Neisseria gonorrhoeae resistance driven by antibiotic use

Huan V. Dong and Jeffrey D. Klausner

A new ecological analysis has shown that antimicrobial consumption is positively associated with decreased antimicrobial susceptibility in Neisseria gonorrhoeae across European countries. Efforts at the policy, provider and community level need to be strengthened to address and help mitigate the continued emergence of antimicrobial resistance in N. gonorrhoeae.


If the historical trend of Neisseria gonorrhoeae acquiring resistance to every new antibiotic used for treatment since the 1930s continues to hold true, then the reported cases from multiple continents of N. gonorrhoeae that are resistant to third-generation cephalosporins should not be taken lightly. One of the primary drivers of the emergence of antimicrobial resistance in N. gonorrhoeae is thought to be the human use of antibiotics, whether from directly treating gonorrhoea (termed a direct effect) or from the treatment of an unrelated infection (termed an indirect or bystander effect). Multifaceted approaches to understanding the drivers of antimicrobial resistance in N. gonorrhoeae and the epidemiology of transmission and spread of resistant strains are essential to address the impending threat of untreatable gonococcal infections.

A recent analysis by Kenyon et al.2 assessed the effect of varying levels of antibiotic use in 24 European countries on the antimicrobial susceptibility of N. gonorrhoeae isolates to cephalosporins, macrolides and quinolones. The study was well positioned to explore potential associations at the national level given the data sources of antimicrobial susceptibility testing (the European Gonococcal Antimicrobial Surveillance Programme) and of antibiotic consumption (a private marketing research database of pharmaceutical sales distributions). This analysis also gave insight to the type of resistance-driving mechanisms present across the different nations by using a unique set of variables: overall prevalence of resistance; mean minimum inhibitory concentration (MIC); and mean MICs of susceptible isolates. The investigators found a positive association between national levels of antibiotic consumption and the prevalence of decreased susceptibility of N. gonorrhoeae isolates to cephalosporins and quinolones but not the azalide azithromycin. The lack of association in this study in regard to azithromycin might be caused by the background levels of MIC drift that has accumulated from decades of use of macrolides, including erythromycin, and azalides, including azithromycin, to treat many common infections, such as lower respiratory tract infections. Notably, their finding of a strong correlation between increased cephalosporin use and increased mean MICs of susceptible N. gonorrhoeae isolates potentially indicates the effect of antibiotic consumption on the overall susceptibility of N. gonorrhoeae beyond the direct selection of resistant isolates and, therefore, supports the influence of the bystander effect in driving antimicrobial resistance.

These findings from an ecological study perspective support other observations of antibiotic use and decreased antibiotic susceptibility in studies in individuals. For example, resistance to the quinolone ciprofloxacin, a previous antibiotic of choice for treatment of N. gonorrhoeae infections, was shown to be positively associated with self-prescribed antimicrobial use. Additionally, to further compound the complexity of indirect acquisition of resistance in N. gonorrhoeae, a proposed mechanism of resistance is that the use of antibiotics selects for resistant oropharyngeal commensal Neisseria species (which have reduced susceptibility to extended-spectrum cephalosporins). These resistant commensals are known to exchange genetic elements with N. gonorrhoeae, potentially leading to resistant N. gonorrhoeae strains (Fig. 1).

To address and help mitigate the continued emergence of antimicrobial resistance in N. gonorrhoeae, efforts at the policy, provider and community level should be strengthened. First, population-wide understanding of how antibiotics are a unique and limited resource should be improved. Second, increased efforts should be made to reduce the inappropriate use of antibiotics through educating medical providers and pharmacists about their correct use, including the substitution of antibiotics with nonantibiotic treatments for upper respiratory symptoms. However, in many countries, a prescription from a medical doctor is not required for the purchase of antibiotics and individuals can easily acquire antibiotics from small pharmacies without proper medical consultation. Hence, policies must be put in place to restrict access to antibiotics and enforce regulations that prohibit over-the-counter sale of antibiotics.

"A positive association between national levels of antibiotic consumption and... decreased susceptibility"

Third, given the myriad of challenges in implementing the above recommendations and the importance of the bystander effect (in which even correctly prescribed antibiotics might inadvertently drive resistance to other or future infections), strong consideration must be given to reserving new antibiotics for unique and specific indications. For example, the new antibiotic zoliflodacin, which was recently shown to be efficacious in the treatment of urogenital gonorrhoea, should be reserved for the treatment of known gonococcal infections. Restricting its use in other infections would be expected to minimize any bystander effect (Fig. 1d). Perhaps another approach to mitigate the upward drift in MIC and potentially preserve specific antibiotics would be to evaluate whether increased doses...
Evidence suggests that direct and indirect ... effects of antibiotics affect clinical pathogens

of antibiotics can be safely administered clinically to prevent growth or selection of the least susceptible bacterium in a heterogeneous population (known as the mutant prevention concentration). If clinically tolerable, increased concentrations of antibiotics might help prevent variations of antibiotic concentrations at different anatomical sites, which can drive selection of resistant organisms (known as the mutant selection window) It. Finally, the use and availability of molecular methods to detect and diagnose gonococcal infections along with molecular methods to predict susceptibility need to be improved. Syndromic management of N. gonorrhoeae (the treatment of people on the basis of symptoms alone) has notoriously poor sensitivity in women, resulting in substantial overtreatment, and does not perform well in men either. Point-of-care testing technology is becoming more available as are technologies that enable resistance-guided therapy on the basis of the detection of genetic mutations or mechanisms associated with decreased antimicrobial susceptibility or resistance It. Patients with symptoms of a sexually transmitted infection often go to urgent care centres or community health centres outside of their primary care provider (potentially owing to sexual stigma); thus, implementing technologies that can effectively guide treatment during a single encounter is important. For example, various surveillance programmes have identified broad differences in patterns of N. gonorrhoeae resistance to ciprofloxacin and reduced susceptibility to cefixime by country. By treating patients on the basis of known infection and susceptibility results, the direct effect of antimicrobial use (FIG. 1b) on future resistance could be greatly reduced.

N. gonorrhoeae infections resistant to our last line of currently used antibiotics are increasing. New evidence suggests that direct and indirect or bystander effects of antibiotics affect clinical pathogens as well as nonpathogenic commensals that make up complex, interactive microbial communities. The relative contribution of each effect can be debated, but these effects must be addressed using multiple overlapping social and medical strategies: improved policies for controlling antibiotic use at the population level and the introduction of new technology are promising ways forward.

Huan V. Doan and Jeffrey D. Klasner 1,2

1Department of Medicine, Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA.
2Division of Infectious Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.
3Department of Epidemiology, Fielding School of Public Health at UCLA, Los Angeles, CA, USA.

*email: JDKlasner@mednet.ucla.edu

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Fig. 1 | Models of antimicrobial resistance selection in Neisseria gonorrhoeae. a | Antibiotic treatment of a population of susceptible Neisseria gonorrhoeae with complete eradication. b | Direct selection: antibiotic treatment of a heterogeneous population of N. gonorrhoeae with selection of nonsusceptible or resistant N. gonorrhoeae leading to expansion and proliferation of the resistant N. gonorrhoeae strain. c | Indirect selection or the bystander effect: antibiotic treatment of unrelated bacterial (or viral) illness (step 1) results in unintentional selection of a nonsusceptible or resistant commensal Neisseria species (step 2). Subsequent infection of susceptible N. gonorrhoeae can occur at the same anatomical site. Eventually, intragenus genetic exchange between commensal Neisseria and N. gonorrhoeae occurs, resulting in resistant N. gonorrhoeae.

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