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# Dual antimicrobial therapy for gonorrhoea: what is the role of azithromycin?

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Antimicrobial resistance in *Neisseria gonorrhoeae* compromises the treatment of gonorrhoea globally.[1,2] After the reports of the first gonococcal strains with highlevel resistance to ceftriaxone, the last remaining option for empirical gonorrhoea monotherapy, dual antimicrobial therapy (mainly ceftriaxone plus azithromycin) was implemented as the first-line treatment for uncomplicated gonorrhoea in many countries.[2–7] Azithromycin resistance is described in many countries, which might threaten this dual therapy in the longer term. However, high-level azithromycin-resistant (HL-AziR) gonococcal isolates (minimum inhibitory concentration [MIC] ≥256 mg/L) have mainly been sporadically identified.

In *The Lancet Infectious Diseases*, Helen Fifer and colleagues[8] describe a sustained transmission of HL-AziR gonococcal infections in England. This well written report describes the detailed characterisation using whole-genome sequencing of 60 HL-AziR isolates from England (between Nov 3, 2014 and Feb 24, 2017). The report compares the English isolates with other HL-AziR isolates, from different isolation timepoints and places, and with susceptible isolates or isolates with low-level azithromycin resistance. The study shows how whole-genome sequencing can be used to investigate outbreaks and inform outbreak control strategy. Most isolates (37 of 60) were genetically highly similar (mean 4·3 single-nucleotide polymorphisms) and belonged to the same clade. The HL-AziR phenotype was caused by a 2059A→G mutation in 3–4 alleles of the 23S rRNA gene; however, the 2059A→G mutation was found also in six isolates with lower azithromycin MICs (in 1–2 2x alleles). The phylogeny suggested that the HL-AziR isolates were descendants of the low-level azithromycin resistant isolates and, accordingly, azithromycin exposure might provide the selection pressure for emergence of the HL-AziR phenotype. One main conclusion of the Article was that “Dual therapy for gonorrhoea using azithromycin with ceftriaxone is clearly under threat and we might not be able to rely on azithromycin to protect ceftriaxone”.[8]

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The use of azithromycin in dual therapy for gonorrhoea has been increasingly questioned during the past few years, particularly because of increasing azithromycin resistance in gonococci in many countries. Notably, the HL-AziR gonococcal isolates remain rare in the UK and in all other countries globally, with mainly sporadic cases being described. Furthermore, in several countries, azithromycin resistance was present, or even higher, before the introduction of dual therapy. For example, in Europe, where dual antimicrobial therapy was introduced in 2012, the resistance to azithromycin (MIC>0·5 mg/L) increased from 4·5% in 2012 to 7·9% in 2014, and stabilised in 2015 (7·1%) and 2016 (7·5%). However, the azithromycin resistance was 13·2% in 2009 and 7·2% in 2010.[9]

In the UK, the total level of azithromycin resistance in gonococci also decreased from 9·8% in 2015 to 4·7% in 2016.[10] In the USA, during 2012–14, the proportion of isolates with reduced azithromycin susceptibility (MIC>1 mg/L) ranged from 0·02% to 1·0%, but during 2014–16, the proportion of isolates increased from 2·4 to 3·6%.[11] This variability highlights the difficulty in comparing resistance data from different regions or countries because if the US breakpoint (MIC>1 mg/L) was used in Europe, only 3·4% (instead of 7·5%) of European isolates in 2016 would be considered azithromycin resistant. This also shows that the vast majority of azithromycin-resistant gonococcal isolates in Europe have a low azithromycin MIC, which is close to the European resistance breakpoint that additionally results in fluctuations of the azithromycin resistance levels over the years.

The clinical relevance of isolates with decreased susceptibility or resistance to azithromycin remains unclear. No clinical treatment failures are described in the Article by Fifer and colleagues,[8] or in a recent cluster of HL-AziR isolates with decreased ceftriaxone susceptibility.[12] Furthermore, the induction or selection of azithromycin resistance in gonococci by the use of dual gonorrhoea therapy is probably limited because ceftriaxone resistance remains exceedingly uncommon, particularly in azithromycin-resistant gonococcal isolates. Accordingly, even if azithromycin resistance was induced or selected for in some gonococci when using dual therapy, ceftriaxone would quickly eradicate the azithromycin resistant organisms with its rapid bactericidal activity. Azithromycin resistance in gonococci, and also in *Mycoplasma genitalium*, could instead be mainly induced or selected by general macrolide use, including the widespread use of azithromycin monotherapy in respiratory infections and non-gonococcal urethritis; this deserves further study.[13,14]

The rationale for gonococcal combination therapy includes using different antimicrobials with different mechanisms of action to potentially mitigate the spread of antimicrobial resistance. Dual gonorrhoea therapy seems to be effective, with only one clinical failure (with pharyngeal gonorrhoea) following dual therapy having been verified globally,[15] and in-vitro resistance concomitantly to ceftriaxone and azithromycin is very uncommon in currently circulating gonococcal strains, possibly due to a poor biological fitness of such strains. Furthermore, in-vitro susceptibility to ceftriaxone or cefixime, or both, has slightly increased or stabilised since the introduction of dual therapy in Europe,[9] the USA,[11] and Canada,[16] with no clinical evidence to suggest that current dual therapy effectiveness is waning.

Ongoing global surveillance is paramount to determine antimicrobial resistance trends, which assist in the development of gonorrhoea treatment recommendations. In addition to surveillance patterns, Monte Carlo simulations have been used to investigate how various cephalosporin dosing regimens are affected by changes in MIC; for example, when using a ceftriaxone 1 g dose, sufficient *f*T>MIC (20–24 h) might not be achieved in up to 5% of patients, even for gonococcal strains with ceftriaxone MICs of 0·125 mg/L,[17] which are not uncommon in many countries.[9,11] This evaluation, based on pharmacodynamics modelling, suggests that many currently circulating gonococcal strains have the potential to cause ceftriaxone treatment failures; however, such an evaluation could overestimate treatment failures with monotherapy because these failures have not been clinically documented.

In conclusion, dual therapy with ceftriaxone plus azithromycin is highly effective for the eradication of gonococcal infection. Ongoing surveillance and public health action are necessary to monitor trends in antimicrobial resistance, and rapidly assess clinical treatment failures. New antimicrobials are currently being assessed and further research should investigate alternative antimicrobial combinations, which will be essential to provide optimum therapy against this formidable pathogen, and probably other sexually transmitted infections also, such as *M genitalium*.[1,2,13,18]

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