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Antibiotic Resistance in *Neisseria gonorrhoeae*: Will Infections be Untreatable in the Future?

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Neisseria gonorrhoeae: a Re-emerging Public Health Threat

Neisseria gonorrhoeae (the gonococcus) is a Gram-negative diplococcal bacterium which infects only humans. It causes gonorrhea, a sexually transmitted infection (STI) described in the ancient texts of several cultures[1]. The prevalence of gonorrhea infections waxes (e.g. high after both world wars) and wanes (e.g. lower in the early 1990s)[2]. Once again, however, *N. gonorrhoeae* is re-emerging as a potent threat to public health both because of its high morbidity (the World Health Organization estimated 106 million new *N. gonorrhoeae* infections in 2008) and because the pathogen can be resistant to all classes of antibiotic making it a 'superbug'[3]. The actual numbers of gonorrhea infections globally are undoubtedly higher; cases can be drastically under-reported due to poor reporting systems, lack of clinical or laboratory diagnostic expertise and high rates of asymptomatic infection, especially in women (as high as 50%)[2,4].

N. gonorrhoeae infects human mucosal surfaces, commonly causing urethritis and cervicitis in women, and urethritis in men[2,3]. Untreated infections can produce severe complications in the female upper reproductive tract (pelvic inflammatory disease) which may lead to infertility and ectopic pregnancy. More rarely, men may also experience serious complications of gonococcal infection. Rectal and pharyngeal infections occur in both sexes. In the pre-antibiotic era, mother-to-child transmission of gonococcal infection during birth was a leading cause of blindness (opthalmia neonatorum). *N. gonorrhoeae* infections are associated with the acquisition and transmission of other sexually transmitted infections such as *Chlamydia trachomatis* and the Human Immunodeficiency Virus (HIV)[2,5].

There are no vaccines against *N. gonorrhoeae*; gonorrhea infections can only be cured by treatment with antibiotics. This effective strategy is now in jeopardy as *N. gonorrhoeae* has, in succession, become resistant to every class of antimicrobial agent (Figure 1) and can be resistant to multiple antibiotics simultaneously[6,7]. Over the last decade, *N. gonorrhoeae* isolates have become resistant to extended spectrum cephalosporins (ESCs), the last class of antibiotic used for monotherapy (i.e. single dose treatment with one antibiotic). Such isolates may be classified as Extremely Drug Resistant (XDR) if they carry resistance to two or more classes of currently recommended antimicrobial agents[8].

The failure to produce new, effective strategies to cure antibiotic resistant gonorrhea infections may lead to a situation reminiscent of the pre-antibiotic era where there were no effective treatments for gonorrhea. In response to this crisis, the World Health Organization (WHO) developed a global action plan, and many countries have established national action plans to control the spread and impact of antimicrobial resistance in *N. gonorrhoeae*[3].

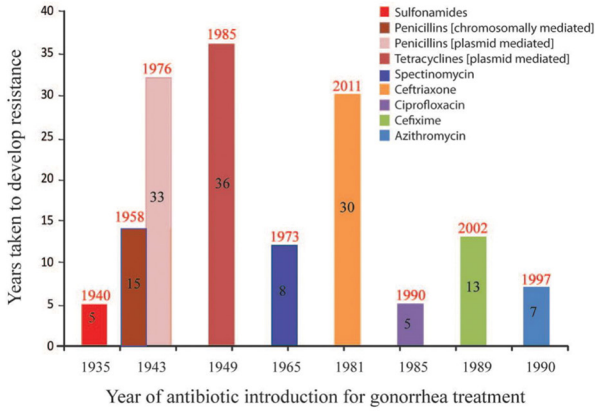


Figure 1 ~ Timeline of antibiotic use and emergence of resistance in *N. gonorrhoeae*. Different antibiotics were introduced for gonorrhea treatment in the specific years depicted on the x-axis. Vertical bars indicate the number of years that a particular antibiotic was used before any report of resistance. The red number on top of each bar is the year when resistance to that antibiotic was first reported.

Emergence of Resistance and Antimicrobial Resistance Mechanisms in *N. gonorrhoeae*

N. gonorrhoeae is a resilient and genetically diverse microorganism which is able to take up DNA at all stages of its life cycle from other gonococci, related pathogenic and commensal *Neisseria* species, as well as from bacteria from other genera. This ability has made *N. gonorrhoeae* particularly efficient at acquiring resistance mechanisms to antimicrobial agents which have undoubtedly helped it persist in the human population.

N. gonorrhoeae may become resistant to antimicrobial agents by mechanisms that include enzymatic destruction of the antibiotic (i.e. penicillin); target modification or protection (e.g. penicillin, tetracycline, ESCs); efflux of antimicrobial agents (most classes of antibiotic) and, decreased influx of antimicrobial agents (e.g. penicillin, tetracycline; Figure 2). Resistance may arise either through spontaneous mutations in different chromosomal genes, the uptake of mutated DNA through transformation or through plasmid-mediated conjugative mechanisms (penicillin and tetracycline resistance only)[9]. A mixture of resistance mechanisms is usually present in a single gonococcal cell (Figure 2) and a combination of genes, coupled with many mutations within a specific gene, is often required to achieve clinical levels of resistance to a particular antibiotic.

Sulfonamides

The steady emergence of resistance to all classes of antibiotics in *N. gonorrhoeae* isolates was foreshadowed with the first antimicrobial agents introduced to treat gonorrhea. Sulfonamides, discovered in 1935, were the first effective anti-gonococcal antimicrobial agents. These antibiotics work by competing with p-aminobenzoic acid (PABA) for the enzyme dihydropteroate synthase (DHPS), preventing the formation of tetrahydrofolate which is needed for DNA synthesis.

Resistance arose by chromosomal mutations emerging in the early 1940s, and by the early 1950s most *N. gonorrhoeae* isolates were resistant to various sulfonamides. Mutations in *folP*, which encodes DHPS, lowers the affinity of DHPS for sulfonamides[5,6]. Gonococci may also hyperproduce PABA overcoming the inhibitory effect of sulfonamides.

A trimethoprim-sulfamethoxazole combination was used to treat gonorrhea up to the late 1970s until resistance also developed to this combination[5,6].

ß-lactam antibiotics

Penicillin was first used to treat gonococcal urethritis in 1943 and remained the antibiotic of choice for treating gonorrhea for many decades (Figure 1)[7-9]. Treatment failures with penicillin were reported as early as the 1950s and over the following decades, the therapeutic dose of penicillin recommended for treatment continued to rise as the susceptibility of the organism to penicillin decreased[10,11]. Although *N. gonorrhoeae* isolates from some regions remain susceptible to penicillin, the step-wise emergence of resistance of high-level chromosomal resistance to penicillin, as well as the appearance of plasmid-mediated resistance to penicillin in 1976, resulted in the widespread discontinuation of penicillin for the treatment of gonorrhea by 1985[11].

A number of different genes, including *penA*, *ponA*, *mtrR*, *porB* and *pilQ* are implicated in chromosomally-mediated resistance to penicillin in *N. gonorrhoeae* isolates[5,6]. The major penicillin binding proteins (PBPs) of *N. gonorrhoeae*, PBP1 (*ponA*) and PBP2 (*penA*), catalyze peptide cross-linkages between adjacent glycan strands of peptidoglycan and are the targets of penicillin action. PBP2 is the primary target in *N. gonorrhoeae* and is inhibited at 10-fold lower concentrations of penicillin as compared to PBP1[5]. Different point mutations in PBP2 lower its acylation rate by penicillin G, resulting in reduced susceptibility to penicillin[5]. Isolates with mutations in *penA* are characterized by the insertion of aspartate residues at position 345 and may also carry several additional mutations in the carboxyl terminal region of the protein[5,6]. Penicillin resistance may also be conferred by 'mosaic' alleles of *penA* that may carry as many as 70 different mutations[5,8,9].

A single nucleotide polymorphism (SNP) in *ponA* (*ponA1* allele; L421P) results in decreased acylation of PBP1 and confers high-level penicillin resistance only when present with other penicillin resistance determinants[12]. *mtrR* encodes the multiple transfer resistance repressor (MtrR) which represses the expression of the MtrC-MtrD-MtrE efflux pump[5]. Mutations in *mtrR*, especially a single nucleotide deletion in the promoter region, results in the overexpression of the efflux pump and increased efflux activity

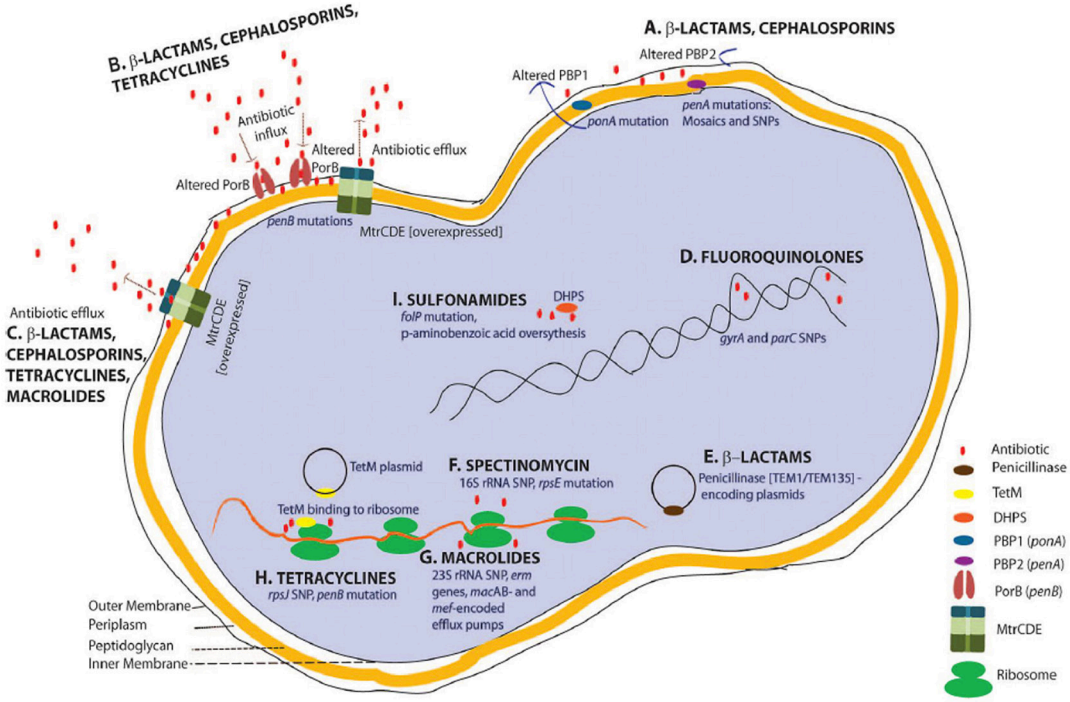


Figure 2 ~ Antibiotic resistance mechanisms in *N. gonorrhoeae* isolates and the respective antimicrobials which become ineffective. **A.** Mutations in penicillin binding proteins (PBP1 and PBP2). **B.** Mutations in *penB*, encoding a major outer membrane protein. **C.** Mutations in *mtrR*, that encodes the MtrR repressor protein, cause over-expression which increases efflux of antimicrobials. **D.** Mutations in DNA gyrase (*gyrA*) and topoisomerase (*parC*) which reduces binding to these enzymes. **E.** Plasmid-encoded penicillinase that hydrolyzes the ß-lactam ring. **F.** A 16S rRNA SNP and rpsE mutation inhibits binding to ribosomal target. **G.** rRNA methylases in 23S rRNA compromise binding. Over-expression of the MtrCDE efflux pump and/or *mef*- and *mac*AB-encoded efflux pumps increases efflux. **H.** An SNP in the ribosomal protein-encoding rpsJ and plasmid-encoded TetM protein reduces affinity for the ribosome. **I.** Mutations in DHPS-encoding *folP* and oversynthesis of p-aminobenzoic acid confer resistance.

causing enhanced resistance. *porB* encodes the outer membrane porin, PorB, that allows the passage of small molecules, such as ß-lactams and tetracyclines, into the periplasm. SNPs in this outer membrane porin, i.e. amino acid substitutions at Gly-120 and Ala-121, result in decreased influx, causing increased Minimum Inhibitory Concentrations (MICs) to these antibiotics. An increase in resistance due to these SNPs occurs only in isolates already harboring *mtrR* mutations[5]. Multimers of PilQ, a component of the gonococcal outer membrane, form a pore around the *pilus* of *N. gonorrhoeae* allowing antibiotics to diffuse into the periplasm. A *pilQ2* missense mutation (E666K) alters pilQ multimerization, destabilizing pore formation and blocking the entry of antibiotics[12]. Such mutations have only been described in laboratory isolates and may not be implicated in clinical resistance as they disrupt pathogenesis[5,6]. An unknown, non-transformable determinant, 'Factor X', is also thought to increase gonococcal MICs to penicillin by 3- to 6- fold[5].

Penicillinase-Producing Neisseria Gonorrhoeae (PPNG) isolates carry a family of related penicillinase-producing plasmids that originated in *Haemophilus parainfluenzae*[13,14]. These related plasmids of different size, named Asia, Africa, Toronto/Rio, Nimes, New Zealand, Johannesburg and Australia after their geographic origin, produce a TEM-1 ß-lactamase (*bla*) encoded by the transposon *Tn2*[5,14]. Some also carry a *bla* variant with a single nucleotide modification of TEM-1 at position 135 which may act as a precursor to further mutations in TEM-1 which could produce an enzyme capable of hydrolyzing ESCs[5]. Only the Asia, Africa and Toronto type plasmids have been associated with epidemic outbreaks. The endogenous gonococcal conjugative plasmid can mobilize the transfer of ß-lactamase-producing plasmids between gonococci and other genera[13].

Tetracyclines

Tetracycline, discovered in 1945, was first used to treat gonorrhea primarily in patients allergic to penicillin. Chromosomal resistance to tetracycline was observed early on; furthermore, a correlation with increasing MICs to both penicillin and tetracycline suggested common genetic mechanisms of resistance[15,16]. Plasmid-mediated resistance to tetracycline was first reported in the USA in 1985 and subsequently globally, leading to the discontinuation of tetracycline for treating gonorrhea[11,17]. Tetracycline is still recommended in some countries for concurrently treating chlamydial co-infections[6].

Some resistance genes implicated in chromosomal resistance to penicillin also impart resistance to tetracycline; intermediate levels of tetracycline resistance (MIC≥1 mg/L) can develop due to various mutations in *mtrR* as well as by the substitution of charged amino acids at positions G120 and A121 in PorB[5]. A mutation in the 30S ribosomal protein S10 (*rpsJ*), involved in the binding of tRNA to ribosomes, modulates the affinity of tetracycline for its rRNA binding site. Together with mutations in *mtrR* and *porB*, this mutation causes high-level chromosomal resistance to tetracycline[5].

Tetracycline resistance in *N. gonorrhoeae* can also be plasmid mediated and is caused by the acquisition of a 25.2-MDa *tetM*-containing plasmid which arose by the insertion of a streptococcal *tetM* sequence into the endogenous gonococcal 24.5-MDa conjugative plasmid[18]. These resistance plasmids can be transferred between gonococci and have been typed into four different classes[5,18]. The plasmid-encoded TetM protein binds to the 30S ribosomal subunit thereby blocking tetracycline from binding to its target[5].

Macrolides

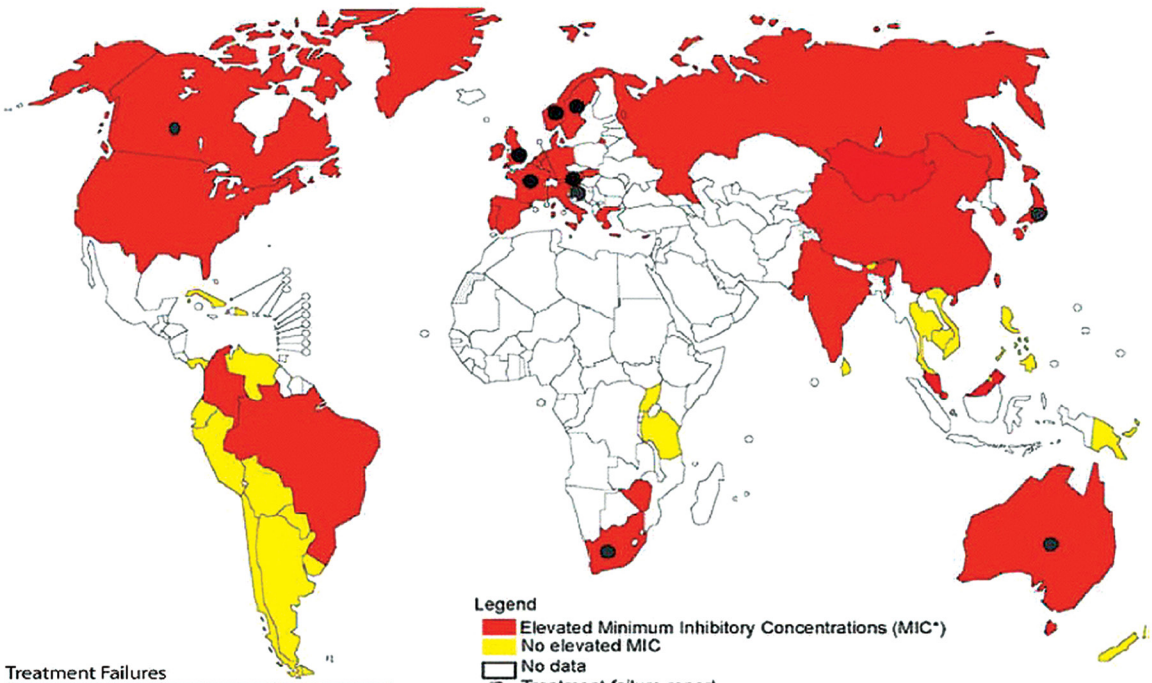
Azithromycin, a macrolide that inhibits protein synthesis, is not recommended for single dose treatment of gonococcal infections because of concerns over the rapid development of resistance[6].

Gonococcal resistance to azithromycin was first reported in Latin America in the 1990s and subsequently in North America and Europe[5,19]. This resistance is a concern since many countries now recommend dual antibiotic treatment of gonococcal infections which includes azithromycin[5,7,9].

Resistance to macrolide antibiotics (azithromycin and erythromycin) in *N. gonorrhoeae* can arise by SNPs in 23S rRNA – the binding site of macrolides – which can cause both low and high level resistance. More rarely, low level azithromycin resistance may be produced by the methylation of 23S rRNA by rRNA methylases (encoded by *ermB*, *ermC* and *ermF*) that also block the binding of macrolides to the ribosome[5,20]. A *mef*-encoded efflux pump which can export macrolides out of the bacterial cell has also been described in gonococcal isolates[5]. Resistance to macrolides may also be conferred by mutations in *mtrR* that cause overexpression of and enhanced efflux of the antibiotic. The overexpression of the efflux pump MacAB is also implicated in decreased susceptibility to macrolides[5].

Fluoroquinolones

The World Health Organization advises that the antibiotic used to treat gonorrhea should be changed if ≥5% of *N. gonorrhoeae* isolates tested are resistant to that antibiotic to ensure >95% therapeutic success with a particular regimen[3]. When resistance



Treatment Failures

Country	Cefixime	Ceftriaxone
Japan	+	+
Norway	+	NV/ND
UK	+	NV/ND
France	+	NV/ND
Austria	+	NV/ND
Australia	NV/ND	+
Slovenia	NV/ND	+
Sweden	NV/ND	+
South Africa	+	NV/ND
Canada	+	NV/ND

Figure 3 ~ Global map of reported resistance and treatment failures to extended spectrum cephalosporins. Modification of figure from WHO[37].

levels above this cut-off were reported for ß-lactam antibiotics (e.g. penicillin and ampicillin), sulfonamides and tetracyclines, fluoroquinolones (e.g. ciprofloxacin, ofloxacin) were then recommended to treat gonorrhea[5,6] (Figure 1). Gonococcal resistance to fluoroquinolones was first reported in the late 1980s from Asia-Pacific regions, North America and then internationally[5,21,22]. Most countries terminated the use of fluoroquinolones for treating gonococcal disease in the mid-2000s. Alarmingly, despite high percentages of resistant isolates, fluoroquinolones are still recommended in some countries largely because of inadequate infrastructure for the active surveillance of antimicrobial resistance and the timely modification of treatment guidelines for gonococcal infections[23].

The quinolones block DNA replication by targeting the enzymes DNA gyrase (*gyrA*) and topoisomerase IV (*parC*). Quinolone resistance in *N. gonorrhoeae* is caused by point mutations arising in specific regions of *gyrA* (position S91 and D95) and *parC* (positions S88 and E91)[5,24]. Mutations in DNA gyrase alone provides low to intermediate (MIC 0.25-0.5mg/L) levels of resistance to ciprofloxacin but a high level of resistance (MIC 4.0-16.0mg/L) also requires mutations in topoisomerase IV.

Spectinomycin and aminoglycosides

Spectinomycin, an aminocyclitol, was developed exclusively for treating gonorrhea in the early 1960s[6]. When introduced as a first line, sole treatment, clinical treatment failures caused by spectinomycin resistant strains rapidly appeared and reports of the sporadic isolation of resistant isolates are on-going[5,19]. Nevertheless, *N. gonorrhoeae* isolates remain susceptible to spectinomycin and this antibiotic is often recommended as an alternative therapy despite its expense and non-availability in certain regions.

Spectinomycin binds the 30S ribosomal subunit and inhibits translocation. High level resistance (i.e. >1000 µg/ml) may be caused by mutations in 16S rRNA and the 30S ribosomal protein S5[5,6,25]. Low level resistance may be imparted with a different mutation in the S5 protein[5].

Aminoglycoside antibiotics, such as streptomycin, were used in the 1950s to treat gonococcal infections[10]. However, their use was not widespread as *N. gonorrhoeae* isolates may become resistant to high levels of these antibiotics in a single mutational step. The aminoglycosides kanamycin and gentamicin have been used in a few countries (Indonesia, Malawi) for the treatment of gonorrhea and gonococcal susceptibility to gentamicin, alone or in combination with other antibiotics, is being actively studied around the world[6]. The aminoglycosides are generally not used for treating gonococcal infections because of their low activity and potential toxicity.

Extended spectrum cephalosporins

Extended-spectrum cephalosporins, currently the recommended primary treatment for gonococcal infections, were first discovered in the late 1940s. They include both cefixime, an oral antibiotic, and ceftriaxone, which is administered intramuscularly; cefixime is the antibiotic of choice due to its ease of administration[5,6,9]. Reports of the emergence of gonococci with both incremental decreasing susceptibility and *de facto* resistance to cefixime and ceftriaxone, coupled with reports of treatment failures with this class of antibiotics, have raised concerns about their continued effectiveness[3-6]. There are now frequent reports from Europe, North America, Japan and South Africa concerning treatment failures of gonococcal infections with cefixime[5,9] (Figure 3). Ceftriaxone is the last remaining treatment option for gonococcal infections utilizing a monotherapy approach and, worryingly, there have been cases of confirmed treatment failure with ceftriaxone in Japan, Australia, Sweden and Slovenia[5,7-9] (Figure 3). Furthermore, many parts of the world are unaware of the true prevalence of resistance to these antibiotics as susceptibility to these agents may not be monitored[23].

Cefixime resistance is primarily conferred by *penA*, with only small contributions by *mtrR* and *porB*, whereas ceftriaxone resistance is nearly equally dependent on these three genes[5]. Although some genes or mutations implicated in reduced susceptibility to ESCs remain unknown (i.e. factor X), most also confer penicillin resistance (Figure 3)[9]. The exact mechanisms of reduced susceptibility to ESCs are complex and involve different combinations of mutations, within a single gene or multiple genes. The first reported *N. gonorrhoeae* strain with resistance to cefixime carried a *penA* allele with 50-60 amino acid changes in PBP2, which was subsequently classified as mosaic PBP2 pattern X[26]. The acquisition of a *penA* mosaic allele by horizontal gene transfer, probably originating in commensal *Neisseria* species colonizing the oropharynx, is the more common mechanism conferring resistance to ESCs. The Japanese *N. gonorrhoeae* strain H041, which caused a treatment failure with ceftriaxone and is resistant to cefixime and to multiple other antibiotics, carries the mosaic allele $penA_{H041}$[27]. A common gonococcal strain type (NG-MAST ST1407), which is circulating worldwide, carries a *penA* mosaic allele[9]. Isolates of ST1407 are usually resistant to ciprofloxacin and may also carry plasmid mediated resistance to tetracycline. In addition to mosaic alleles of *penA*, various point mutations in *penA* (PBP2) can also contribute to reduced susceptibility to ESCs (Figure 3)[5,9,28-30].

Strategies for combating antimicrobial resistance in *N. gonorrhoeae*

A number of strategies are available for combating resistance in *N. gonorrhoeae* isolates. The World Health Organization has developed a global action plan and several countries have established national action plans to control the spread and impact of antimicrobial resistance in *N. gonorrhoeae*[3,7]. These plans include extensive antimicrobial susceptibility monitoring through regional/national Gonococcal Antimicrobial Surveillance

Programs (GASP) coupled with strategies such as the intelligent use of existing antimicrobials; development of novel antimicrobial agents; identification of alternative effective treatment regimens; development of effective molecular methods for monitoring and detecting antibiotic resistance; and, a renewed emphasis on research leading to the development of a vaccine against *N. gonorrhoeae*.

An immediate option has been to recommend and test combinations of newer and older antimicrobials used for therapy as well as designing and testing new antibiotics. ESCs, especially ceftriaxone, still remain a viable option for treating gonococcal disease worldwide. To counter the possibility of the emergence of XDR gonococcal isolates, many countries modified their guidelines[5,9]; the USA, Canada, European and other countries now recommend combination therapy with ceftriaxone (250 or 500 mg 1x IM) plus 1g azithromycin as a first-line treatment regimen[5]. However, treatment recommendations for gonococcal infections must be continually updated in response to the development of resistance. Interestingly, shortly before the implementation of the combined antimicrobial regimens which included increased doses of ceftriaxone, countries in Europe and North America reported declining percentages of *N. gonorrhoeae* isolates resistant to ESCs[5]. The reasons for these declines are not clear, but more rigorous antibiotic regimens may help to prevent the re-emergence of resistant isolates. Such findings attest to the importance of on-going global surveillance of gonococcal AMR to permit the prudent use and conservation of effective antibiotics. Many countries are not yet able to undertake such surveillance owing to a lack of capacity and specific expertise in gonococcal specimen taking, growth, identification and antimicrobial susceptibility testing (AST). Also complicating matters is the use of nucleic acid amplification tests (NAATs) for the identification of gonococcal isolates, which does not require pathogen culture, in resource-rich countries[8]. As a result, antimicrobial testing of a comprehensive population of *N. gonorrhoeae* isolates has been declining as this requires culture of the organism. Thus, the opportunity to utilize older and less expensive antimicrobials, such as penicillin and even ciprofloxacin, in areas where gonococci may remain susceptible to these antibiotics, is lost. The development of regional programs for gonococcal AMR surveillance coupled with regional treatment guidelines may also help to preserve the use of effective antimicrobials locally.

In addition to active national and regional surveillance programs to monitor the antimicrobial susceptibility of *N. gonorrhoeae* isolates, finding ways to detect resistance early is critical. Current antimicrobial susceptibility testing is a process that can take two to three days. The development of NAATs for antimicrobial susceptibility, or the development of point-of-care tests both for pathogen diagnosis and simultaneous AMR detection, seems like a logical next step for better diagnosis and treatment of gonococcal infections. Due to the plethora of AMR determinants involved in resistance to ESCs and other agents, research into models of AMR prediction based on molecular testing and population-based studies is required. Novel technologies, such as inexpensive, rapid genome sequencing platforms to diagnose AMR determinants may also change diagnostic and treatment paradigms.

Returning to the use of 'older' antibiotics may be another viable option for gonorrhea treatment. Although the efficacy of gentamicin does not meet recommended treatment efficacy criteria (≥ 95% treatment efficacy) specified for *N. gonorrhoeae*, it could potentially prove to be a valuable treatment option in patients with cephalosporin resistance or severe cephalosporin allergy[31]. Some antimicrobial agents such as ertapenem, a carbapenem, and tigecycline, a glycylcycline derived from tetracycline, are active against gonococci but require further testing[32]. A new fluoroketolide, solithromycin (CEM-101), has also been shown to have high *in vitro* activity against gonococci[33]. A novel, dual bacterial topoisomerase inhibitor (VT12-008911) showed anti-gonococcal activity against a wide range of isolates that were resistant to ceftriaxone, ciprofloxacin or multidrug resistant[34]. Novel combinations of antibiotics, both new and old, should be tested for *in vitro* synergy. Azithromycin given in combination with either gentamicin or gemifloxacin was an effective combination therapy to treat gonococcal infections[5]. A variety of other antimicrobials which may inhibit gonococcal isolates, such as pluromutalins (inhibit protein synthesis), novel topisomerases, inhibitors of efflux pumps and other compounds must be actively investigated by multiple groups for their effectiveness against gonococcal isolates[9]. Perhaps it is time for natural products to make a comeback; a number of medicinal plant extracts used for traditional purposes have shown inhibitory activity against resistant *N. gonorrhoeae* isolates[35]. A significant limitation in screening new compounds and agents against *N. gonorrhoeae* is having an accessible panel of isolates with an up-to-date array of all the different gonococcal resistance determinants. The developmental pipeline for such antimicrobial innovation is long and smaller private companies have taken the initiative in this challenge.

A gonococcal vaccine is urgently needed. The reasons for the failure to develop a gonococcal vaccine are complex and include the antigenic heterogeneity of the gonococcus, the lack of an effective animal model for testing potential vaccines and a poor adaptive immune response to infection. Meeting these challenges requires new and sustained research investment worldwide. In addition to reducing the global health burden caused by gonococcal disease, including reproductive complications, a gonococcal vaccine may have unintended benefits. The introduction of pneumococcal vaccines in Africa and elsewhere resulted not only in a reduction in cases of invasive pneumococcal disease, but also reduced the prevalence of *Streptococcus pneumoniae* infections resistant to front-line antibiotics. In some countries it also led to less antibiotic use overall[36]. One could hope that a gonococcal vaccine would also lead to a reduction in gonococcal resistance and antibiotic use.

Conclusion

In conclusion, while gonorrhea may very well become resistant to most antibiotics, at least those used in monotherapy, a number of possibilities may limit the dire prediction that *N. gonorrhoeae* will become an untreatable disease. These options include the introduction of novel antibiotic combinations for therapy; the prudent use of older, still effective antimicrobial agents, where applicable; the development of new effective antimicrobial agents and combinations of agents; better global surveillance and evaluation of the on-going extent of the problem; better diagnostics which will ultimately allow point-of-care testing for pathogen identification and appropriate antibiotic treatment; and, eventually, the introduction of a gonococcal vaccine which may limit disease as well as AMR.

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