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Challenges with gonorrhea in the era of multi-drug and extensively drug resistance – are we on the right track?

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Abstract

Neisseria gonorrhoeae has retained antimicrobial resistance to drugs previously recommended for first-line empiric treatment of gonorrhea, and resistance to ceftriaxone, the last option for monotherapy, is evolving. Crucial actions to combat this developing situation include implementing response plans; considering use of dual antimicrobial regimens; enhancing surveillance of gonorrhea, gonococcal antimicrobial resistance, treatment failures and antimicrobial use/misuse and improving prevention, early diagnosis, contact tracing and treatment. The ways forward also include an intensified research to identify novel antimicrobial resistance determinants and develop and evaluate appropriate use of molecular antimicrobial resistance testing, ideally point-of-care and with simultaneous detection of gonococci, to supplement culture-based methods and ideally guide tailored treatment. It is crucial with an enhanced understanding of the dynamics of the national and international emergence, transmission and evolution of antimicrobial-resistant gonococcal strains. Genome sequencing combined with epidemiological metadata will detail these issues and might also revolutionize the molecular antimicrobial resistance testing. Ultimately, novel antimicrobials are essential and some antimicrobials in development have shown potent *in vitro* activity against gonococci. Several of these antimicrobials deserve further attention for potential future treatment of gonorrhea.

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Gonorrhea is a major public health concern globally that requires immediate international public health resources and attention. The WHO estimated that the global burden of gonorrhea in adults was 106 million cases in 2008, a 21% increase compared to 2005 [1]. The transmission of *Neisseria gonorrhoeae* can be controlled only through effective prevention, diagnostics and particularly antimicrobial treatment of patients and traced contacts. Untreated infections can result in severe reproductive complications, leading to infertility or loss of life through ectopic pregnancy or promoted transmission of other sexually transmitted infections, including HIV. Unfortunately, *N. gonorrhoeae* has developed antimicrobial resistance to all drugs introduced for treatment of gonorrhea [2–5]. In most countries globally, the only remaining options for empiric first-line monotherapy are the extended-spectrum cephalosporins, cefixime and ceftriaxone. However, treatment failures, particularly with cefixime and more rarely with the more potent ceftriaxone (mainly pharyngeal gonorrhea), have been verified in Japan, Australia, several European countries, Canada and South Africa [4,6,7]. Furthermore, multidrug-resistant gonococcal strains are common, and the first extensively drug resistant *N. gonorrhoeae* isolates with high-level ceftriaxone resistance were recently found [2–5].

As a response to this international spread of multi-drug-resistant and extensively drug resistant gonococcal strains and possible emergence of untreatable gonorrhea, the WHO, US CDC and European CDC have published a global action plan and regional response plans [2,8–10]. These plans recommend more holistic actions, for example, to reduce the global burden of gonorrhea and to substantially improve the early prevention, diagnosis, contact tracing, treatment and epidemiological surveillance of gonorrhea cases. These efforts need to be combined with strategies for general antimicrobial control (appropriate use, selection, supplies, quality, etc.) and an increased awareness among microbiologists, epidemiologists and clinicians and on political levels. Enhanced focus is crucial on high-risk populations and on appropriate prevention (promoting condom use when practicing oral sex), diagnosis and treatment of pharyngeal gonorrhea, which is harder to eradicate and represents an asymptomatic reservoir for gonorrhea and emergence of antimicrobial resistance. Widespread implementation of test of cure is crucial to identify treatment failures and reinfections. It is also essential to substantially enhance the quality-assured surveillance of gonococcal antimicrobial resistance and verified treatment failures to extended-spectrum cephalosporins, locally, nationally and internationally. The WHO Global Gonococcal Antimicrobial Surveillance Programme, which acts in liaison with other regional and national gonococcal antimicrobial surveillance programs, was relaunched in 2009 [4,8]. The gonococcal antimicrobial surveillance programs are imperative to timely monitor the trends in antimicrobial resistance, identify newly emerging antimicrobial resistance and inform revisions of evidence-based empiric treatment recommendations. Worryingly, gonococcal antimicrobial surveillance programs are lacking in many regions, including the WHO Eastern Mediterranean Region, Eastern Europe, Central Asia and Africa [2,8,11,12]. These

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latter regions have a high incidence of gonorrhea, suboptimal diagnostics and surveillance (cases and antimicrobial resistance), and antimicrobials are mostly easily available 'over-the-counter', which needs to be abandoned. These factors create effective prerequisites for rapid emergence and spread of gonococcal antimicrobial resistance. It is accordingly crucial to establish gonococcal antimicrobial surveillance programs in these regions. This requires training in quality-assured sample taking, gonococcal culture and antimicrobial resistance testing, collection of appropriate epidemiological data and analysis and use of the surveillance data, for example, for prompt revisions of empiric treatment guidelines. This will require substantial political advocacy, clear national and international evidence-based guidelines, funding (internal and external) and national and international collaboration in the investment in laboratory infrastructure and staff training. Unfortunately, the syndromic management of sexually transmitted infections, based on patient symptoms and pre-established antimicrobial treatment guidelines, introduced by the WHO in many resource-poor settings has resulted in loss of skills in sample taking and laboratory methodologies, as well as dismantling of the local infrastructures for etiologically based diagnosis and surveillance. Furthermore, the implementation, use and updating of the pre-established empirical treatment guidelines have not been ideal in several settings, creating prerequisites for emergence of antimicrobial resistance. Accordingly, in these settings, gonococcal antimicrobial resistance surveillance needs to be (re)established, and this surveillance should ideally be integrated in the diagnostics and/or surveillance of sexually transmitted infections. Nevertheless, also well-established gonococcal antimicrobial surveillance programs should increase the number and representativeness (geographic, in public and private sectors, and with regard to infections [gender and age] and anatomical site) of gonococcal isolates (consecutive, but also where indicated oversampling of particular risk groups) and the quality of associated epidemiological data. Methods to increase the sample for antimicrobial resistance testing include using targeted culture of *N. gonorrhoeae* microscopy and/or nucleic acid amplification test (NAAT)-positive samples. For comparison of valid antimicrobial resistance data internationally, ideally MIC-based and harmonized methods, interpretative breakpoints and internal and external quality assurance, should be used.

In many more-resourced settings, NAATs have replaced culture for diagnosis of gonorrhea, and research on the development and appropriate use of rapid, sensitive and specific point-of-care NAATs for detection of antimicrobial resistance, ideally combined with simultaneous detection of gonococci, is imperative. Unfortunately, currently developed methods for molecular detection of antimicrobial resistance possibly only reflect the MICs of given antimicrobials, and for most antimicrobials (particularly the recommended extended-spectrum cephalosporins with their ongoing evolution of resistance) and antimicrobial resistance determinants (ciprofloxacin possible exception), the sensitivity and specificity in their prediction of antimicrobial resistance are often low. Additionally, many of the gonococcal antimicrobial resistance determinants are also present in, for example, commensal *Neisseria* species, making it hard to predict antimicrobial resistance in particularly pharyngeal samples [4]. Intensified research is also essential to identify novel antimicrobial resistance determinants (focus on extended-spectrum cephalosporins), to agree on the nomenclature of antimicrobial resistance determinants (e.g., *penA* alleles) and to develop an internationally accessible database containing the sequence information and,

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ideally, appropriate microbiological, genetic, clinical and epidemiological data. Despite the fact that the molecular antimicrobial resistance testing might still be in its infancy, research is crucial to evaluate how such methods could be used in gonococcal antimicrobial surveillance programs and for ideally guiding tailored treatment of individual patients (by confirming resistance or susceptibility), which can ensure the rational use of antimicrobials and affect the control of both gonorrhea and antimicrobial resistance. Appropriate mathematical modeling should explore the impact of these methods, and dynamic transmission models can capture the net effects of competing factors, for example, increased detection and treatment of gonorrhea (cases and contacts), increased reinfection risk and reduced or delayed detection of antimicrobial resistance on the transmission of gonorrhea and of antimicrobial-resistant strains [13]. It might never be possible to replace culture-based antimicrobial resistance testing as the correlates between phenotype and genotype is mostly insufficient and new resistance determinants continuously evolve. However, molecular antimicrobial resistance detection methods, particularly highly multiplexed ones that can be quickly adjusted in response to novel antimicrobial resistance determinants, can supplement the culture-based antimicrobial resistance surveillance and, for example, can be used for rapid and comprehensive testing of a population for particular antimicrobials [14].

Most of the gonococcal antimicrobial resistance appears to have originated in the WHO Western Pacific region and then has subsequently spread internationally, which emphasizes that gonococcal antimicrobial resistance requires global actions to combat [3,4]. It is crucial with enhanced understanding of the dynamics of the national and international emergence and transmission of antimicrobial-resistant gonococcal strains. Using high-throughput genome sequencing combined with appropriate epidemiological metadata and phylogenomic and phylogeographic analysis, these issues will be possible to elucidate in more depth [15,16]. Accordingly, genome sequencing provides the resolution to infer the micro- and macro-epidemiology of gonococcal strains across time, geography and sexual networks. This knowledge can inform public health strategies for prevention, screening of asymptomatic reservoirs of infection, outbreak analysis, core group surveillance, targeted interventions and development of novel diagnostics and treatment of gonorrhea. We might even be able to elucidate how, when and where transmission-successful gonococcal clones and their possible antimicrobial resistance emerge, further evolve and spread (mechanisms and time scale) in communities, nationally and internationally – information important to mitigate and ideally predict the emergence and spread of current and newly evolved antimicrobial-resistant gonococcal strains. Likely, in the coming years, high-throughput genome sequencing and other novel technologies will also revolutionize the molecular antimicrobial resistance testing for both cultured gonococcal strains and NAAT-positive samples.

Due to the emergence of resistance to extended-spectrum cephalosporins, dual antimicrobial treatment regimens (mainly ceftriaxone plus azithromycin) for gonorrhea are now recommended in the USA and Europe [17,18]. These regimens are currently effective and should be considered in all settings where comprehensive, quality-assured local antimicrobial resistance data are lacking or not clearly supporting any other treatment regimen [4,19,20]. Nevertheless, susceptibility to ceftriaxone has been decreasing globally and resistance to azithromycin is emerging rapidly in settings where it has been used

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frequently, and gonococcal strains with resistance to both ceftriaxone and azithromycin have been found [4,19]. Further, the dual antimicrobial regimens might not be affordable in resource-poor settings, many of which suffer from the highest gonorrhea burden, and accordingly may not significantly mitigate emergence and global spread of antimicrobial resistance. Consequently, novel antimicrobials or other therapeutic compounds for effective monotherapy or at least for inclusion in new dual therapy regimens are essential. For monotherapy, spectinomycin, gentamicin and solithromycin have been suggested as theoretical options. However, none of these antimicrobials are ideal for empiric first-line monotherapy of gonorrhea, due to many reasons detailed elsewhere [4,19]. Most likely, these antimicrobials are instead options for salvage therapy for gonorrhea cases resistant to extended-spectrum cephalosporins and/or inclusion in a dual antimicrobial treatment regimen [4,19]. Promisingly, several derivates of previously developed antimicrobials have recently shown potent *in vitro* activity against gonococci. These include the tetracycline derivates/analogs tigecycline and eravacycline, lipoglycopeptide dalbavancin, 2-acyl carbapenems SM-295291 and SM-369926 and fluoroquinolones, avarofloxacin and delafloxacin. However, for more sustainable future treatment, ideally new targets/mechanisms (ideally multiple to suppress resistance emergence), new antimicrobial classes and other therapeutic or immunostimulating compounds will be developed and investigated. Notably, several such compounds have recently been developed and several shown to be promising against gonococcal isolates. These include the pleuromutilin BC-3781, boron-containing inhibitor AN3365, novel inhibitors of bacterial topoisomerases AZD0914 and VT12-008911, Fab-I inhibitor MUT056399, non-cytotoxic nanomaterials, efflux pump inhibitors, LpxC inhibitors, host defense peptides such as LL-37 and the therapeutic vaccine IL12 NanoCap. Several of these compounds deserve further attention for potential future treatment of gonorrhea. All novel potential treatment options ideally require up-to-date and comprehensive *in vitro* and *in vivo* evaluations, including well-designed, randomized clinical trials, evaluating efficacy, safety, toxicity, cost, optimal dose and pharmacokinetic/pharmacodynamic data for genital and extra-genital, especially pharyngeal, gonorrhea. Furthermore, knowledge regarding current and future antimicrobial resistance determinants (*in vitro* selected and *in vivo* emerged) for these compounds, both in gonococci and in bystander organisms, when treating gonorrhea, is important. Finally, research regarding which factors influence (and how they influence) the emergence and spread of antimicrobial resistance in *N. gonorrhoeae* is crucial, that is, examining impact of specific mutations versus acquisition of antimicrobial resistance determinants through transformation, behavioral characteristics (e.g., risk groups, sexual practices, anatomical site of infection), pharmacokinetic parameters of antimicrobials (e.g., long half-life etc., of antimicrobials, increase of dose to respond to antimicrobial resistance) and overall use/misuse of antimicrobials (related and unrelated to treatment of sexually transmitted infections) [21].

In conclusion, novel antimicrobials for effective treatment of gonorrhea are essential. Genomic, transcriptomic and proteomic studies combined with further advances in drug chemistry, high-throughput screening of compound libraries and insights gained from physiological experiments can identify novel bacterial targets and provide opportunities for rational design of new drugs. Additional knowledge regarding the structure and evolution of bacterial targets for antimicrobials or those that participate in antimicrobial resistance,

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prediction of the evolution of these targets and emergence of antimicrobial resistance (before the introduction of a given antimicrobial for treatment) and whether the current or future antimicrobial resistance mechanisms have a biological fitness cost or benefit will further support the development of effective and sustainable antimicrobials. Presently, strict implementation of action/response plans, dual antimicrobial treatment regimens (where indicated), gonococcal antimicrobial surveillance programs for surveillance of antimicrobial resistance and treatment failures worldwide and substantially intensified research activities are urgent public health priorities. Future molecular antimicrobial resistance methods might effectively supplement the culture-based gonococcal antimicrobial surveillance programs and also permit region-specific and tailor-made antimicrobial therapy.

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Biography

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