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Future treatment of gonorrhoea - novel emerging drugs are essential and in progress?

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1. Background

Gonorrhoea is a major public health concern, causing significant morbidity and socioeconomic consequences globally [1]. *Neisseria gonorrhoeae* has developed antimicrobial resistance (AMR) to all drugs available for treating gonorrhoea. In most countries, the only option for first-line empirical antimicrobial monotherapy is the extended-spectrum cephalosporin (ESC) ceftriaxone. Rare treatment failures of pharyngeal gonorrhoea with ceftriaxone and emergence of gonococcal strains exhibiting high-level clinical ESC resistance, combined with resistance to nearly all other antimicrobials, have resulted in development of global and regional action/ response plans [2–6], and introduction of dual antimicrobial therapy (ceftriaxone 250 – 500 mg and azithromycin 1 – 2 g) in Europe, the USA and additional countries [3, 7, 8]. However, the susceptibility of gonococcal strains to ceftriaxone has decreased globally, resistance to azithromycin is already prevalent in many settings and concomitant resistance to both ceftriaxone and azithromycin has been identified in several settings [2, 3, 7, 9]. Consequently, these dual antimicrobial regimens might not be long-term solutions. Furthermore, these might not be affordable in many less-resourced settings, suffering from the highest gonorrhoea burden, and accordingly may not significantly mitigate AMR emergence and spread in a global perspective [3, 9]. Improved treatment and novel therapeutic antimicrobials are essential.

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Declaration of interest

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2. Conventional treatment of gonorrhoea

Public health control of gonorrhoea relies on effective antimicrobial treatment, that is, combined with prevention efforts, sensitive and specific diagnostics (index cases and traced sexual contacts) and epidemiological surveillance. Therapy is mostly given empirically, using first-line therapy according to management guidelines [7, 8] and before laboratory results are available. Ideally, the first-line therapy should be highly effective, widely available in appropriate quality, dose and cost, lack toxicity, possible to administer as single dose and cure > 95% of infected patients [4, 10]. Nevertheless, the evidence base for this > 5% threshold for changing recommended treatment is limited and levels of > 1 and > 3% AMR in high-frequency transmitting populations have also been suggested [10, 11]. Additional criteria, for example, prevalence, local epidemiology, transmission frequency, treatment strategies and cost, diagnostic tests and sexual contact tracing strategies, should ideally be considered when deciding when to alter recommended treatment. An identical AMR threshold and treatment strategy might not be the most cost-effective solution in all settings and populations [9, 12]. Unfortunately, the strategy of using a single antimicrobial in a single dose, slightly increased repeatedly over time due to resistance emergence, has likely selected for resistance [2, 3].

3. Future treatment of gonorrhoea

Future treatment must be in strict accordance with regularly updated management guidelines, which should be informed by quality assured surveillance of local AMR and treatment failures. Dual antimicrobial therapy (ceftriaxone and azithromycin [7, 8]), which also eradicates any concurrent chlamydial infection, should be considered in all settings where local quality assured AMR data do not support other therapeutic options. Nevertheless, in some settings compliance with therapy is a limited problem and, when evaluated, multiple doses of a single antimicrobial might also be considered in the future. Appropriate pharmacokinetic/pharmacodynamic simulations and clinical studies for both currently used and novel antimicrobials would be exceedingly valuable and, preferably, both monotherapy and dual therapy of urogenital and extragenital gonorrhoea with different combinations of antimicrobials and multiple doses, should be evaluated.

In the future, ideally treatment at first healthcare visit will be directed by rapid genetic point-of-care (POC) AMR tests, including simultaneous detection of gonococci. This POC test could directly provide a diagnosis and guide individually tailored treatments, which will ensure rational antimicrobial use (including sparing last-line antimicrobials), timely notification of sexual contacts and affect the public health control of both gonorrhoea and AMR. No commercially available gonococcal molecular diagnostic tests detect any AMR determinants. However, laboratory-developed molecular assays exist for detection of gonococcal AMR determinants [3, 13]. Unfortunately, for most genetic AMR determinants the sensitivity and specificity in their AMR prediction are relatively low (particularly for ESCs with their ongoing resistance evolution involving many different genes, mutations and their epistasis) [2, 3]. Genetic AMR testing will never entirely replace phenotypic AMR testing because the relationship between phenotype and genotype is not ideal and genetic methods can only detect previously known resistance determinants. However, enhanced

research is imperative to continuously identify new resistance determinants and appropriately evaluate how current and future molecular AMR assays can supplement traditional AMR surveillance and guide individually tailored treatment [3, 13]. High-throughput genome sequencing, transcriptomics and other novel technologies might, initially in reference laboratories, revolutionize the genetic AMR prediction for both gonococcal isolates and primary samples positive for gonococci in genetic diagnostics.

4. Future treatment options for gonorrhoea

The dual antimicrobial treatment regimens with ceftriaxone and azithromycin [7, 8] are currently highly effective, however, as mentioned above these regimens might not be long-term solutions. Novel affordable treatments and/or antimicrobials for monotherapy or inclusion in dual treatment regimens, which might need to where feasible be considered for all newly developed antimicrobials, are essential.

A recent study evaluated two different novel dual antimicrobial regimens, that is, gentamicin (240 mg) plus azithromycin (2 g) and gemifloxacin (320 mg) plus azithromycin (2 g), for treatment of uncomplicated gonorrhoea. Microbiological cure was 100% with gentamicin + azithromycin and 99.5% with gemifloxacin + azithromycin, but adverse events were frequent with both regimens [14]. Generally, for dual antimicrobial therapy additional research is crucial to determine which antimicrobials (at what dosages) could be combined, and to appropriately document efficacy, side effects, pharmacokinetic/pharmacodynamic parameters, *in vitro* and *in vivo* synergistic relationship between antimicrobials, suppression of or increased resistance emergence (in gonococci and bystander organisms) and microbiological resistance breakpoints.

From a global public health perspective, where dual therapy is not affordable or feasible due to other reasons an effective antimicrobial monotherapy remain exceedingly valuable. ‘Old’ antimicrobials such as the aminocyclitol spectinomycin, aminoglycoside gentamicin, fosfomycin [15] and carbapenem ertapenem have been suggested and the *in vitro* susceptibility to all these appears relatively high. However, for empirical monotherapy all of these antimicrobials have shortcomings, for example, resistance is easily selected or resistance/decreased susceptibility already exist (spectinomycin, fosfomycin, ertapenem), mainly no recent appropriate clinical efficacy data for empiric monotherapy of urogenital and particularly extragenital gonorrhoea (gentamicin [mainly used in combination with doxycycline in Malawi], fosfomycin and ertapenem), evidenced suboptimal efficacy for treatment of pharyngeal gonorrhoea (spectinomycin) and lack of evidence-based correlates between MICs, pharmacokinetic/pharmacodynamic parameters and gonorrhoea treatment outcome (gentamicin, fosfomycin and ertapenem). Consequently, these antimicrobials are most likely mainly options for salvage therapy of ceftriaxone-resistant gonorrhoea and/or in novel dual antimicrobial treatment regimens [2, 3].

In recent years, several derivates of earlier developed antimicrobials have been evaluated *in vitro* against gonococcal strains [3]. The novel fluoroketolide solithromycin (family: macrolides) has high activity against gonococci, including ESC-resistant and multidrug-resistant (MDR) isolates. Nevertheless, gonococcal strains with high-level azithromycin

resistance (MIC ≥ 256 μg/ml) appear to be solithromycin resistant (MICs = 4 - 32 μg/ml) [16]. An open-label, randomized, multicenter Phase III clinical trial is currently recruiting participants with uncomplicated gonorrhoea. The study aims to enroll 300 participants and treatment with solithromycin 1 g orally will be compared with a dual antimicrobial therapy regimen, that is, ceftriaxone 500 mg plus azithromycin 1 g (www.clinicaltrials.gov). Also two 'bicyclic macrolides', that is, modithromycin (EDP-420) and EDP-322, recently showed potent *in vitro* activity against ESC-resistant and MDR gonococci. However, high-level azithromycin-resistant isolates (MIC ≥ 256 μg/ml) were resistant also to modithromycin and EDP-322 [17]. Several novel fluoroquinolones, that is, avarofloxacin (JNJ-Q2), sitafloxacin, WQ-3810 and delafloxacin, have a high *in vitro* activity against gonococci, including ciprofloxacin-resistant isolates. A Phase III clinical trial to compare delafloxacin (2 × 450 mg tablets administered once) with ceftriaxone (250 mg) for treatment of uncomplicated gonorrhoea in 757 patients was also designed, however, this study was recently terminated (www.clinicaltrials.gov). The glycylcycline tigecycline and fluorocycline eravacycline (TP-434) (family: tetracyclines) appear also potent against gonococci *in vitro*. However, a limited proportion of administered tigecycline is excreted unchanged in urine, which questions the use in gonorrhoea treatment. Finally, the lipoglycopeptide dalbavancin and two new 2-acyl carbapenems SM-295291 and SM-369926 have also recently shown a high *in vitro* activity against a limited number of gonococcal isolates [3].

Clearly, novel antimicrobial targets, compounds and treatment strategies are essential to develop and evaluate. Therapeutic compounds with multiple targets might be important to suppress resistance emergence, however, further research is important to provide an appropriate evidence base for this. Interestingly, several antimicrobials or other compounds, using new targets or bactericidal or bacteriostatic strategies, have been designed in recent years. Several of these have also shown a high *in vitro* activity against gonococcal isolates. Some examples of these are new protein synthesis inhibitors such as pleuromutilin BC-3781 and the boron-containing inhibitor AN3365; LpxC inhibitors; species-specific FabI inhibitors such as MUT056399 and novel inhibitors of bacterial topoisomerases that target regions different from the fluoroquinolone-binding sites such as VT12-008911 and AZD0914 [3]. Regarding AZD0914, no resistance was indicated examining geographically and genetically diverse isolates including many fluoroquinolone, ESC and MDR isolates [18]. An open-label, randomized, multicenter Phase II clinical trial is also currently recruiting participants with uncomplicated gonorrhoea. The study aims to enroll 180 participants and treatment with AZD0914 2 g orally (n = 70) and AZD0914 3 g orally (n = 70) will be evaluated with ceftriaxone 500 mg (n = 40) as the active comparator (www.clinicaltrials.gov). Interestingly, several examples of 'thinking out of the box' for future management of gonorrhoea have also been presented recently. These include efflux pump (particularly MtrCDE) inhibitors, particularly co-administered with antimicrobials, which increase the susceptibility to certain antimicrobials, innate host defense and toxic metabolites; non-cytotoxic nanomaterials; host defense peptides such as LL-37 (multifunctional cathelicidin peptide); molecules mimicking host defensins; factor H-Fc chimeric immunotherapeutic molecule [19] and IL-12 NanoCap, a biodegradable sustained-release formulation of human IL-12 that aims to be a therapeutic vaccine against gonococci (http://therapyxinc.com/pipeline) [3].

5. Conclusions

Several of the recently developed novel antimicrobials or therapeutic compounds deserve increased attention for potential future treatment of gonorrhoea. Ideally, their activity should initially be evaluated *in vitro* against large collections of geographically, temporally and genetically diverse gonococcal isolates, including MDR strains, particularly with ESC resistance and azithromycin resistance. Understanding of the effects and biological fitness of current and future genetic resistance determinants (*in vitro* induced/selected, including spontaneous resistance mutation frequency and mutant prevention concentration, and *in vivo* emerged) for these antimicrobials (both in gonococci and bystander organisms when treating gonorrhoea), time-kill curve analysis to evaluate bactericidal activity and clear correlates between genetic and phenotypic laboratory parameters and clinical treatment outcomes, would also be extremely valuable. Subsequently, *in vivo* evaluations ideally including mice model experiments and then appropriately designed, randomized controlled clinical trials evaluating parameters such as efficacy, safety, toxicity, cost, ideal dose and pharmacokinetic/pharmacodynamics data for genital and extragenital (especially pharyngeal) gonorrhoea. It is also important to determine the susceptibility of *Chlamydia trachomatis* and *Mycoplasma genitalium* to novel antimicrobials, which will indicate if the antimicrobials might be options for treatment of additional sexually transmitted infections (STIs) and STI syndromes, for example, urethritis and vaginal discharge. In general, for more sustainable gonorrhoea treatment in the future all newly developed antimicrobials might need to where feasible be considered for inclusion in a dual therapy regimen. Ideally, a gonococcal vaccine would be developed.

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