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REVIEW

Drug-resistant *Neisseria gonorrhoeae*: latest developments

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Abstract Gonorrhea is the second most frequently reported notifiable disease in the United States and is becoming increasingly common in Europe. The purpose of this review was to assess the current state of drug-resistant *Neisseria gonorrhoeae* in order to evaluate future prospects for its treatment. An exhaustive literature search was conducted to include the latest research regarding drug resistance and treatment guidelines for gonorrhea. Gonococci have acquired all known resistance mechanisms to all antimicrobials used for treatment. Currently, the European Union, the United States, and the United Kingdom have established surveillance programs to assess, on a yearly basis, the development of gonococcal resistance. Current treatment guidelines are being threatened by the increasing number of ceftriaxone-, cefixime-, and azithromycin-resistant *N. gonorrhoeae* strains being detected worldwide. This has led the scientific community to develop new treatment options with new molecules in order to persevere in the battle against this "superbug".

Introduction

Gonorrhea is the second most frequently reported notifiable disease in the United States. In fact, about 820,000 new gonorrhea infections occur each year in the United States, of which an estimated 246,000 are resistant to at least one antibiotic (http://www.cdc.gov/drugresistance/biggest_threats.html). The latest report of the European Centre for Disease Prevention and Control (ECDC) showed a 25% increase in the number of reported cases between 2013 and 2014, with a total of 66,413 cases reported in 2014 (http://ecdc.europa.eu/en/healthtopics/gonorrhoea/Pages/Annual-Epidemiological-Report-2016.aspx). Seeing as there is no gonococcal vaccine, the public health control of gonorrhea relies entirely on prevention, sexual contact notification, epidemiological surveillance, diagnosis, and, especially, antibiotic treatment.

Since sulfonamides were first introduced to treat gonorrhea in the 1930s, *Neisseria gonorrhoeae* has continuously shown an extraordinary ability to develop resistance to all antimicrobials introduced for treatment [1] (Fig. 1). In fact, the recent emergence of resistance to the third-generation extended-spectrum cephalosporins (ESCs) cefixime and ceftriaxone, combined with resistance to practically all other available gonorrhea antimicrobials, has turned *N. gonorrhoeae* infection into a great public health issue [2]. So much so that, in 2012, the Centers for Disease Control and Prevention (CDC) classified it as a "Superbug", alerting about the prospect of untreatable gonorrhea in the near future [3].

This review describes the latest discoveries regarding gonococcal resistance and future prospects for *N. gonorrhoeae* treatment.

Molecular mechanisms of drug resistance

Neisseria gonorrhoeae has proven to have the capacity to alter its DNA, due to the fact that it is naturally competent for transformation during its entire life cycle. Moreover, when exposed to selective pressure, it can also change its genome effectively through all types of mutations. In fact, studies [4] show that, after introducing a new antimicrobial drug, gonococci become resistant and replace sensitive bacterial

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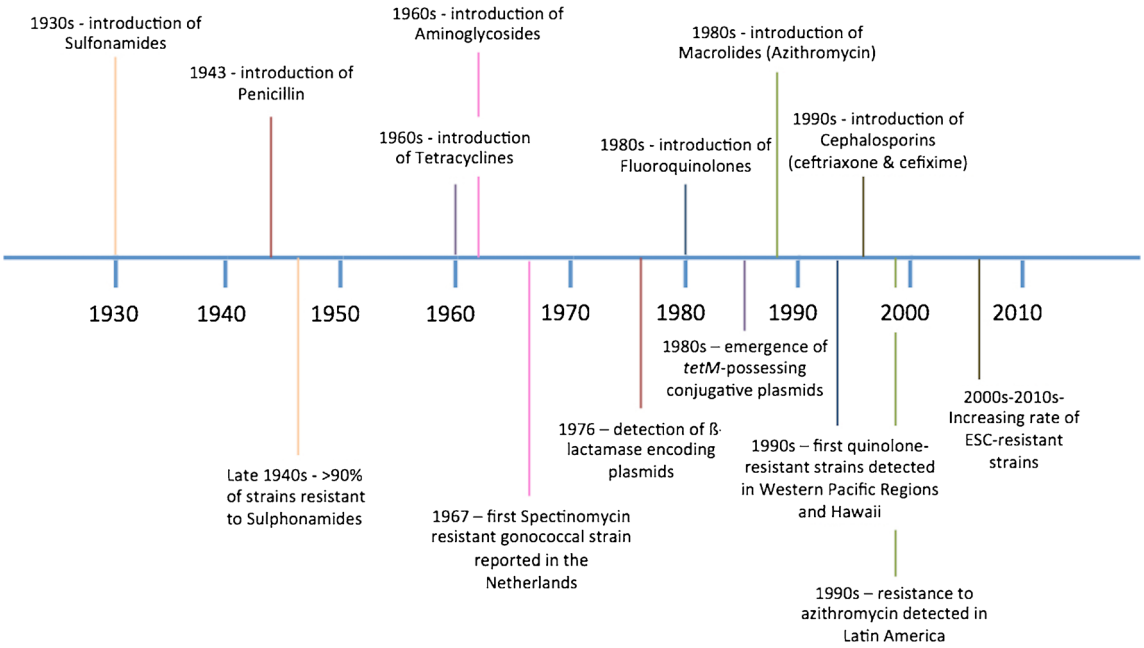

Fig. 1 Timeline representing the introduction and first reports of resistance for all treatments used against gonorrhea

population within two decades. In this way, gonococci have evolved and acquired or developed all known physiological resistance mechanisms to all antimicrobials used for treatment [5]: (i) enzymatic antimicrobial destruction or modification; (ii) target modification or protection reducing affinity for the antimicrobials; (iii) decreased influx of antimicrobials; and (iv) increased efflux of antimicrobials (Table 1).

Penicillinase is the main antimicrobial resistance determinant by which gonococcal strains decrease their susceptibility to antibiotics through their destruction or modification. *Neisseria gonorrhoeae* strains containing a plasmid with the $bla_{\text{TEM-1}}$ or $bla_{\text{TEM-135}}$ genes encode TEM-1 or TEM-135 β-lactamases, which hydrolyze the cyclic amide bond of β-lactamase-susceptible penicillins, opening the β-lactam ring, and, therefore, rendering it inactive [6, 7].

One of the main mechanisms of resistance in *N. gonorrhoeae* is target modification or reduction of target affinity. There are different genes that can alter antibiotic binding depending on the antimicrobial family. In this sense, alterations in the *folP* gene, which encodes the drug target DHPS for sulfonamides, is responsible for sulfonamide resistance [8]. The *penA* and *ponA* genes are responsible for chromosomally mediated β-lactam resistance due to specific mutations that modify the primary target PBP2 (*penA*) and the secondary target PBP1 (*ponA*), therefore reducing the penicillin acylation rate [6, 9, 10]. Similarly, tetracycline resistance is also due to two genes, *rpsJ* and *tetM*. The *rpsJ* gene produces resistance by encoding an altered form of a ribosomal protein, whereas *tetM* encodes a protein which binds to the ribosome, causing the release of the tetracycline molecule [11, 12]. Along these lines, the *rpsE* gene causes spectinomycin resistance by encoding an altered 30s ribosomal protein which disrupts the antimicrobial's binding to 16s RNA [13, 14]. The main resistance mechanism for quinolones is also target modification. In this case, two genes are involved, *gyrA* and *parC* [15, 16]. Mutations in *gyrA* cause alterations in the primary target of DNA gyrase, which results in reduced quinolone binding affinity. As for *parC*, it is responsible for high-level resistance, as mutations in this gene affect the two *parC* subunits in topoisomerase IV. Finally, macrolide resistance also occurs due to this mechanism. In this case, a series of *erm* genes encode rRNA methylase, which produce resistance by blocking macrolide binding to 23s rRNA by methylating an adenosine residue at position 2058 [17].

Finally, *N. gonorrhoeae* can also develop antibiotic resistance by controlling the concentration of antibiotic entering the gonococci. Mutations in the genes *porB1b* [5, 10] and *pilQ* [8] produce alterations in porins, which result in a decreased influx of antibiotic into the cell. Similarly, overexpression of the pore-encoding *mtrR* [10, 16, 18] and *mef* [17] genes result in a higher number of efflux pumps, which decrease the concentration of antibiotic inside the cell.

Most gonococcal antimicrobial resistance (AMR) determinants have a chromosomal origin and only the bla_{TEM} gene [12] and the *tetM* gene [19], which are responsible for high-level resistance to penicillin and tetracycline, respectively, are known to be plasmid-borne.

Generally, the acquisition of a single AMR determinant only results in an increase in the minimum inhibitory concentration (MIC) without it having any clinical importance. However, the cumulative effect of two or more AMR determinants and their interactions can ultimately result in clinical

Table 1 Antimicrobial resistance responsible for the different resistance mechanisms in Neisseria gonorrhoeae

Resistance mechanism	Genes	References
Enzymatic antimicrobial destruction or modification	• Penicillinase (TEM-1 or TEM-135 encoding plasmids)	[6, 7]
Target modification or protection reducing antimicrobial affinity	• *folP* (sulfonamides)	[8]
	• *penA* (decrease PBP2 acylation rate, reducing susceptibility 6- to 8-fold)	[6, 9, 10]
	• *ponA* (reduces penicillin acylation of PBP1 2- to 4-fold)	[6, 10]
	• *rpsJ* (reduces tetracycline affinity for the 30S ribosomal target)	[11]
	• *tetM* (blocks tetracycline target binding)	[11, 17]
	• *rpsE* (disrupts the binding of spectinomycin to the ribosomal target)	[12, 13]
	•*gyrA* (reduces quinolone binding to DNA gyrase)	[14, 20]
	• *parC* (reduces quinolone binding to topoisomerase IV)	[14]
	• *erm* genes (macrolides)	[15]
Decreased influx of antimicrobials	• *porB1b*	[5, 10]
	• *pilQ*	[8]
Increased efflux of antimicrobials	• *mtrR* (overexpression of the MtrCDE efflux pump)	[10, 16, 20]
	• *mef* (encodes efflux pumps for macrolides)	[15]

treatment failure [20]. Furthermore, some AMR determinants, such as *mtrR* and *gyrA*, are thought to enhance the fitness of some *N. gonorrhoeae* strains [16].

Current resistance status

As the CDC [2] predicted in 2012, *N. gonorrhoeae* has become a "Superbug" and, thus, an urgent public health threat. The increasing detection of gonococcal strains resistant to ESCs and azithromycin may lead to a situation where gonorrhea becomes untreatable. In fact, *N. gonorrhoeae* strains H041 (ceftriaxone MIC of 2 mg/L), F89 (ceftriaxone MIC of 1 mg/L), and A8806 (ceftriaxone MIC of 0.5 mg/L) with high-level resistance to ceftriaxone were isolated from patients in Japan [21], France [22], and Australia [23], respectively. Moreover, a new ceftriaxone- and multidrug-resistant *N. gonorrhoeae* strain was recently isolated in Japan [24]. This strain contained a novel mosaic *penA* allele encoding a new mosaic penicillin-binding protein 2 (PBP2) with an almost identical resistance-determining 3′-terminal region when compared to the same regions in strains previously reported in Australia and Japan.

Interestingly, another study recently published in Canada [25] showed that the proportion of isolates with decreased susceptibility to cephalosporins declined significantly between 2011 and 2014, whereas azithromycin resistance increased considerably during the same period. This study concluded that continued surveillance of gonococcal antimicrobial susceptibility is vital to modify treatment guidelines in order to slow down the spread of isolates with decreased susceptibility to cephalosporins and resistance to azithromycin.

The problem with resistant *N. gonorrhoeae* is such that the first case of failure of the standard dual antimicrobial treatment for gonorrhea was recently reported in the UK [26]. The results of the antimicrobial susceptibility tests showed that the strain was resistant to ceftriaxone, azithromycin, cefixime, cefotaxime, penicillin, tetracycline, and ciprofloxacin, but it was susceptible to spectinomycin.

As these reports show, treatment for gonococcal infection is being seriously threatened by the emergence of antimicrobial resistance. Bearing this in mind, governments all over the world have created programs to collect data in order to study the ways in which this species is developing resistances and presenting itself at a community level. Three of the most established programs are the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in the United Kingdom (https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report), the Gonococcal Isolate Surveillance Project (GISP) in the United States (https://www.cdc.gov/std/gisp/), and the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) (http://ecdc.europa.eu/en/healthtopics/gonorrhoea/response-plan/pages/strengthening-antimicrobial-surveillance.aspx). All three programs share a common aim: to detect the emergence of any AMR which could threaten the effectiveness of current first-line treatments.

Reports from all three of these programs provide insights as to how antibiotic resistance is evolving within *N. gonorrhoeae* strains. Figure 2a–c show said evolution for the 2004–2014 period. As these graphs illustrate, different treatment policies between the United Kingdom, the United States, and the European Union have resulted in different antibiotic resistance trends. For example, the GRASP reports a decrease in

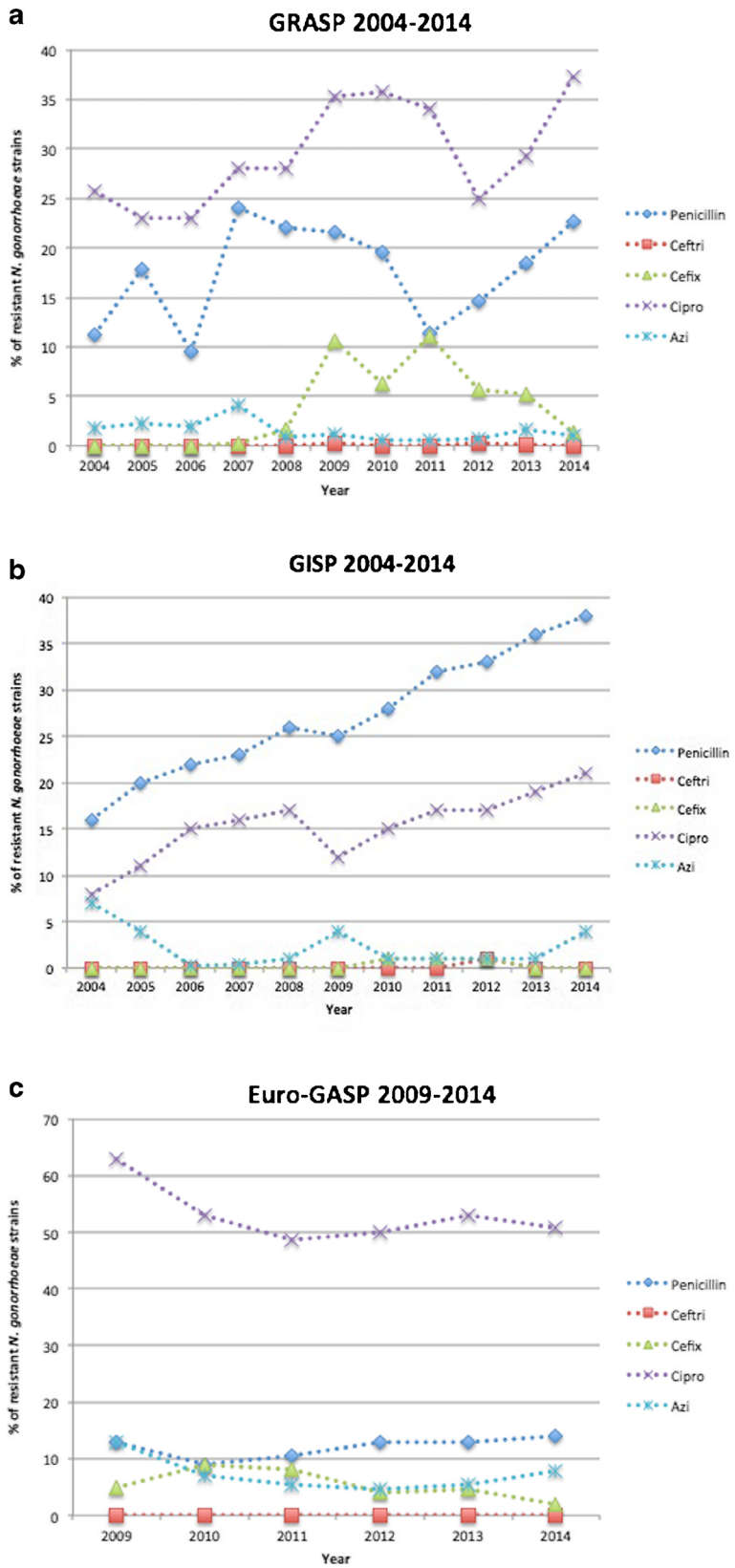

Fig. 2 Evolution of Neisseria gonorrhoeae resistant strains detected by the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) (a), the Gonococcal Isolate Surveillance Project (GISP) (b), and the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) (c) from 2004 to 2014

penicillin resistance from 2007 to 2011, followed by an increasing trend ever since, having reached 22.6% in 2014. Similarly, the GISP reports also show a consistently increasing trend in penicillin resistance having more than doubled during the last ten reports (from 16% in 2004 to 38% in 2014). On the other hand, the Euro-GASP shows a stable rate of penicillin resistance at around 13–14% since 2004. In regard to ceftriaxone, all three reports show resistance rates close to 0%. GRASP and Euro-GASP detected a peak in cefixime resistance in 2011 and 2010, respectively, after which resistance rates decreased considerably in both cases (11 to 1.4% for GRASP and 9 to 2% for Euro-GASP). The detection of ciprofloxacin-resistant strains increased in GRASP since 2012 (25 to 37.3% in 2014) and in GISP since 2009 (12 to 21% in 2014). On the other hand, Euro-GASP reports show a decrease in ciprofloxacin resistance from 63% in 2009 to 50% in 2014. Finally, azithromycin resistance varies considerably among reports. The GRASP shows rates of azithromycin resistance below 2% since 2007, whereas the GISP and the Euro-GASP show increasing detection of resistance in their 2014 reports (from 1 to 4% in GISP and from 5.4 to 7.9% for Euro-GASP).

Treatment options

In clinical practice, treatment for gonococcal infection is mostly given empirically at the first clinical visit; thus, antimicrobial susceptibility is rarely performed prior to prescription. According to the World Health Organization (WHO) guidelines [27], first-line antimicrobial therapy should be highly effective, widely available and affordable, lack toxicity, single dose, and (rapidly) cure at least >95% of infected patients. However, identical cut-off levels and treatment regimen(s) will not be the most cost-effective solution in all geographic regions and populations [28].

For the last decade, in many geographic regions worldwide, cefixime 400 mg orally or ceftriaxone 125–1000 mg intramuscularly or intravenously had been the recommended first-line monotherapy for gonorrhea [28, 29]. However, due to the previously commented emergence of resistance to all extended-spectrum cephalosporins (ESCs), including the most potent ESCs cefixime and ceftriaxone, dual antimicrobial therapy has been introduced as first-line empirical therapy for uncomplicated anogenital and pharyngeal gonorrhea in the USA [30], Canada [31], Australia [32], and Europe [33]. This

Table 2 Treatment guidelines according to different health organizations worldwide

CDC	EU	WHO
Uncomplicated	Uncomplicated	Dual therapy
Ceftriaxone 250 mg IM single dose	Ceftriaxone 200 mg IM single dose	Ceftriaxone 250 mg IM single dose
+	+	+
Azithromycin 1 g oral single dose	Azithromycin 2 g oral single dose	Azithromycin 1 g oral single dose
		Or
		Cefixime 400 mg oral single dose
		+
		Azithromycin 1 g oral single dose
Alternative	Alternative	After treatment failure
Cefixime 400 mg oral single dose	Cefixime 400 mg oral single dose	Ceftriaxone 500 mg IM single dose
+	+	+
Azithromycin 1 g oral single dose	Azithromycin 2 g oral single dose	Azithromycin 2 g oral single dose
		Or
		Cefixime 800 mg oral single dose
		+
		Azithromycin 2 g oral single dose
		Or
		Gentamicin 240 mg IM single dose
		+
		Azithromycin 2 g oral single dose
		Or
		Spectinomycin 2 g IM single dose
		+
		Azithromycin 2 g oral single dose

treatment generally consists of a single 250–500 mg dose of ceftriaxone along with 1–2 g of azithromycin, which additionally eradicates concomitant *Chlamydia trachomatis* infection.

However, the decreased susceptibility to ceftriaxone and increased resistance to azithromycin worldwide suggest that the recently introduced dual antimicrobial regimens might not be effective long-term solutions. Two new dual antimicrobial therapies were recently proposed and evaluated: 240 mg of gentamicin intramuscularly plus 2 g of azithromycin orally and 320 mg of gemifloxacin orally plus 2 g of azithromycin orally [34]. The cure rate was 100 and 99.5%, respectively, which proves any of these two regimes suitable as alternative treatment options in the presence of ceftriaxone resistance, treatment failure with the recommended regimen, or ESC allergy [30]. Table 2 shows the suggested treatment guidelines by the Centers for Disease Control and Prevention (CDC), the European Union, and the WHO. Furthermore, many analogues of previously described and used antimicrobials have also been shown to have a high in vitro activity against *Neisseria gonorrhoeae*. These include several new fluoroquinolones [35–38], tetracyclines [39, 40], carbapenems [41], macrolides [42, 43], and the lipoglycopeptide dalbavancin [44]. The new oral fluoroketolide solithromycin [43] (macrolide family) is the most advanced in development, currently having a multicenter, open-label, randomized Phase 3 clinical trial running.

Concluding remarks

Gonorrhea is becoming an even bigger worldwide public health problem with the emergence of multidrug-resistant gonococcal strains. In order to avoid the scenario where gonococcal infections become untreatable, efforts in the areas of drug development and research on vaccines are essential. Moreover, surveillance programs are key in the validation and modification of the suggested treatment guidelines.

Compliance with ethical standards

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