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Mycoplasma genitalium nongonococcal urethritis is likely to increase in men who have sex with men who practice unsafe sex: What should we do?

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In this issue McIver et al document in men who have sex with men (MSM) with nongonococcal urethritis (NGU) an increase in *Mycoplasma genitalium* (Mgen) positivity from 4.5% to 12.8% over a 12 yr period.(1) Mgen was observed to be as common in MSM with NGU as men who have sex with women (MSW), which has not been observed previously.(2) High rates of Mgen macrolide antimicrobial resistance (MAMR) were also observed which was significantly higher in MSM (89.7%) with NGU compared to MSW (50%). They speculate that the higher MAMR among MSM, probably reflects that MSM are more likely to be exposed to azithromycin because they test more frequently and have higher rates of sexually transmissible infections (STIs) compared to the general population. Although their study design differed from the historical comparison in that in this study men with urethral irritation but no symptoms of urethral discharge or dysuria were excluded, in whom Mgen is less commonly detected, this would only account for only a small part of the increase in positivity.(2) The authors go on to conclude that their observations support recommendations to test all men with NGU for *M. genitalium* and to incorporate real-time resistance assays into clinical care to guide treatment decisions and to limit use of azithromycin when treating NGU and other STIs.

During the past 20 years the sexual behaviour of MSM has changed with an increase in unprotected anal intercourse (UPAI) with both regular and casual partners.(3-6) This has been associated with a continued increase in gonorrhoea, syphilis and chlamydia and until recently substantial ongoing HIV transmission despite condom use continuing to be a key component of prevention initiatives.(7, 8) While the increase in these three bacterial STIs may in part be due to better detection of chlamydia and gonorrhoea in the earlier part of this decade it is believed that this increase in the number of UPAI partners as a result of behaviours such as HIV sero-adaptive behaviours, group sex facilitated by geosocial networking applications, and 'chemsex' is playing a major role.(5-8) The introduction of

effective antiretroviral therapy based control strategies such as treatment as prevention and more recently pre-exposure prophylaxis (PrEP) have seen substantial falls in HIV incidence in the United Kingdom despite this increase in UPAI.(8) There is a concern that PrEP will increase unsafe sex in users and there is some evidence to support that this might happen in some but not all persons taking PrEP.(9, 10)

Given that these 3 bacterial STIs have increased it should be no surprise that Mgen has also increased in MSM. Mgen is only rarely carried in the pharynx, so MSM with Mgen NGU will have predominantly acquired it through UPAI.(11-13) The basic reproductive number R_0 i.e. the average number of secondary infections generated by one infectious individual in an entirely susceptible population, will have increased as this is dependent on:

$R_0 = \beta cD$

Where *c* denotes the average rate of partner change, β records the transmission probability per partnership, and *D* is the mean duration of infectiousness.(14) Thus for MSM both the average rate of partner change and the risk of transmission will have increased over time which, assuming no change in the duration of infection, would result in an increase in rectal carriage which is predominantly asymptomatic.(15-17) There is limited empirical evidence to support this but what there is, is consistent with this hypothesis. Bradshaw et al observed in high risk MSM attending a Melbourne sauna in 2000-2001 a rectal prevalence of 1.6% and in 2016-17 Read et al observed a rectal prevalence of 7% in asymptomatic men attending the Melbourne Sexual Health clinic. (16, 18) Asymptomatic carriage appears to be higher in the rectum than the urethra, suggesting that duration of infection may be longer in the rectum than the urethra. (15, 16, 18) Although biologically it would seem likely that Mgen causes proctitis at least in some men, a recent case control study from Melbourne suggested that it is not associated with symptomatic proctitis.(16) There is no

evidence that screening would result in a decrease in prevalence in MSM and does more good than harm.(12, 16, 17)

Mgen prevalence in Australia is relatively high in asymptomatic high risk MSM (>7%) and partner change frequent, 2->16 every 3 months. (9, 16, 19) Thus exposure of MSM practising unsafe sex to Mgen, will not be uncommon. Given the persistence of sub minimum inhibitory concentration (MIC) of azithromycin for at least 2-4 weeks following treatment with higher levels intra-cellularly than extracellularly this is probably also a source of selection pressure for MAMR in Mgen in MSM recently treated with azithromycin.(20) A recent meta-analysis concluded that 12% of Mgen infections will develop macrolide resistance following treatment with azithromycin 1g.(21) Azithromycin in Australia at the time of the study was the treatment of choice for Mgen, for NGU, for chlamydia, and part of dual therapy for *Neisseria gonorrhoeae* in which Mgen co-infection is common ~10%.(1, 16) McIver et al. and other experts attribute the high prevalence of macrolide resistance in Mgen in Australia to both treatment of Mgen and NGU with azithromycin and inadvertent exposure when treating other infections.(1, 16) There is little information on the proportion of MSM who receive treatment with azithromycin annually. In this study by McIver et al.(1) 24% of MSM had received azithromycin in the previous year, which is likely to be an overestimate for MSM as a whole, as not all MSM will attend a sexual health departments annually for screening. Nevertheless, if we assume 24% are treated with azithromycin every year and of these 12% develop resistance then only (0.24x 0.12)2.88% of all infections would develop resistance which over 10 yrs would result in (1- 0.9712^{10}) 25.4% and 35.5% MAMR over 15yrs, substantially lower than the 89.7% resistance rate reported in the McIver study.(1, 21) Clearly this is a simplistic analysis which does not reflect the dynamic nature of sexual transmission but it does suggest that selection pressure from direct treatment cannot by itself explain the rapid increase in MAMR Mgen which has occurred over the past 15 yrs.(1, 12, 16, 17, 20, 22, 23) The prolonged persistence of sub-MIC levels following azithromycin treatment could theoretically promote induction or selection of MAMR if the person is then re-exposed (or exposed) to Mgen either following unprotected sexual

intercourse with an untreated partner or a new partner who is infected with Mgen which is not uncommon in MSM (see above). (9, 16, 19, 20) How long this MAMR selection pressure could potentially persist for following azithromycin treatment is uncertain, BASHH has recommended 2 weeks but it could be as long as 4 weeks.(12, 20, 24) However, there is only limited evidence to support this hypothesis and although no association with previous azithromycin use and MAMR was found by McIver et al or in the study by Read et al., this probably reflects the high background MAMR in MSM.(1, 16) This hypothesis would benefit from an evaluation using mathematical modelling as it has implications for patient management and how long patients should abstain from sexual intercourse following azithromycin treatment.(12, 20, 25)

Given the asymptomatic nature of Mgen, the high rates of partner change and carriage in high risk MSM and increasing MAMR, it is likely that mixed infections of macrolide sensitive and resistant infections are occurring. MAMR nucleic acid amplification tests (NAATs) will miss some infections containing low numbers of MAMR micro-organisms and conversely are likely to identify infections as resistant when the majority of micro-organisms are sensitive.(19, 26) The former could at least in part explain why the observation that extended azithromycin 1.5g was associated with higher treatment failure due to selection for MAMR in MSM from a high MAMR Mgen prevalent population compared to low prevalent populations. (17, 19, 21,) While the latter could potentially explain why azithromycin 1 g is clinically effective in some cases of apparent MAMR Mgen by reducing the load but does not eradicate the infection.(27) Clearly a better understanding of the natural history of Mgen including duration of infection in the urethra and rectum, risk of transmission, risk of developing disease and how this is influenced by load and the pharmacokinetics of antimicrobials and the lowest MIC at which a selection pressure in Mgen occurs would better inform mathematical models and improve our understanding of the most effective strategies for managing this relatively new and increasingly complex STI.(25, 27)

In conclusion, this study provides further evidence for treating all men with NGU with doxycycline and testing them for Mgen in order to enable resistance guided therapy if found to be Mgen-positive.(12, 17, 26, 27) When extended azithromycin is used to treat macrolide sensitive infections patients should be advised not to be sexually active for at least 2 weeks and possibly 4 because of the risk of re-exposure to Mgen particularly in high prevalence networks.(12) It also provides support for the recent approach adopted in the UK of discontinuing the use of azithromycin 1 g to treat chlamydia, Mgen, gonorrhoea and NGU. (https://www.bashh.org/guidelines) Mgen is likely to continue to increase as a cause of NGU in MSM with high rates of partner change and practising UPAI and there is no evidence that screening could avert this and does more good than harm. (12, 17) Finally a better understanding of the natural history of Mgen infection and antimicrobial pharmacokinetics would help inform public health control measures in addition to the continued promotion of condom use and improve the efficacy of antimicrobial treatment regimens and reduce the risk of Mgen AMR developing. (20, 25, 27)

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