] enrolled one hundred and ninety three males into a prospective cohort study between May and September 2001, looking at the detection of *M. genitalium* in 3 groups of attendees, Group 1 - 83 patients with urethritis, Group 2 - 60 patients with urethral symptoms but no urethritis, and Control group - 50 asymptomatic men. Microbial cure with a negative *M. genitalium* PCR occurred in 4/9 (44%) patients with 3 receiving minocycline 100 mg orally daily for 7 days, and 1 receiving spectinomycin 2g IM and minocycline 100 mg daily for 7 days. Maeda et al [29] enrolled 72 heterosexual Japanese men with Non-Gonococcal Urethritis (NGU) and treated with levofloxacin. The participants were enrolled between April 1999 and May 2000 in Japan. Five patients out of the seven who returned for follow up at visit 3, continued to have a positive *M. genitalium* result. A total of 3/5 (60%) men were treated with 100mg minocycline orally twice daily for 14 days and 2/5 (40%) were treated with clarithromycin. There was no discussion around the cure rates of these interventions and thus interpretation as to minocycline's effectiveness in the treatment of *M. genitalium* cannot be determined. Doyle et al [30] report on a prospective cohort study looking at non-quinolone options in the treatment of *M. genitalium*. The two arms of the study were (i) Pristinamycin 1 gram three times daily with concomitant doxycycline 100 mg twice daily for 10 days between September 2018 and December 2019 OR (ii) minocycline 100 mg twice daily for 14 days between May 2018 and February 2020. In the Pristinamycin and doxycycline arm, a total of 55/73 (75%) patients were cured, and in the minocycline arm a total of 25/35 (71%) were cured. Glaser et al [1] report on two cases of multi-drug resistant *M. genitalium* in the United States of America. Both cases were in men who have sex with men. Both men had been treated with Azithromycin, moxifloxacin and doxycycline before being commenced on 100 mg minocycline PO BD for 14 days. Both men achieved cure post minocycline treatment.

CONCLUSION: There is a paucity of evidence of the effectiveness of minocycline in the treatment of multi-drug resistant *M. genitalium*. Small patient numbers and differing dosages and durations of treatment show an efficacy rate of between 43-100%. Discrepancies between minocycline dosage and length of treatment within the reviewed papers prohibit the provision of strong recommendations as to the use of minocycline in multi-drug resistant *M. genitalium*.