Antimicrobial resistance in gonorrhoea: Diagnostics to the rescue?

M Marks[1,2], E Harding-Esch[1]

1 Clinical Research Department, London School of Hygiene & Tropical Medicine, London, United Kingdom, WC1E 6HT

2 Hospital for Tropical Diseases, Mortimer Market Centre, Mortimer Market, London, United Kingdom WC1E 6JB

Author for Correspondence

Michael Marks

Clinical Research Department,

London School of Hygiene & Tropical Medicine,

London,

United Kingdom,

WC1E 6HT

michael.marks@lshtm.ac.uk

Alternative Author for Correspondence

Emma Harding-Esch

Clinical Research Department,

London School of Hygiene & Tropical Medicine,

London,

United Kingdom,

WC1E 6HT

emma.harding-esch@lshtm.ac.uk

Gonorrhoea, a sexually transmitted infection (STI) caused by *Neisseria gonorrhoeae*, remains a major public health issue worldwide with the World Health Organization (WHO) estimating that 87 million new cases of gonorrhoea occur annually[1]. Untreated gonorrhoea contributes to serious reproductive and sexual health sequelae, including pelvic inflammatory disease, infertility and an increased risk of transmission of HIV. Current international guidelines recommend ceftriaxone, with or without azithromycin, as treatment for gonorrhoea but this approach has been threatened by rising Minimum-Inhibitory Concentrations (MICs) in *N. gonorrhoeae* and the emergence of multi-drug resistant strains[2]. Indeed, the emergence of antimicrobial resistance (AMR) in *N*. *gonorrhoeae* has represented a constant challenge to the management of the disease in both low- and high-income settings. The history of gonorrhoea treatment is characterised by the successive introduction of new therapeutic agents followed rapidly by the emergence of widespread resistance. Such a phenomenon has occurred with sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and early-generation cephalosporins[3]. In light of the threat of AMR to the control of gonorrhoea, WHO has launched a global action plan including priority actions for gonorrhoea infection and AMR prevalence and incidence surveillance, national laboratory capacity strengthening, including the introduction of point-of-care tests (POCTs), and adapting national treatment guidelines to resistance patterns[4].

A number of strategies might be considered in order to combat the growing threat of AMR in *N. gonorrhoeae*. In common with other infectious diseases, the use of alternative or newer antimicrobial agents for treatment has been a priority area for research. In some regards the pipeline for gonorrhoea might be considered promising with a wide number of repurposed and newer agents undergoing trials. However, the challenges of developing agents that fit the desired profile of extremely high efficacy achieved with a single dosing regimen make identification of new agents challenging. Recent studies have evaluated Gentamicin[5], Solithromycin[6], Zoliflodacin[7] and gepotidacin[8]. The former two agents failed to achieve acceptable levels of cure in clinical trials whilst Phase 3 studies of the latter two agents are awaited. However, the historical evidence suggests that the benefit of any new agent is likely to be short-lived and that clinicians and policy makers should anticipate emergence of resistance to these agents within a relatively short time-frame. An alternative therapeutic strategy would be to identify multi-dose regimens, as are commonly utilised in other infectious diseases and increasingly in the treatment of STIs, such as prolonged doxycycline for the treatment of *Chlamydia trachomatis* or extended treatment of *Mycoplasma genitalium*.

Inherent in both current and emerging antimicrobial treatment strategies is the use of empiric therapy for patients presenting with urethritis, cervicitis or other syndromes consistent with gonorrhoea. The need for empiric therapy requires easy to administer, highly efficacious treatment regimes. An alternative strategy would be to deploy targeted antimicrobial therapy guided by the antimicrobial susceptibility data. Such a strategy might allow re-use of previously discarded therapies[9] and in turn, reduce the selection pressure on *N. gonorrhoeae* by diversifying the treatment regimens in use.

To facilitate individualised treatment, it is necessary for clinicians to have access to reliable, accurate and rapid diagnostic tests. Culture is critical in gonorrhoea diagnosis for antimicrobial susceptibility testing, allowing phenotypic determination of resistance patterns and MICs. However, the sensitivity

of culture is low and the turn-around time several days making it unhelpful for routine clinical care. In high-income settings, Nucleic Acid Amplification Tests (NAATs) are recommended for detection of infection because of their high sensitivity and specificity, and their relatively rapid turn-around time. There is increasing interest in the use of NAATs not only for diagnosis of infection, but also detection of AMR genes and to guide treatment strategies.

In this issue of Clinical Infectious Diseases, Klausner and colleagues **[KLAUSNER ARTICLE HERE]** report how a genotype-testing NAAT could be implemented in a real-world setting. The authors used residual DNA from the diagnostic *C. trachomatis/N. gonorrhoeae* NAAT to perform a PCR targeting a point mutation in the gyrase A gene (*gyrA*), which is known to result in resistance to ciprofloxacin in *N. gonorrhoeae.* To confirm the association of genotypic testing with in-vitro susceptibility, they performed culture and determination of ciprofloxacin MICs. Individuals with asymptomatic gonorrhoea were recruited from sexual health clinics across seven cities in the United States of America, treated with a single oral dose of ciprofloxacin and re-tested for proof of cure five to ten days after treatment. As expected, all wild-type isolates had an MIC <1µg/ml. The results of the study clearly demonstrate that in the presence of a wild-type *gyrA* allele, ciprofloxacin remains a highly efficacious treatment for gonorrhoea with 100% microbiological cure in the patient population. Introduction of the test into routine clinical practice, as a second step assay following a diagnostic NAAT, would allow clinicians to bring ciprofloxacin back into their clinical armamentarium at a time when new approaches to the management of gonorrhoea are badly needed.

It is worth considering the features of ciprofloxacin resistance in *N. gonorrhoeae* that make this approach viable. Importantly, the relationship between *gyrA* mutations and resistance is characterised by extremely high genotype-phenotype correlation. This means that presence of the mutation strongly predicts resistance, and that absence (a wild-type allele) strongly predicts a susceptible strain. Indeed, as Klausner and colleagues point out, a single point mutation predicted more than 98% of ciprofloxacin resistance in *N. gonorrhoeae*. This could allow genotypic AMR detection and resistance-testing guided therapy to become a part of the standard-of-care. How large an impact this strategy can be expected to have depends strongly on the proportion of cases, where if genotypic AMR detection was available, that ciprofloxacin would be a viable treatment for which will vary markedly across different regions of the world [3]. Such strong genotype-phenotype correlations are, however, not universal. In *N. gonorrhoeae*, the proportion of resistance conferred by different mutations varies markedly between different classes of agents such as fluoroquinolones, macrolides and extended spectrum cephalosporins [10].

It is important we recognise the limitations of the approach utilised in this study. Enrolled patients were selected on the basis of an initial positive NAAT result, and had not received empiric therapy. Such an approach may be possible in high-income settings for asymptomatic individuals detected on screening, or even some symptomatic individuals, but would not be possible for patient populations where empiric therapy is commonly used (e.g. those with high loss to follow-up) or in low-income settings where treatment is often based on syndromic management due to lack of access to any STI diagnostic testing. Can the assay utilised in this study be multiplexed with near-patient diagnostic assays to provide a same day result and appropriate management? Can such assays and platforms be made available in low-income settings? Implementing resistance-based therapies would require a

fundamental shift in the way in which sexual health services are delivered worldwide, but would be transformative and represent a significant step forward in our fight against AMR.

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