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Review

Should we still use azithromycin for gonorrhoea treatment?

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Abstract. This review presents the evidence for azithromycin in the treatment of gonorrhoea, both as monotherapy and as a component of dual therapy. Uncertainties are explored regarding the efficacy of a dual treatment strategy, combining ceftriaxone and azithromycin, in the context of resistance trends and extra-genital infections. The association between microbiological testing and clinical outcome for the individual patient, and the effect of azithromycin use on other sexually transmissible infections, are considered. Finally, in the absence of imminent new antimicrobials, optimising the dose of azithromycin while maintaining tolerability is discussed.

Additional keywords: antimicrobial, *Neisseria gonorrhoeae*, resistance.

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Introduction

Neisseria gonorrhoeae has successfully developed resistance to a wide variety of first-line treatment options since the 1930s, including sulfonamides, penicillins, tetracyclines and fluoroquinolones, and there is now a real threat of widespread resistance to extended spectrum cephalosporins, including parenteral ceftriaxone.[1] Surveillance programs exist in many countries to track changing resistance patterns,[2–6] and this information is being used to develop new management strategies based on point-of-care diagnostic and antimicrobial susceptibility testing to maximise the use of older, legacy antibiotics while preserving newer agents that are in development. However, in addition, there is a need to maintain ceftriaxone as an effective treatment for as long as possible. One widely adopted approach has been the introduction of dual therapy combining ceftriaxone with azithromycin to 'protect' the ceftriaxone and provide antimicrobial cover if it fails. However, this approach remains unproven and has been called into question, particularly following reports of extended-drug resistant (XDR) gonorrhoea, which is resistant to both ceftriaxone and azithromycin.[7,8] This paper reviews the evidence for azithromycin in the treatment of gonorrhoea, both as monotherapy and as a component of combination dual therapy.

Azithromycin

Azithromycin is a second generation azalide antibiotic, derived from the macrolide class and its mode of action is to inhibit RNA-dependent peptide synthesis at the 50s ribosomal subunit. Azithromycin is used to treat a broad range of infections including soft tissue, gastrointestinal, respiratory and sexually transmissible infections, and can be used during pregnancy. It is commonly prescribed in the sexual health setting as a single dose due to the favourable pharmacokinetics of the drug.

Azithromycin is rapidly absorbed, with time to peak plasma concentration being 2–3 h.[9] Specific data for genital tract tissues are limited. Small studies do not differentiate between intra and extracellular concentrations, but have demonstrated significant concentrations of azithromycin in the rectum and vagina after ~5 h, peaking at 24–48 h.[10,11] Tissue penetration of azithromycin is excellent, with levels up to 50-fold higher than those in serum,[9] yet it should be noted that tissue penetration may be overestimated and vulnerable to contamination by other fluids (such as blood) through sampling.[12] Azithromycin is also taken up by phagocytic cells, which deliver and release the antibiotic at the site of infection, further increasing local drug concentrations.[13] Administration of larger single doses (2 g) lead to early high levels of the drug in both serum and white cells compared with a daily dosing of 500 mg for 3 days, maximising antimicrobial concentrations early, when bacterial load is likely to be highest.[14]

Azithromycin in metabolised by the liver with a half-life of 2–4 days, and time to elimination may be up to 30 days in some tissues with a significant time period during which sub-therapeutic levels precede complete clearance.[9,15,16] Tissue concentrations of azithromycin exceeding those required to treat chlamydia occur in the pharynx, prostate, vagina and rectum, and are maintained beyond 7 days, but similar studies have not been performed for gonorrhoea.[10,11,17,18] Although initial azithromycin levels are higher following a single 2 g dose of azithromycin, serum and

white cell concentrations beyond 70–80 h are similar for both the single 2 g dose or 3-day course of treatment.[14]

Following a single 1 g dose, azithromycin has an excellent side-effect profile, with low rates of 'mild' gastrointestinal adverse events;[19] however, other dose options are not as well tolerated. Kirkcaldy *et al*. reported high rates of diarrhoea (17%), nausea (26%) and vomiting (10.5%) in a randomised controlled trial comparing gentamicin plus azithromycin (2 g) with oral gemifloxacin plus azithromycin (2 g).[20] In addition to being unpleasant for the patient, this would have implications for adequate drug absorption, especially where vomiting occurs soon after dosing, as occurred in 3% of patients. Gastrointestinal side-effects are reported at similar rates in other studies assessing a 2 g dose, either in standard or modified release formulation.[21,22] Dean *et al*. reported poor tolerability in participants receiving a 1 g single dose of azithromycin followed by 500 mg daily for 4 days in a treatment study on Pelvic Inflammatory Disease (PID); 61% of the cohort experienced diarrhoea, of whom nearly 75% described this as being moderate or severe.[23]

Interestingly, studies for the treatment of syphilis using a 2 g single dose of azithromycin report lower rates of nausea and diarrhoea (9–13%)[24,25] for reasons that are unclear, but may reflect the subjective nature of reporting side-effects and lack of standardisation.

Azithromycin resistance patterns

Several gonococcal resistance surveillance programs have reported an upward trend in azithromycin minimum inhibitory concentrations (MICs) over recent years, and cases of clinical resistance have also occurred.[22,25–31] High-level resistance to azithromycin (HLAzi-R) is conferred by three or four mutations in the 23S rRNA (A2059G) and may be selected in isolates with low-level resistance due to mutations in just one or two of the mutated alleles. Phylogenetic analysis of HLAzi-R strains in a recent UK outbreak suggested that HLAzi-R strains were descendants of low-level resistant isolates.[32] This risk becomes of greater concern as the proportion of low-level resistant strains increases; for example, in England where it is now above 5%.[33] Other mechanisms of low-level resistance are mutations at an alternative position in the 23S rRNA gene (C2611T) or mutations affecting the expression of the mtr (multiple transferable resistance)-encoded efflux pump (efflux pump composed of mtr-C, -D and -E cell envelope proteins).

High-level resistance to azithromycin (HLAzi-R) was first verified from an isolate from Argentina in 2001[34] and since then, cases have been reported in the UK, Ireland, Sweden, USA, China and Australia.[35–41] Initial cases were sporadic or occurred in small clusters, suggesting that resistance may be associated with a reduction in fitness and reversion to full sensitivity can occur.[32] However, more recently, there is evidence for sustained transmission of these HLAzi-R strains, both within and between heterosexual and MSM networks,[42,43] and an adaptive increase in biological fitness in animal and cellular models has been described.[44] Developing a further understanding of this is essential to inform future management strategies such as the recycling of azithromycin in previously resistant populations.

Azithromycin as monotherapy

Recommendations for the use of azithromycin as monotherapy to treat gonorrhoea differ between countries. The UK includes a 2 g stat dose as a second line treatment option,[45] and the European guideline advises on its use only in specific circumstances and with supportive sensitivity testing.[46] It does not appear as a recommended option in the Australian, USA or World Health Organization (WHO) guidelines.[47–49] In a 2010 review of azithromycin monotherapy,[19] the authors concluded that azithromycin given as a 2 g single dose (total cases = 396) was an effective treatment, with a 95% cure rate and a lower 95% confidence interval also exceeding 95%, but the 1 g dose failed to meet these criteria.[50] A relatively low efficacy using the 1 g dose also occurred in a recent UK trial where, even when given in combination with gentamicin, it was associated with a 9% failure rate.[51]

There are several factors that may affect the interpretation of data from older studies that evaluated the efficacy of azithromycin as a treatment for gonorrhoea. First, gonococcal culture was used to assess cure, which may have overestimated treatment efficacy because culture has a relatively low sensitivity compared with nucleic acid amplification tests (NAAT); more recent studies, which assessed cure using NAATs, have reported lower cure rates.[22,25] Second, azithromycin resistance has increased over time, as described above, which reduces the relevance of previous treatment studies. Third, the data supporting the use of a 2 g dose have predominantly been in patients with genital infection,[21,52] but extra-genital gonorrhoea is also common, especially in men who have sex with men (MSM). Several studies suggest that treatment is less effective against pharyngeal infection, possibly due to reduced tissue penetration of the drug, or the presence of commensal bacteria, including other *Neisseriae* species, which are able to transfer resistance determinants to *N. gonorrhoeae*.[53] Some studies have found higher antibiotic minimum inhibitory concentrations (MICs) for isolates at extra-genital sites,[28,54] but this is not universal.[55] It is difficult to draw firm conclusions because the relevant studies are small, involve few extra-genital infections, underrepresent women and do not always take account of sexual orientation.[29,31]

Laboratory antimicrobial susceptibility testing is used both for the surveillance of gonococcal resistance and also to predict the treatment response for individual patients, but there is limited data on the correlation between laboratory MIC and clinical cure (M. Cole, pers. comm.), and there are several reasons why we may not be able to rely on MIC testing to reliably guide treatment for the individual. Bacterial growth conditions may be different *in vivo*, MIC accuracy may be affected by variations in assay or bacterial strain,[56] and as described above, rates of resistance also change over time. Culture is relatively insensitive compared with NAAT, meaning that *in vitro* antimicrobial susceptibility test results will be unavailable for a proportion of isolates, especially in patients with extra-genital infections. It is likely that those with a positive culture have a higher bacterial load, which may

reduce the treatment response. Discordance between predicted response based on the laboratory MIC and confirmed clinical cure can occur in both directions – azithromycin may be clinically effective despite an MIC predicting resistance,[25] but treatment failures can also occur despite the MIC predicting azithromycin sensitivity.[53] A recent large trial found only a limited association between the MICs in those who cleared and did not clear gonorrhoea, and selecting treatment based on pre-treatment MIC breakpoints was not useful in predicting treatment failure.[51] There is therefore a danger that a low MIC report may provide false reassurance to clinicians.

Azithromycin as dual treatment

The use of oral azithromycin (1 g) in combination with parenteral ceftriaxone is widely recommended as first-line treatment for gonorrhoea,[47–49] although the European guideline recommends a higher dose of 2 g azithromycin in their dual therapy regimen.[46] Using combination therapy has the potential for 'synergy' to occur between the two antibiotics to increase potency,[57,58] although *in vitro* studies suggest that this probably does not occur between azithromycin and ceftriaxone.[59–61] It is postulated that if ceftriaxone resistance is present, the addition of azithromycin in the regimen will still treat the infection and prevent the spread of resistance. This approach works in the treatment of infections that sequentially acquire resistance mutations during replication, like tuberculosis and HIV. In this scenario, concurrent resistance to two agents requires the simultaneous development of multiple mutations, and the probability of this happening is low. Although the major contributor to extended spectrum cephalosporin resistance seems to be mutation in the *penA* gene,[62] mutations in the *mtr* coding sequence of *N. gonorrhoeae* lead to overexpression of the multidrug efflux pump, MtrCDE, which increases the MIC to both ceftriaxone (4-fold) and azithromycin (16-fold), indicating that selection for resistance in both antibiotics may not be totally independent.[63]

Ceftriaxone resistance is rare but increasing, with the first case identified in Japan in 2009[64] and subsequently resistant strains described in Spain, Australia, Canada, France and Denmark, where simultaneous low-level azithromycin resistance has also been observed.[65–70] A MtrCDE mutation was identified in the French strain with the potential to reduce sensitivity to both ceftriaxone and azithromycin. The first case of ceftriaxone resistance in combination with high-level azithromycin resistance was reported from the UK in 2018, closely followed by two similar cases from Australia,[7,8] highlighting the potential for simultaneous resistance to occur.

Differences in the pharmacodynamics of ceftriaxone and azithromycin also have the potential to reduce the effectiveness of the combination. The longer half-life of azithromycin means that if ceftriaxone should fail, any gonococci not eradicated in the first 30 h after treatment will be exposed to azithromycin 1 g monotherapy for up to 14 days.[71] Even when infection is successfully cleared with ceftriaxone, there may be an ongoing risk. Clinicians recommend sexual abstinence for 2–4 weeks following treatment until repeat testing is performed to confirm cure. Many patients do not adhere to this advice[51] and any new gonorrhoea infection acquired in the subsequent 14 days will be exposed to sub-therapeutic levels of azithromycin, with case reports illustrating the potential for resistance to develop rapidly after such exposure.[71–73] The significance of prior exposure to azithromycin for the development of resistance is unclear. In a large European cohort, those with a history of recent gonorrhoea (and likely treatment with azithromycin) had reduced azithromycin sensitivity when they presented with reinfection.[29] Wind *et al*. also found that the use of azithromycin within 30 days of presenting with gonorrhoea was associated with significantly higher MICs, but not if exposure was 31–60 days before presentation.[74] In comparison, a recent UK study using national surveillance data from over 4000 patients with gonorrhoea found no significant difference in azithromycin MIC between groups receiving azithromycin in the previous month or 6 months compared with no prior exposure, using a diagnosis of non-gonococcal urethritis, non-rectal chlamydial infection or gonorrhoea as a proxy for azithromycin exposure.[75] The widespread use of azithromycin in the community outside a sexual health setting (reported as being the most commonly prescribed antibiotic in the USA[76]) makes it difficult to further quantify the importance of prior exposure as a driver for developing resistance in gonorrhoea; however, a recent ecological study using a mathematical model to link seasonal patterns of antibiotic use with resistance has further assessed this. The authors found that population-wide increased use of azithromycin in winter months resulted in a small but significant elevation in azithromycin MICs for gonorrhoea in spring.[77] It is currently unclear to what extent general prescribing drives azithromycin resistance, and any changes in prescribing practices, which were confined to sexual health services, would only account for a small proportion of all azithromycin prescriptions, although they would target those at highest risk of repeated gonococcal infection.

Effect of azithromycin use on other STIs

The use of azithromycin also has implications for patients at high risk for having other sexually transmissible infections, especially *Mycoplasma* and syphilis. Single-dose azithromycin selects for macrolide resistance in *Mycoplasma genitalium*, which occurs in 30–100% of patients.[78–81] Diagnostic and antimicrobial susceptibility testing for *M. genitalium* is not widely available to guide therapy and, to reduce exposure to azithromycin, guidelines no longer support its use as a first-line treatment of chlamydia or non-specific urethritis.[82,83]

Macrolide resistance is well recognised in syphilis, and the use of azithromycin has been associated with the development of high rates of resistance.[84,85] The possibility of inadvertent exposure of patients with asymptomatic syphilis to single-dose azithromycin if they are co-infected with gonorrhoea is therefore a concern.

There is a general move away from using azithromycin in sexual health patients both because of reduced efficacy but also to slow the development of future resistance to a variety of sexual transmitted pathogens.

Conclusions

Azithromycin has good activity against *N. gonorrhoeae* and achieves high tissue levels, which are maintained for a prolonged period of time. Its use as a component of dual therapy in combination with ceftriaxone is widespread, with the aim of slowing the development and spread of resistance. However, *N. gonorrhoeae* has the potential to develop high-level resistance to azithromycin, and the effect of dual therapy on the development of ceftriaxone resistance remains uncertain. The 1 g dose of azithromycin has limited efficacy, especially for extra-genital infections. The 2 g dose is more likely to be effective at genital sites, but is poorly tolerated. The extent to which widespread azithromycin use determines gonococcal resistance remains uncertain, but the use of single-dose azithromycin is associated with the rapid development of resistance in *Mycoplasma genitalium*. Recent guidelines suggest that its empirical use in those at high risk of STIs should be avoided where possible. Reflecting these concerns, recently updated guidelines recommend ceftriaxone monotherapy or the use of a higher dose of azithromycin when pharyngeal infection is present.[45,47] The use of a 1 g dose of azithromycin as part of a dual therapy regimen for gonorrhoea requires urgent review.

Conflicts of interest

Sarah Mensforth has no conflict of interest to declare. Jonathan Ross reports personal fees from GSK Pharma, Hologic Diagnostics, Mycovia and Janssen Pharma, as well as ownership of shares in GSK Pharma and Astrazeneca Pharma; and is author of the UK and European Guidelines on Pelvic Inflammatory Disease; is a Member of the European Sexually Transmitted Infections Guidelines Editorial Board; is a Member of the National Institute for Health Research HTA Commissioning Board; was previously a Member of the National Institute for Health Research HTA Primary Care, Community and Preventative Interventions Panel (2013–16). He is an NIHR Journals Editor and Associate Editor of the *Sexually Transmitted Infections* Journal. He is an officer of the British Association for Sexual Health and HIV (Vice President) and the International Union against Sexually Transmitted Infections (Treasurer).

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